animals touched the wire with at least one of the hind-paws within 2 s (traction) and remained hanging for at least 1 min (suspension). The ED_{50} for each test was the dose causing 50% of the mice to fall, without traction and suspension.

Antagonism against Tremorine-Induced Parasympathetic Stimulation in Mice.[26] Tremorine (20 mg/kg ip) was given to male mice 1 h after the test compounds, and the presence of central (tremor) and peripheral parasympathetic stimulation (salivation) was recorded thereafter. The ED_{50} was considered the neuroleptic dose protecting 50% of rats from tremorine-induced effects.

Antagonism against Catecholamine-Induced Lethality in Rats.[22] The rats (80–90 g of body weight) were injected with a dose of norepinephrine (0.5 mg/kg iv) that caused their death within 30 min when not protected with active drugs. The ED_{50} was the neuroleptic dose protecting 50% of rats from norepinephrine-induced lethality.

In Vitro Interaction with Dopamine Rat Striatum Receptors Labeled with [^{3}H]Spiroperidol.[27] The binding experiments were performed on crude membrane preparations of rat striata that were stored at −80 °C until used. Aliquots (2.5 mL) of thawed and freshly washed membrane fractions were incubated for 15 min at 37 °C with increasing concentrations (10^{-10} to 10^{-4} M) of drugs to be tested and with [^{3}H]spiroperidol (0.5 nM, 24.5 Ci/mmol; New England Nuclear Corp.) in the presence of 1 μM pargyline and of 0.1% ascorbic acid. The membranes were than filtered, washed three times, dried overnight in an oven, and counted in toluene–POPOP fluor. Specific binding was considered as that bound without the addition of 1 μM of haloperidol minus that bound in its presence. IC_{50} was considered as the concentration of drug causing 50% binding inhibition and was calculated from the displacement curve.

Acute Toxicity in Mice. The toxicity was evaluated by the intraperitoneal route and the LD_{50} was considered the dose causing the death in 50% of treated mice.

Registry No. **2**, 52867-87-5; **2a**, 51037-47-9; **3**, 120944-08-3; **3** base, 120944-47-0; **3a**, 120944-34-5; **4**, 120944-09-4; **4a**, 120944-35-6; **5**, 52867-74-0; **5a**, 51037-51-5; **6**, 120944-10-7; **6** base, 120944-48-1; **6a**, 120944-36-7; **7**, 120944-11-8; **7a**, 120944-37-8; **8**, 120944-12-9; **8a**, 95217-32-6; **9**, 120944-13-0; **9a**, 120944-38-9; **10**, 120944-14-1; **10a**, 95217-30-4; **11**, 120944-15-2; **11a**, 120944-39-0; **12**, 120944-16-3; **12** base, 120944-49-2; **12a**, 95217-34-8; **13**, 120944-17-4; **13** base, 120944-50-5; **13a**, 95217-33-7; **14**, 120944-18-5; **14** base, 72444-63-4; **14a**, 95217-35-9; **15**, 120944-19-6; **15** base, 120944-51-6; **15a**, 120944-40-3; **16**, 120944-20-9; **16** base, 120944-52-7; **16a**, 120944-41-4; **17**, 120944-21-0; **17** base, 120944-53-8; **17a**, 120944-42-5; **18**, 120944-22-1; **18** base, 120944-54-9; **18a**, 120944-43-6; **19**, 120944-23-2; **19** base, 120944-55-0; **19a**, 120944-44-7; **20**, 120944-24-3; **20** base, 120944-56-1; **20a**, 120944-45-8; **21**, 52867-80-8; **21a**, 51037-58-2; **22**, 120944-25-4; **22** base, 120944-57-2; **22a**, 120944-46-9; **23**, 120944-26-5; **23** base, 120944-58-3; **23a**, 95217-36-0; **24**, 52868-12-9; **24a**, 51037-52-6; **25**, 120944-28-7; **25** base, 120944-27-6; **25a**, 95217-25-7; **26**, 52868-09-4; **26a**, 51037-54-8; **27**, 120944-29-8; **27** base, 120944-59-4; **27a**, 95217-26-8; **28**, 120944-30-1; **28** base, 120944-60-7; **28a**, 95217-27-9; **29**, 52868-08-3; **29a**, 51037-53-7; **30**, 120944-31-2; **30** base, 120944-61-8; **31**, 52867-94-4; **32**, 52867-95-5; **33**, 52867-99-9; **34**, 52867-97-7; **35**, 52867-96-6; **36**, 120944-32-3; **37**, 52868-03-8; **38**, 52868-05-0; **38** base, 120944-62-9; **39**, 120944-33-4; **39** base, 120944-63-0; **40**, 52985-68-9; **40** base, 120944-64-1; **41**, 52868-06-1; **41** base, 120944-65-2; $MeNH_2$, 74-89-5; $EtNH_2$, 75-04-7; n-$C_4H_9NH_2$, 109-73-9; $(C_2H_5)_2N(CH_2)_2NH_2$, 100-36-7; $C_6H_5CH_2NH_2$, 100-46-9; MeNCO, 624-83-9; EtNCO, 109-90-0; n-C_4H_9NCO, 111-36-4; C_6H_5NCO, 103-71-9; 4-(4-chlorophenyl)-2(3*H*)-oxazolone, 36404-33-8; phenylpiperazine, 92-54-6.

(26) Christensen, J. A.; Hernestam, S.; Lassen, J. B.; Sterner, N. *Acta Pharmacol. Toxicol.* **1965**, *23*, 109.
(27) Fields, J. Z.; Reisine, T. D.; Yamamura, H. I. *Brain Res.* **1977**, *136*, 578.

Linear and Proximal Benzo-Separated Alkylated Xanthines as Adenosine-Receptor Antagonists

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The linear and proximal benzo-separated derivatives of 8-phenyltheophylline, 1,3-diethyl-8-phenylxanthine, 1,3-dipropylxanthine, 1,3-dibutylxanthine, 3-isobutyl-1-methylxanthine, theophylline, caffeine, and isocaffeine have been synthesized and evaluated for affinity at the A_1 and A_2 adenosine receptors. Although structure–activity relationships in the benzo-separated series differed from the relationships in the simple xanthines, the most potent of the benzo-separated xanthines were about equal in affinity to the most potent of the corresponding xanthines. On the basis of the present results and the diverse structures reported in the literature as non-xanthine adenosine antagonists, it appears that the primary requirement for adenosine-receptor affinity in nonnucleosides is a flat, neutral, fused-ring heterocycle and that once this requirement is met there are numerous potential binding modes.

Membrane receptors sensitive to adenosine are receiving considerable attention[1-3] because of the role of adenosine in regulating a variety of physiological responses. Activation of these receptors by extracellular adenosine can cause inhibition or stimulation of the formation of intracellular adenosine 3′,5′-cyclic monophosphate from adenosine 5′-triphosphate by adenylate cyclase. The existence of two types of adenosine receptors has been proposed: an A_1 receptor, which mediates inhibition of adenylate cyclase, and an A_2 receptor, which stimulates the cyclase.[2] Antagonism of either the A_1 or A_2 receptor would permit the selective control of the effects caused by the binding of adenosine to that particular receptor. Included among the antagonists are various alkylated xanthines[4] (e.g., **1b**).

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(1) Williams, M. *Annu. Rev. Pharmacol. Toxicol.* **1987**, *27*, 315–345.
(2) Hamprecht, B.; van Calker, D. *Trends Pharmacol. Sci.* **1985**, *6*, 153–154.
(3) (a) Daly, J. W.; Bruns, R. F.; Snyder, S. H. *Life Sci.* **1981**, *28*, 2083–2097. (b) Schwabe, U. *Trends Pharmacol. Sci.* **1981**, *2*, 299–303. (c) Bruns, R. F.; Daly, J. W.; Snyder, S. H. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 2077–2080. (d) Stiles, G. L.; Daly, D. T.; Olsson, R. A. *J. Biol. Chem.* **1985**, *260*, 10806–10811. (e) Olsson, R. A.; Kusachi, S.; Thompson, R. D.; Ukena, D.; Padgett, W.; Daly, J. W. *J. Med. Chem.* **1986**, *29*, 1683–1689. (f) Bruns, R. F.; Lu, G. H.; Pugsley, T. A. *Mol. Pharmacol.* **1986**, *29*, 331–346.

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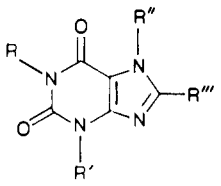
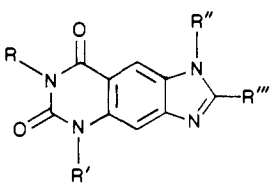
Except for the 8-cycloalkylxanthines,[3f,4g-i] these agents do not distinguish greatly between the A_1 and A_2 receptors. Thus, the search for xanthine-derived, selective adenosine-receptor antagonists continues.[4c-f] In this direction, the benzo-separated molecular modification[5-9] offers a means[8] for designing structurally novel xanthine antagonists. As a result of the broad range of antagonistic potencies of the alkylated xanthines **1a–g** toward the A_1 and



1



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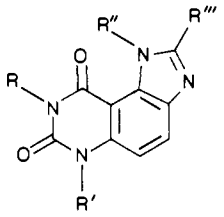


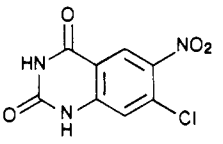
3

a: series, R = R′ = Me; R″ = H; R‴ = Ph
b: series, R = R′ = Et; R″ = H; R‴ = Ph
c: series, R = R′ = Pr; R″ = R‴ = H
d: series, R = R′ = nBu; R″ = R‴ = H
e: series, R = Me; R′ = iBu; R″ = R‴ = H
f: series, R = R′ = Me; R″ = R‴ = H (theophylline series)
g: series, R = R′ = R″ = Me; R‴ = H (caffeine series)

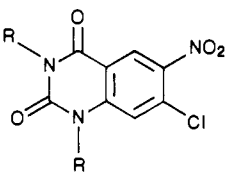
A_2 receptors,[2] the linear and proximal benzo-separated derivatives **2a–g** and **3a–g**, respectively, were chosen as target molecules. The synthesis and A_1 and A_2 receptor antagonism properties of **2a–g** and **3a–g** are described here.

Chemistry

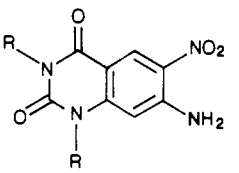
Linear Derivatives. For compounds **2a–d**, the quinazolinedione **4**[8a] was alkylated with 2 equiv of methyl, ethyl, *n*-propyl, and *n*-butyl iodide to afford the corresponding dialkyl derivatives **5a**,[8a] **5b**, **5c**, and **5d**, respectively. Amination of **5a–d** gave **6a**,[8a] **6b**, **6c**, and **6d**. The 8-phenyl compounds **2a** and **2b** were obtained by next



4



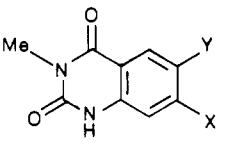
5a: R = Me
b: R = Et
c: R = nPr
d: R = nBu



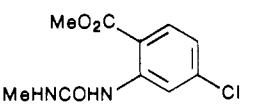
6a: R = Me
b: R = Et
c: R = nPr
d: R = nBu

subjecting **6a** and **6b** to catalytic hydrogenation in the presence of hydrochloric acid. The resultant products, which were assumed to be diamine hydrochlorides, were not fully characterized but were refluxed in pyridine containing 1 equiv of benzoyl chloride to give the desired **2a** and **2b**. Catalytic hydrogenation of **6c** and **6d** in formic acid yielded **2c** and **2d**, respectively.

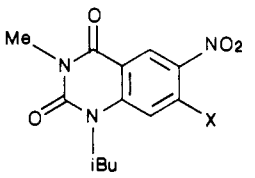
The route to **2e** began with the reaction of methyl 2-amino-4-chlorobenzoate[8a] with methyl isocyanate in toluene in the presence of triethylamine to afford **7a**[10] without



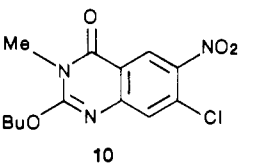
7a: X = Cl; Y = H
b: X = Cl; Y = NO_2



8



9a: X = Cl
b: X = NH_2



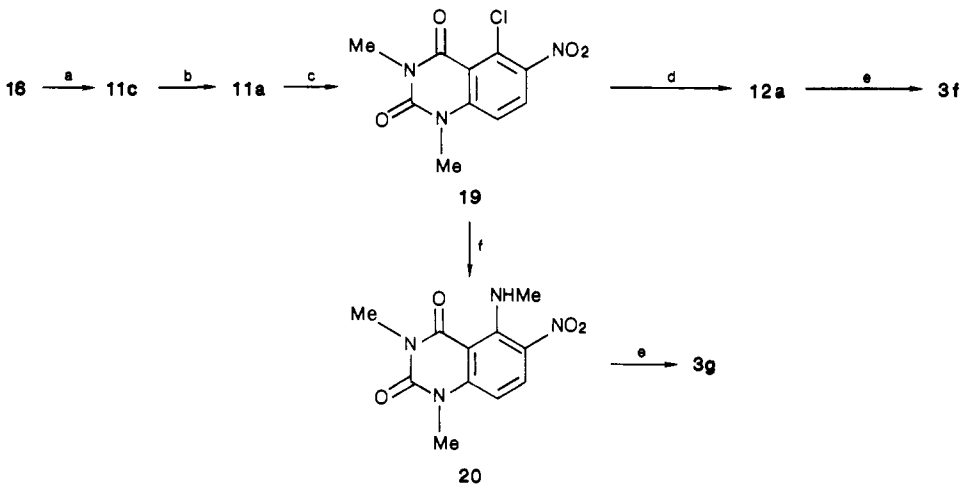
10

any appearance of the intermediate ureido ester **8**. Nitration of **7a** with 1 equiv of fuming nitric acid in cold, concentrated sulfuric acid produced **7b**.[10] Subsequent alkylation of **7b** with 1-iodo-2-methylpropane formed **9a** and **10**.[11,12] These two products were separated by column chromatography and distinguished by ^{13}C NMR wherein the isobutyl methylene carbon of **10** displayed a higher field absorption[13] compared to that of the same carbon bound to the nitrogen in **9a**. Amination of **9a** gave **9b**, which, upon catalytic hydrogenation in formic acid, was transformed into **2e**.

The *lin*-benzotheophylline (**2f**) and *lin*-benzocaffeine (**2g**) derivatives were available for this study by employing

(4) (a) Bruns, R. F. *Biochem. Pharmacol.* **1981**, *30*, 325–333. (b) Hamilton, H. W.; Ortwine, D. F.; Worth, D. F.; Badger, E. W.; Bristol, J. A.; Bruns, R. F.; Haleen, S. J.; Steffen, R. P. *J. Med. Chem.* **1985**, *28*, 1071–1079. (c) Burnstock, G.; Hoyle, C. H. V. *Brit. J. Pharmacol.* **1985**, *85*, 291–296. (d) Jacobson, K. A.; Ukena, D.; Kirk, K. L.; Daly, J. W. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4089–4093. (e) Daly, J. W.; Padgett, W. L.; Shamim, M. T. *J. Med. Chem.* **1986**, *29*, 1305–1308. (f) Daly, J. W.; Padgett, W. L.; Shamim, M. T. *J. Med. Chem.* **1986**, *29*, 1520–1524. (g) Bruns, R. F.; Fergus, J. H.; Badger, E. W.; Bristol, J. A.; Santay, L. A.; Hartman, J. D.; Hays, S. J.; Huang, C. C. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1987**, *335*, 59. (h) Martinson, E. A.; Johnson, R. A.; Wells, J. N. *Mol. Pharmacol.* **1987**, *31*, 247. (i) Ukena, D.; Jacobson, K. A.; Padgett, W. L.; Ayala, C.; Shamim, M. T.; Kirk, K. L.; Olsson, R. A.; Daly, J. W. *FEBS Lett.* **1986a**, *209*, 122.
(5) See: Leonard, N. J. *Acc. Chem. Res.* **1982**, *15*, 128–135 and references cited therein.
(6) Schneller, S. W.; Christ, W. J. *J. Heterocycl. Chem. Suppl.* **1982**, *19*, S-139–S-161.
(7) Lichtenthaler, F. W.; Moser, A. *Tetrahedron Lett.* **1981**, *22*, 4397–4400 and references cited therein.
(8) (a) Schneller, S. W.; Christ, W. J. *J. Org. Chem.* **1981**, *46*, 1699–1702. (b) Schneller, S. W.; Ibay, A. C.; Martinson, E. C.; Wells, J. N. *J. Med. Chem.* **1986**, *29*, 972–978.
(9) Schneller, S. W.; Christ, W. J. *J. Heterocycl. Chem.* **1981**, *18*, 653–654.
(10) Schneller, S. W.; Ibay, A. C.; Christ, W. J. *J. Heterocycl. Chem.* **1984**, *21*, 791–795.
(11) It should be noted that none of the other alkylations of quinazolinediones described herein resulted in O-alkylated products similar to **10**.[12]
(12) The amount of **10** obtained can be reduced considerably, but not eliminated, if the stoichiometry of 1-iodo-2-methylpropane is carefully controlled to insure that only 1 equiv is used.
(13) G. E. Martin, University of Houston, personal communication.

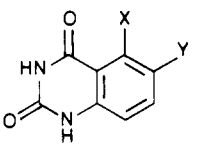
Scheme I. Synthesis of **3b** and **3g**[a]



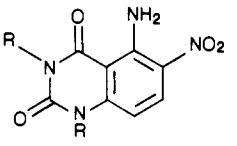
[a] Reaction conditions: (a) urea, 190 °C; (b) fuming HNO_3/concentrated H_2SO_4; (c) Et_4NOH/Me_2SO_4; (d) NH_3 in 1-BuOH at 125 °C; (e) H_2/10% Pd–C, HCO_2H; (f) $MeNH_2$ in 1-BuOH at 140 °C.

previously reported procedures.[8a]

Proximal Derivatives. Similar to the linear series, synthesis of the proximal derivatives **3a–d** began with **11a**,[9]



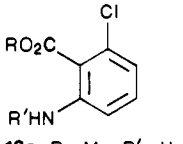
11a: X = Cl, Y = NO_2
b: X = NH_2, Y = NO_2
c: X = Cl, Y = H



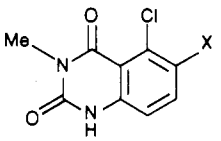
12a: R = Me
b: R = Et
c: R = nPr
d: R = nBu

an isomer of **4**. However, in this case, increased yields occurred if amination to **11b**[9] preceded alkylation. Dialkylation of **11b** with methyl, ethyl, *n*-propyl, and *n*-butyl iodide formed **12a–d**, respectively. These four products were converted into the desired **3a–d** in the same manner as described earlier for realizing **2a–d** from **6a–d**.

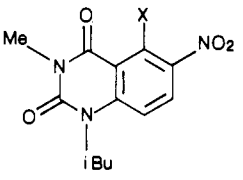
The preparation of **3e** was patterned after the route to its linear isomer (**2e**) and, therefore, required 2-amino-6-chlorobenzoic acid as the starting material for esterification to **13a**. However, the desired benzoic acid could not be



13a: R = Me; R' = H
b: R = H; R' = Ac
c: R = Me; R' = Ac



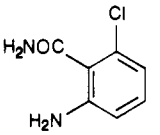
14a: X = H
b: X = NO_2



15a: X = Cl
b: X = NH_2

prepared by the reported method of Piper and Stevens.[14] In an attempt to overcome this difficulty, 2-methyl-3-chloroaniline was acetylated and, without purification, subsequently oxidized to **13b**. Treatment of **13b** with hydrogen chloride saturated methanol with the intention of obtaining **13c** (or **13a**) gave, instead, 3-chloroaniline via apparent decarboxylation of the resultant 2-amino-6-chlorobenzoic acid. Compound **13c** was obtained, however, upon reaction of **13b** with diazomethane. Subsequent refluxing of **13c** in hydrogen chloride saturated methanol then formed **13a**. Without purification, **13a** was treated with methyl isocyanate to produce the dione **14a**. Product **3e** was then obtained by employing the same sequence of reactions that led to **2e** (i.e., nitration to **14b**), isobutylation (to **15a** with no accompanying O-alkylation),[11] amination (to **15b**), and finally, reduction (ring closure in formic acid).

An alternative route to **14a** was considered by reacting **16**[15] with methyl isocyanate. Ring closure was effected; however, the product was **11c**[9] rather than **14a** due to the preferential loss of methylamine (instead of ammonia) upon cyclization.



16

The preparation of the *prox*-benzotheophylline (**3f**) and *prox*-benzocaffeine (**3g**) derivatives have been described in a previous paper.[9] For the purposes of literature documentation, however, the synthetic details leading to **3f** and **3g** (Scheme I) are presented in the Experimental Section.

Biological Results and Discussion

Certain benzo-separated xanthines are potent inhibitors of the binding of [^{3}H]-N^6-cyclohexyladenosine to the A_1 adenosine receptor in rat brain membranes (Table I). The most potent inhibitor (namely, the linear benzo-separated derivative of 1,3-dipropylxanthine (**2c**)) had a K_i of 123 nM at the A_1 receptor, about the same as the potent adenosine antagonist 8-phenyltheophylline (**1a**) (K_i = 86 nM). In view of the fluorescent properties of the benzo-separated purines,[5] this affinity of **2c** for the A_1 receptor suggests that the benzo-separated xanthines may be useful as fluorescent probes of the A_1 receptor. On the other hand, the potential of benzo-separated xanthines as in vivo adenosine-receptor antagonists may be limited by their low solubility in water, a property reminiscent of other potent xanthine antagonists.

Beginning with the 1,3-dimethyl compounds, it is meaningful to compare the structure–activity relationships (SAR) for the xanthines at the A_1 receptor with the SAR for the two benzo-separated series. *lin*-Benzotheophylline (**2f**) was about one-third as potent as theophylline (**1f**), while *prox*-benzotheophylline (**3f**) was about one-half as potent as theophylline (**1f**). The addition of a 7-methyl

(14) Piper, J. R.; Stevens, F. J. *J. Org. Chem.* **1962**, *27*, 3134–3137.

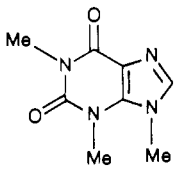
(15) Koopman, H. *Recl. Trav. Chim Pays-Bas* **1961**, *80*, 1075–1083.

Table I. Affinities of Benzo-Separated Xanthines for the Adenosine A_1 and A_2 Receptors

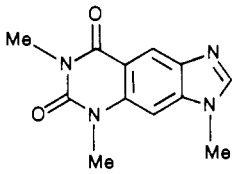
	K_i,[a] nm											
	xanthine				linear derivative				proximal derivative			
	A_1	A_2	A_2/A_1		A_1	A_2	A_2/A_1		A_1	A_2	A_2/A_1	
1,3-dimethyl-8-phenyl	86	850	9.8	(1a)	>100000[b]	>100000		(2a)	450	10400	23	(3a)
1,3-diethyl-8-phenyl	44	860	19.4	(1b)	>100000	>100000		(2b)	>100000	58000		(3b)
1,3-dipropyl	450	5200	11.5	(1c)	123	1320	10.7	(2c)	296	790	2.7	(3c)
1,3-dibutyl					179	670	3.7	(2d)	174	1960	11.2	(3d)
3-isobutyl-1-methyl	2500	13800	5.6	(1e)	620	2400	3.9	(2e)	860	1970	2.3	(3e)
1,3-dimethyl	8500	25000	3.0	(1f)	24000	85000	3.6	(2f)	13400	17900	1.34	(3f)
1,3,7-trimethyl	29000	48000	1.65	(1g)	11600	23000	1.99	(2g)	10300	12700	1.23	(3g)
1,3,9-trimethyl	>1000000			(17)	15200	58000	3.8	(18)				

[a] A_1 affinities were determined in [^{3}H]-N^6-cyclohexyladenosine binding to rat brain membranes and A_2 affinities were determined in [^{3}H]NECA binding to rat striatal membranes.[3f] Affinities of all xanthines except 17 are from reference 3f. All values are means of two or more independent experiments. Average standard errors of K_i values were 13.5% for A_1 binding and 5.3% for A_2 binding. Hill coefficients were not significantly different from 1.0. [b] Inactive up to the limit of solubility.

group (i.e., caffeine, **1g**) resulted in a 4-fold loss of affinity in the xanthine series, but produced an increase in affinity in both of the benzo-extended systems (compare **2g** and **3g** with **2f** and **3f**, respectively). An even more striking divergence is evident with the addition of a 9-methyl group to theophylline (to give isocaffeine, **17**),[8a] which resulted



17



18

in a more than 100-fold loss of affinity (compared to **1f**), while the same modification when applied to *lin*-benzotheophylline (to give **18**) resulted in a small increase in affinity (i.e., compare **18** to **2f**). Replacement of the 3-methyl group in the **f** series with an isobutyl substituent also had markedly different effects in the three series: a 2-fold increase in the xanthine series (**1e**), a 40-fold increase in the *lin*-benzoxanthine series (**2e**), and a 16-fold increase in the *prox*-benzoxanthine series (**3e**).

An 8-phenyl substituent greatly enhanced affinity in the xanthine (compare **1a** with **1f**) and *prox*-benzoxanthine (compare **3a** and **3f**) series but resulted in a potentially inactive compound in the *lin*-benzoxanthine series (compare **2a** with **2f**). The results for **2a** as well as for both benzo-separated derivatives of 1,3-diethyl-8-phenylxanthine (**2b** and **3b**) must, however, be interpreted with caution due to the very poor solubility of these compounds in the test system.

In general, the SAR for the benzo-separated xanthines show little correlation to the xanthine SAR. This suggests that the benzo-separated xanthines bind in a different geometrical orientation to the A_1 receptor than the xanthines themselves. These results are not surprising in light of the previous observation that the xanthine, adenine, and alloxazine families bind to adenosine receptors in different modes.[4a] Other nonnucleosides that bind to adenosine receptors include pyrazolo[3,4-*b*]pyridines,[16-18] β-carbolines,[18] triazolo[4,3-*b*]pyridazines,[18] pyrazolo[4,3-*c*]-quinolin-3-ones,[19] carbamazepine,[20,21] pyrazolo[3,4-*d*]pyrimidines,[22,23] and pyrazolo[4,3-*d*]pyrimidines.[24] A large SAR study encompassing many of these series has been published.[25] This diversity of structures suggests that the primary structural requirement for A_1-receptor affinity in nonnucleosides is a flat, neutral, fused-ring heterocycle and that, once this requirement is met, there are numerous potential binding modes. In contrast, there appears to be only one binding mode for nucleosides.[26]

The SAR for benzo-extended xanthines at the A_2 receptor was generally very similar to the SAR at the A_1 receptor. The A_1 selectivities of the *lin*-benzoxanthines ranged from 2-fold to 10-fold, and the selectivities of the *prox*-benzoxanthines ranged from 1.2-fold to 23-fold.

Experimental Section

General Methods. All melting points were obtained on a Thomas-Hoover or a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman AccuLab 3 spectrophotometer. The ^{1}H NMR spectra were determined at 60 MHz with a Varian EM-360 spectrometer and are reported in parts per million downfield from Me_4Si as an internal standard. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), m (multiplet), and br (broad). The ^{13}C NMR spectrum for compound **10** was obtained on a JEOL FX90Q. The silica gel used for the column chromatographic separation was Baker 60–200 mesh. The dry DMF was obtained by distillation from CaO and then stored over 4A molecular sieves. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ, and are represented by symbols of the elements, which indicates that the analytical results obtained for those elements were within ±0.4% of the theoretical values.

Preparation of 5b–d and 12b–d via Dialkylation of 7-Chloro-6-nitro-2,4(1*H*,3*H*)-quinazolinedione (4) and 5-Amino-6-nitro-2,4(1*H*,3*H*)-quinazolinedione (11b). General Procedure. For every gram of quinazolinedione **4**[8a] or **11b** to be alkylated, 20 mL of dry DMF was used. To a stirred mixture of the quinazolinedione and 2 equiv of anhydrous K_2CO_3 in dry DMF was added 2 equiv of iodoethane, 1-iodopropane, or 1-iodobutane. The mixture was warmed to 60 °C and stirred for 6 h at this temperature. After removal of the insoluble salts by filtration, a volume of H_2O, which was 3 times that of the DMF used, was added to the filtrate. The resulting precipitate was

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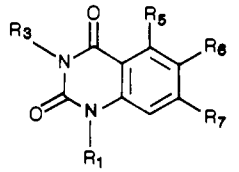
Table II. Data for Substituted Quinazoline-2,4(1*H*,3*H*)-diones



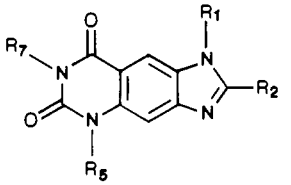
compd	R_1	R_3	R_5	R_6	R_7	mp, °C	solvent[a]	% yield[b]	formula[c]	^{1}H NMR,[d] δ (relative to Me_4Si)
5a	Me	Me	H	NO_2	Cl	*g*				
5b	Et	Et	H	NO_2	Cl	140–141	C	84[e]	$C_{12}H_{12}ClN_3O_4$	(Me_2SO-d_6) 1.02–1.3 (t over t, 6 H, Me), 3.73–4.3 (q over q, 4 H, NCH_2), 7.82 (s, 1 H, H-8), 8.58 (s, 1 H, H-5)
5c	Pr	Pr	H	NO_2	Cl	93–94	A	57	$C_{14}H_{16}ClN_3O_4$	($CDCl_3$) 1.0–1.2 (t over t, 6 H, Me), 1.56–2.0 (m over m, 4 H, CH_2), 3.98–4.26 (t over t, 4 H, NCH_2), 7.3 (s, 1 H, H-8), 8.86 (s, 1 H, H-5)
5d	Bu	Bu	H	NO_2	Cl	118–119	E	89[e]	$C_{16}H_{20}ClN_3O_4$	(Me_2SO-d_6) 0.72–1.06 (t over t, 6 H, Me), 1.06–1.82 (m over m, 8 H, CH_2CH_2), 3.8–4.22 (t over t, 4 H, NCH_2), 7.8 (s, 1 H, H-8), 8.58 (s, 1 H, H-5)
6a	Me	Me	H	NO_2	NH_2	*g*				
6b	Et	Et	H	NO_2	NH_2	201–204	E	91[e]	$C_{12}H_{14}N_4O_4$	(Me_2SO-d_6) 1.02–1.32 (t over t, 6 H, Me), 3.75–4.2 (q over q, 4 H, NCH_2), 6.78 (s, 1 H, H-8), 7.76 (br s, 2 H, NH_2), 8.59 (s, 1 H, H-5)
6c	Pr	Pr	H	NO_2	NH_2	155–157	A	71	$C_{14}H_{18}N_4O_4$	($CDCl_3$) 0.8–1.12 (t over t, 6 H, Me), 1.5–1.8 (m over m, 4 H, CH_2), 3.82–4.11 (t over t, 4 H, NCH_2), 6.39 (s, 1 H, H-8), 6.6 (br s, 2 H, NH_2), 9.0 (s, 1 H, H-5)
6d	Bu	Bu	H	NO_2	NH_2	158–159	E	95[e]	$C_{16}H_{22}N_4O_4$	($CDCl_3$) 0.72–1.13 (t over t, 6 H, Me), 1.13–1.82 (m over m, 8 H, CH_2CH_2), 3.86–4.11 (t over t, 4 H, NCH_2), 6.45 (s, 1 H, H-8), 6.66 (br s, 2 H, NH_2), 8.9 (s, 1 H, H-5)
9a	*i*Bu	Me	H	NO_2	Cl	156–157	E	57	$C_{13}H_{14}ClN_3O_4$	(Me_2SO-d_6) 0.93 (d, J = 6 Hz, 6 H, Me), 2.04 (m, 1 H, CH), 3.32 (s, 3 H, NMe), 4.02 (d, J = 6 Hz, 2 H, NCH_2), 7.88 (s, 1 H, H-8), 8.6 (s, 1 H, H-5)
9b	*i*Bu	Me	H	NO_2	NH_2	226–228	E	85	$C_{13}H_{16}N_4O_4$	(Me_2SO-d_6) 0.92 (d, J = 6 Hz, 6 H, Me), 2.05 (m, 1 H, CH), 3.26 (s, 3 H, NMe), 3.75 (d, J = 6 Hz, 2 H, NCH_2), 6.68 (s, 1 H, H-8), 7.75 (br s, 2 H, NH_2), 8.56 (s, 1 H, H-5)
11a	H	H	Cl	NO_2	H	>340 dec	B	97	$C_8H_4ClN_3O_4 \cdot Me_2SO$	(Me_2SO-d_6) 7.25 (d, 1 H, J = 4 Hz, H-8), 8.15 (d, 1 H, J = 4 Hz, H-7), 11.65 (br s, 1 H, NH), 11.75 (br s, 1 H, NH)
11b	H	H	NH_2	NO_2	H	>340 dec	B	84	$C_8H_6N_4O_4$	(Me_2SO-d_6) 6.35 (d, 1 H, J = 5 Hz, H-8), 8.25 (d, 1 H, J = 5 Hz, H-7), 8.6 (br s, 1 H, NH), 9.8 (br s, 1 H, NH), 10.7 (br s, 2 H, NH_2)
11c	H	H	Cl	H	H	375–376	B	78	$C_8H_5ClN_2O_2 \cdot Me_2SO$	(Me_2SO-d_6) 7.0–7.8 (m, 3 H, aromatic H), 11.2 (br s, 2 H, NH)
12a	Me	Me	NH_2	NO_2	H	261–263	D	91	$C_{10}H_{10}N_4O_4$	(Me_2SO-d_6 at 128 °C) 3.2 (s, 3 H, N-1 Me), 3.5 (s, 3 H, N-3 Me), 5.8–6.9 (br s, 2 H, NH_2), 6.6 (d, 1 H, J = 5 Hz, H-8), 8.15 (d, 1 H, J = 5 Hz, H-7)
12b	Et	Et	NH_2	NO_2	H	128–130	E	52	$C_{12}H_{14}N_4O_4$	(Me_2SO-d_6) 1.09–1.29 (t over t, 6 H, Me), 3.84–4.23 (q over q, 4 H, NCH_2), 6.71 (d, J = 8 Hz, 1 H, H-8), 8.33 (d, J = 8 Hz, 1 H, H-7), 8.69 (br s, 1 H, NH), 9.85 (br s, 1 H, NH)
12c	Pr	Pr	NH_2	NO_2	H	133–135	A	40	$C_{14}H_{18}N_4O_4$	($CDCl_3$) 0.8–1.1 (t over t, 6 H, Me), 1.4–1.85 (m over m, 4 H, CH_2), 3.8–4.15 (t over t, 4 H, NCH_2), 6.4 (d, J = 8 Hz, 1 H, H-8), 8.35 (d, J = 8 Hz, 1 H, H-7), 8.6 (br s, 1 H, NH), 10.1 (br s, 1 H, NH)
12d	Bu	Bu	NH_2	NO_2	H	84–85	E	81	$C_{16}H_{22}N_4O_4$	(Me_2SO-d_6) 0.9–1.2 (t over t, 6 H, Me), 1.3–1.7 (m, 8 H, CH_2CH_2), 3.78–4.2 (t over t, 4 H, NCH_2), 6.64 (d, J = 8 Hz, 1 H, H-8) 8.3 (d, J = 8 Hz, 1 H, H-7), 8.7 (br s, 1 H, NH), 9.92 (br s, 1 H, NH)
14a	H	Me	Cl	H	H	>300[f]	F	61[e]	$C_9H_7ClN_2O_2$	(Me_2SO-d_6) 3.22 (s, 3 H, Me), 7.0–7.18 (d over t, 2 H, H-7 and H-8), 7.42 (d, J = 8 Hz, 1 H, H-6), 11.42 (br s, 1 H, NH)
14b	H	Me	Cl	NO_2	H	320–322	F	84[e]	$C_9H_6ClN_3O_4$	(Me_2SO-d_6) 3.22 (s, 3 H, NMe), 7.18 (d, J = 8 Hz, 1 H, H-8), 8.09 (d, J = 8 Hz, 1 H, H-7), 11.8 (br s, 1 H, NH)
15a	*i*Bu	Me	Cl	NO_2	H	145–146	A	85	$C_{13}H_{14}ClN_3O_4$	($CDCl_3$) 1.02 (d, J = 6 Hz, 6 H, Me), 2.18 (m, 1 H, CH), 3.46 (s, 3 H, NMe), 4.02 (d, J = 6 Hz, 2 H, NCH_2), 7.16 (d, J = 8 Hz, 1 H, H-8), 7.9 (d, J = 8 Hz, 1 H, H-7)
15b	*i*Bu	Me	NH_2	NO_2	H	184–185	E	quant.	$C_{13}H_{16}N_4O_4$	(Me_2SO-d_6) 0.89 (d, J = 6 Hz, 6 H, Me), 2.04 (m, 1 H, CH), 3.25 (s, 3 H, NMe), 3.91 (d, J = 6 Hz, 2 H, NCH_2), 6.65 (d, J = 8 Hz, 1 H, H-8), 8.3 (d, J = 8 Hz, 1 H, H-7), 8.68 (br s, 1 H, NH), 9.93 (br s, 1 H, NH)
19	Me	Me	Cl	NO_2	H	162–163	B	67	$C_{10}H_8ClN_3O_4$	(Me_2SO-d_6 at 128 °C) 3.2 (s, 3 H, N-1 Me), 3.55 (s, 3 H, N-3 Me), 7.45 (d, 1 H, J = 5 Hz, H-8), 8.15 (d, 1 H, J = 5 Hz, H-7)
20	Me	Me	NHMe	NO_2	H	203–205	B	89	$C_{11}H_{12}N_4O_4$	(Me_2SO-d_6 at 108 °C) 2.6 (d, 3 H, J = 3 Hz, NHMe), 3.15 (s, 3 H, N-1 Me), 3.35 (s, 3 H, N-3 Me), 6.3 (d, 1 H, J = 5 Hz, H-8), 7.65 (d, 1 H, J = 5 Hz, H-7), 9.5 (br s, 1 H, NH)

[a] Recrystallization solvent: A, aqueous EtOH; B, aqueous Me_2SO; C, AcOEt; D, Me_2SO; E, EtOH; F, aqueous DMF. All compounds were obtained as either white or light yellow crystals. [b] Yields are not optimized. [c] All compounds in this table gave satisfactory microanalysis for C, H, and N (±0.4%). [d] Spin multiplicities are given by the abbreviations s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. [e] Unrecrystallized yield. [f] Partial sublimation and decomposition. [g] See ref 8a.

isolated by filtration and purified and characterized as **5b–5d** and **12b–12d** (Table II). The preparation of **12a** from **19** can be found elsewhere in this section.

Preparation of 6b–d, 9b, 11b, and 15b via Amination of the 2,4(1*H*,3*H*)-Quinazolinediones 5b–5d, 9a, 11a, and 15a. General Method. For every gram of quinazolinedione (**5b–d**,

Table III. Data for *lin*-Benzoxanthines



compd	R_1	R_2	R_5	R_7	mp, °C	solvent[a]	% yield[b]	formula[c]	^{1}H NMR,[d] δ (relative to Me_4Si)
2a	H	Ph	Me	Me	300–303	F	78[e]	$C_{17}H_{14}N_4O_2 \cdot H_2O$	(Me_2SO-d_6) 3.22 (s, 3 H, Me), 3.4 (s, 3 H, Me), 6.53 (s, 1 H, H-4), 7.51 (m, 3 H, ArH), 7.74 (s, 1 H, H-9), 7.92 (m, 2 H, ArH), 9.61 (br s, 1 H, NH)
2b	H	Ph	Et	Et	255–257	F	37	$C_{19}H_{18}N_4O_2 \cdot {}^3/_2H_2O$	(Me_2SO-d_6) 1.16 (t over t, 6 H, Me), 3.45 (q over q, 4 H, CH_2), 6.6 (s, 1 H, H-4), 7.52 (m, 3 H, ArH), 7.77 (s, 1 H, H-9), 7.92 (m, 2 H, ArH), 9.62 (br s, 1 H, NH)
2c	H	H	Pr	Pr	238–240	A	48	$C_{15}H_{18}N_4O_2$	(Me_2SO-d_6) 0.75–1.1 (t over t, 6 H, Me), 1.42–1.88 (m over m, 4 H, CH_2), 3.8–4.22 (t over t, 4 H, NCH_2), 7.53 (s, 1 H, H-4), 8.3 (s, 1 H, H-9), 8.45 (s, 1 H, H-2), 12.7 (br s, 1 H, NH)
2d	H	H	Bu	Bu	223–225	A	91[e]	$C_{17}H_{22}N_4O_2$	(Me_2SO-d_6) 0.7–1.02 (t over t, 6 H, Me), 1.2–1.65 (m over m, 8 H, CH_2CH_2), 3.8–4.2 (t over t, 4 H, NCH_2), 7.41 (s, 1 H, H-4), 8.21 (s, 1 H, H-9), 8.34 (s, 1 H, H-2), 11.0 (br s, 1 H, NH)
2e	H	H	*i*Bu	Me	265–268	E	86	$C_{14}H_{16}N_4O_2$	(Me_2SO-d_6) 0.95 (d, J = 6 Hz, 6 H, Me), 2.1 (m, 1 H, CH), 3.32 (s, 3 H, NMe), 4.02 (d, J = 6 Hz, 2 H, NCH_2), 7.48 (s, 1 H, H-4), 8.25 (s, 1 H, H-9), 8.38 (s, 1 H, H-2)
2f	H	H	Me	Me	*f*				
2g	Me	H	Me	Me	*f*				

[a] Recrystallization solvent: F, aqueous DMF; A, aqueous EtOH; E, EtOH. All compounds were obtained as either white or light yellow crystals. [b] Yields are not optimized. [c] All compounds in this table gave satisfactory microanalysis for C, H, and N (±0.4%). [d] Spin multiplicities are given by the abbreviations s, singlet; d, doublet; t, triplet, q, quartet; m, multiplet; br, broad. [e] Unrecrystallized yield. [f] See ref 8a.

9a, **11a**, or **15a**) to be aminated, 10 mL of absolute 1-BuOH (for **5b**, **9a**, and **11a**) or absolute EtOH (for **5c**, **5d**, and **15a**) was used. To the appropriate volume of alcohol, which had been saturated at room temperature with anhydrous NH_3, was added the quinazolinedione, and this mixture was heated at 120–130 °C in a sealed, stainless steel reaction vessel for 24 h. After the solution cooled, the precipitated, yellow product was isolated by filtration and dried to give **6b–d**, **9b**, **11b**, and **15b** as described in Table II.

Preparation of Benzo-Separated Xanthines 2c–e and 3c–g. General Method. A mixture of 1 g of the appropriate quinazolinedione (**6c**, **6d**, **9b**, **12c**, **12d**, **15b**, **12a**, or **20**) in 25 mL of 97% formic acid containing a catalytic amount of 10% Pd–C was shaken for 4 h under 52 psi of H_2. Following this, the catalyst was removed by filtration and the filtrate was refluxed for 2 h under N_2. The formic acid was then evaporated in vacuo and a volume of toluene equal to the original volume of formic acid was added. The volume of this new mixture was reduced in vacuo to form a residue, which yielded a product, after trituration with petroleum ether (60–100 °C), that was isolated by filtration to give **2c**, **2d**, **2e**, **3c**, **3d**, **3e**, **3f**, or **3g** as shown in Tables III and IV.

Preparation of Benzo-Separated 8-Phenylxanthines 2a, 2b, 3a, and 3b. General Method. A mixture of 1 g of the appropriate quinazolinedione (**6a**, **6b**, **12a**, or **12b**), 50 mL of absolute EtOH, 1 mL of concentrated HCl, and a catalytic amount of 10% Pd–C was shaken under 52 psi of H_2 for 12 h. The suspension of hydrochloride salts and catalyst was isolated by filtration and added to a stirred mixture containing 1 equiv of benzoyl chloride in 50 mL of dry pyridine. This mixture, still with catalyst, was refluxed for 1 h and then separated from the catalyst by filtration. The filtrate was evaporated to dryness in vacuo to give **2a**, **2b**, **3a**, or **3b** (Tables III and IV).

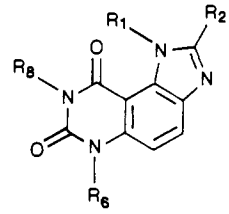
7-Chloro-3-methyl-1-(2-methylpropyl)-6-nitro-2,4-(1*H*,3*H*)-quinazolinedione (9a). A mixture of 5 g (19.6 mmol) of **7b**,[10] 2.71 g (19.6 mmol) of anhydrous K_2CO_3, 100 mL of dry DMF, and 3.8 g (20.6 mmol) of 1-iodo-2-methylpropane was heated at 60 °C with stirring for 20 h under the exclusion of moisture. This mixture was allowed to cool to room temperature and was filtered and 100 mL of H_2O was added to the filtrate. The resulting precipitate was isolated by filtration, dried, and subjected to column chromatography (toluene–AcOEt, 9:1). The first major fraction (0.4 g) yielded light yellow flakes of **10** whereas the second fraction gave the desired **9a** (3.5 g) as light yellow plates (Table II).

Structural assignment of the isomers was accomplished by comparing the ^{13}C NMR spectra of the two products. The O-alkyl carbon of **10** gave an absorption at 74.92 ppm whereas the *N*-alkyl carbon of **9a** appeared at 50 ppm. The ^{1}H NMR spectra were identical and of little use in distinguishing the products. Compound **10** was recrystallized from EtOH as light yellow plates, mp 138–139 °C. Anal. ($C_{13}H_{14}ClN_3O_4$) C, H, N.

5-Chloro-3-methyl-2,4(1*H*,3*H*)-quinazolinedione (14a). A solution of 70.8 g (0.5 mol) of 3-chloro-2-methylaniline in 70 mL of glacial AcOH was gradually treated, with stirring, with 52 g (0.51 mol) of acetic anhydride. The resulting solution was refluxed for 30 min and then poured into 500 mL of H_2O. The precipitated acetyl derivative was suspended, with stirring, in 2 L of 0.25 M $MgSO_4$ solution and heated to 85–90 °C. A total of 240 g (1.52 mol) of solid $KMnO_4$ was gradually added to the vigorously stirred mixture over 1.5 h with periodic heating so that the temperature was maintained at 85–90 °C. The mixture was stirred 1.5 h longer at 85–90 °C. The excess $KMnO_4$ was then destroyed by the dropwise addition of saturated sodium bisulfite solution. The mixture was filtered and the thick cake of MnO_2 was thoroughly stirred in 1 L of hot H_2O. This mixture was filtered and the extraction process was repeated several times. Acidification (20% H_2SO_4) of the combined filtrates produced a precipitate, which was isolated by filtration, washed with water, and dried to afford 74.6 g (0.419 mol, 84%) of **13b**, which was of sufficient purity to use in the next step: mp 212–215 °C; ^{1}H NMR ($CDCl_3$) δ 2.0 (s, 3 H, Me), 7.21–7.5 (m, 3 H, aromatic), 9.58 (br s, 1 H, COOH).

To compound **13b** (10 g, 56.1 mmol) in 200 mL of anhydrous Et_2O was added an ethereal solution of diazomethane[8a] until all of the **13b** had dissolved and a light yellow color persisted. The solution was stirred for 30 min longer and then glacial AcOH was added, dropwise, until the evolution of gas ceased. The mixture was treated with charcoal, filtered, evaporated to dryness with a rotary evaporator and the residue was recrystallized from benzene–petroleum ether (60–110 °C) to give 9.52 g (41.8 mmol, 74%) of **13c** as white crystals: mp 91–92 °C; ^{1}H NMR ($CDCl_3$) δ 2.2 (s, 3 H, Me), 4.05 (s, 3 H, Me), 7.05–7.4 (m, 2 H, aromatic), 8.2 (d of d, 1 H, aromatic). These crystals were used directly in the next step.

Table IV. Data for *prox*-Benzoxanthines



compd	R_1	R_2	R_6	R_8	mp, °C	solvent[a]	% yield[b]	formula[c]	^{1}H NMR,[d] δ (relative to Me_4Si)
3a	H	Ph	Me	Me	229–232	F	57[e]	$C_{17}H_{14}N_4O_2$	(Me_2SO-d_6) 3.3 (s, 3 H, Me), 3.48 (s, 3 H, Me) 7.09 (d, J = 8 Hz, 1 H, H-5), 7.48 (m, 3 H, ArH), 7.88 (d, J = 8 Hz, 1 H, H-4), 8.23 (m, 2 H, ArH), 12.4 (br s, 1 H, NH)
3b	H	Ph	Et	Et	225–226	F	44	$C_{19}H_{18}N_4O_2 \cdot H_2O$	(Me_2SO-d_6) 1.16 (t over t, 6 H, Me), 3.98 (q over q, 4 H, CH_2), 6.5 (d, J = 8 Hz, 1 H, H-5), 7.24 (d, J = 8 Hz, 1 H, H-4), 7.49 (m, 3 H, ArH), 8.0 (m, 2 H, ArH), 9.65 (br s, 1 H, NH)
3c	H	H	Pr	Pr	220–222	A	70	$C_{15}H_{18}N_4O_2$	(Me_2SO-d_6) 0.8–1.1 (t over t, 6 H, Me), 1.45–1.9 (m over m, 4 H, CH_2), 3.88–4.25 (t over t, 4 H, NCH_2), 7.3 (d, J = 8 Hz, 1 H, H-5), 8.1 (d, J = 8 Hz, 1 H, H-4), 8.25 (s, 1 H, H-2), 12.8 (br s, 1 H, NH)
3d	H	H	Bu	Bu	210–212	A	76	$C_{17}H_{22}N_4O_2$	(Me_2SO-d_6) 0.8–1.0 (t over t, 6 H, Me), 1.2–1.82 (m, 8 H, CH_2CH_2), 3.82–4.2 (t over t, 4 H, NCH_2), 7.2 (d, J = 8 Hz, 1 H, H-5), 7.98 (d, J = 8 Hz, 1 H, H-4), 8.1 (s, 1 H, H-2)
3e	H	H	*i*Bu	Me	298–301	F[f]	85	$C_{14}H_{16}N_4O_2$	(Me_2SO-d_6) 0.9 (d, J = 6 Hz, 6 H, Me), 2.16 (m, 1 H, CH), 3.32 (s, 3 H, Me), 4.02 (d, J = 6 Hz, 2 H, NCH_2), 7.25 (d, J = 8 Hz, 1 H, H-5), 8.0 (d, J = 8 Hz, 1 H, H-4), 8.18 (s, 1 H, H-2)
3f	H	H	Me	Me	>318[g]	D	98	$C_{11}H_{10}N_4O_2$	(Me_2SO-d_6) 3.35 (s, 3 H, N-6 Me), 3.65 (s, 3 H, N-8 Me), 7.2 (d, 1 H, J = 5 Hz, H-5), 8.1 (d, 1 H, J = 5 Hz, H-4), 8.15 (s, 1 H, H-2)
3g	Me	H	Me	Me	236–238	D	70	$C_{12}H_{12}N_4O_2$	(Me_2SO-d_6 at 118 °C) 3.35 (s, 3 H, N-6 Me), 3.55 (s, 3 H, N-8 Me), 4.15 (s, 3 H, N-1 Me), 7.3 (d, 1 H, J = 5 Hz, H-5), 8.0 (d, 1 H, J = 5 Hz, H-4), 8.13 (s, 1 H, H-2)

[a] Recrystallization solvent: F, aqueous DMF; A, aqueous EtOH; D, Me_2SO. All compounds were obtained as either white or light yellow crystals. [b] Yields are not optimized. [c] All compounds in this table gave satisfactory microanalysis for C, H, and N (±0.4%). [d] Spin multiplicities are given by the abbreviations s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. [e] Unrecrystallized yield. [f] Can also be purified by sublimation. [g] Partial sublimation and decomposition.

A mixture of 10.2 g (44.8 mmol) of **13c** in 380 mL of anhydrous MeOH was saturated with anhydrous HCl while cooling in an ice bath. After refluxing this mixture for 1 h with the exclusion of moisture, the solvent was evaporated to dryness on a rotary evaporator. The white, crystalline, solid residue that resulted was suspended in 300 mL of $CHCl_3$ and this mixture was neutralized with a saturated solution of Na_2CO_3. The layers were separated, and the aqueous one was extracted with a second 300-mL portion of $CHCl_3$. The combined $CHCl_3$ extracts were washed with H_2O, dried over anhydrous $MgSO_4$, and filtered. The filtrate was evaporated to dryness to leave an oily residue (assumed to be **13a**) that was taken up in dry toluene (30 mL). To the resulting mixture was added 1 mL of triethylamine and 3 mL of methyl isocyanate and this mixture was refluxed for 24 h in an oil bath at 110–120 °C with the exclusion of moisture. After cooling, the white precipitate that resulted was isolated by filtration, washed with Et_2O, and dried to provide **14a** as given in Table II.

5-Chloro-3-methyl-6-nitro-2,4(1*H*,3*H*)-quinazolinedione (14b). A solution of 8.5 g (40.4 mmol) of **14a** in 40 mL of concentrated H_2SO_4 was cooled to −10 °C (dry ice–ice H_2O bath) and stirred mechanically. To the mixture was added, dropwise, 1.58 mL of fuming HNO_3 at such a rate that the temperature did not rise above −10 °C. After the addition was completed, the mixture was allowed to warm to room temperature and was then heated on a steam bath for 10 min. It was then poured over ice and neutralized with solid Na_2CO_3. The precipitate that resulted was isolated by filtration and washed successively with EtOH and Et_2O to afford **14b** as given in Table II.

5-Chloro-3-methyl-1-(2-methylpropyl)-6-nitro-2,4-(1*H*,3*H*)-quinazolinedione (15a). To a stirred mixture of 5 g (19.6 mmol) of **14b** and 2.71 g (19.6 mmol) of anhydrous K_2CO_3 in 100 mL of dry DMF was added, dropwise, 3.8 g (20.6 mmol) of 1-iodo-2-methylpropane. After further (6 h) stirring at 80 °C, the insoluble salts were removed by filtration, and the filtrate was evaporated in vacuo. The residue was suspended in H_2O. The resulting product was obtained by filtration and washed successively with EtOH and Et_2O and dried to afford **15a** as described in Table II.

5-Chloro-2,4(1*H*,3*H*)-quinazolinedione (11c). A mixture of 1 g (5.86 mmol) of **16**[15] and 2.6 (43.3 mmol) of urea was heated at 190 °C (bath) in an open flask for 1 h (or until the melt solidified) and then heated an additional 30 min. Water was added to the solid mass (still warm) and, following boiling of this mixture, the light-yellow-brown solid was isolated by filtration (0.9 g, 4.58 mmol, 78%), recrystallized as white crystals of **11c** from aqueous Me_2SO, and then sublimed (310 °C/1 mmHg) for microanalysis (see Table II).

5-Chloro-6-nitro-2,4(1*H*,3*H*)-quinazolinedione (11a). A mixture of 100 mL of concentrated H_2SO_4 and 20 g (101 mmol) of **11c** was cooled to −10 °C under mechanical stirring. To the cooled mixture was added, dropwise, 4 mL of fuming HNO_3. The addition rate was done to maintain the reaction temperature at −10 °C. Following the addition, the mixture was stirred on a steam bath for 10 min and then poured over 600 g of ice with stirring. The light yellow solid that resulted was isolated by filtration and dried in vacuo over P_2O_5 (65 °C for 24 h) to give **11a** (see Table II).

5-Chloro-1,3-dimethyl-6-nitro-2,4(1*H*,3*H*)-quinazolinedione (19). To a mixture of 2 g (8.28 mmol) of **11a** and 20 mL of H_2O was added 6.1 g of a 20% aqueous solution of tetraethylammonium hydroxide. When **11a** dissolved, 2 g (15.9 mmol) of Me_2SO_4 was added dropwise at 30–35 °C. The precipitated solid that resulted was isolated by filtration and air dried to give **19** as described in Table II.

5-Amino-1,3-dimethyl-6-nitro-2,4(1*H*,3*H*)-quinazolinedione (12a). A mixture of 3 g (12.4 mmol) of **19** and 25 mL of absolute 1-BuOH (that had been saturated with anhydrous NH_3 at room temperature) was heated in a sealed, stainless steel reaction vessel at 125 °C for 2 h. After this period, the vessel was cooled and the precipitated product was isolated by filtration and washed with Et_2O followed by warm H_2O. The dried yellow solid was **12a** as described in Table II.

6,8-Dimethyl-1*H*-imidazo[4,5-*f*]quinazoline-7,9-(6*H*,8*H*)-dione (3f, *prox*-Benzotheophylline). A mixture of 1 g (4 mmol) of **12a** in 20 mL of 97% formic acid, to which 100 mg of 10% Pd–C was added under N_2, was shaken under H_2 (initial pressure 52 psi) for 3 h. The catalyst was removed by filtration and the filtrate was then refluxed under N_2 for 2 h. This solution was evaporated to dryness on a rotary evaporator and a mixture of 25 mL of formic acid and 25 mL of toluene was added to the residue and the reflux was resumed for an additional 5 h under N_2. This solution was also evaporated to dryness to result in **3f** (Table IV).

1,3-Dimethyl-5-(methylamino)-6-nitro-2,4(1*H*,3*H*)-quinazolinedione (20). A mixture of 1 g (3.7 mmol) of **19** and 10 mL of absolute 1-BuOH (which had been saturated with anhydrous $MeNH_2$ at room temperature) was heated at 140 °C for 24 h in a sealed, stainless steel reaction vessel. Following this period, the vessel was cooled to −20 °C for 12 h and the precipitated solid was isolated by filtration and washed with Et_2O to give **20** as described in Table II.

1,6,8-Trimethyl-1*H*-imidazo[4,5-*f*]quinazoline-7,9-(6*H*,8*H*)-dione (3g, *prox*-Benzocaffeine). A mixture of 0.5 g (1.89 mmol) of **20** and 50 mL of 97% formic acid, to which 100 mg of 10% Pd–C was added under N_2, was shaken under H_2 (initial pressure 50 psi) for 3 h. The catalyst was removed by filtration and the filtrate was refluxed for 3 h under N_2. The formic acid was then removed in vacuo and 50 mL of toluene was added to the residue. The toluene was, in turn, removed to dryness and the residue was purified to give **3g** as described in Table IV.

Adenosine-Receptor Assay. A_1 affinities were determined in [^{3}H]-N^6-cyclohexyladenosine binding in rat brain membranes,[3f] and A_2 affinities were determined in [^{3}H]NECA binding in rat striatal membranes in the presence of 50 nM N^6-cyclopentyladenosine.[3f] A_1 and A_2 assays were carried out at 25 °C for 1 h with 1 nM [^{3}H]-N^6-cyclohexyladenosine (25 Ci/mmol) or 4 nM [^{3}H]NECA (30 Ci/mmol), respectively. All values are means of two or more independent determinations.

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Registry No. **2a**, 121496-93-3; **2b**, 121496-94-4; **2c**, 121496-95-5; **2d**, 121496-96-6; **2e**, 101031-51-0; **2f**, 76822-71-4; **2g**, 76832-42-3; **3a**, 121496-97-7; **3b**, 121496-98-8; **3c**, 121496-99-9; **3d**, 121497-00-5; **3e**, 101031-57-6; **3f**, 78754-88-8; **3g**, 78754-89-9; **4**, 76822-66-7; **5b**, 107731-67-9; **5c**, 121496-85-3; **5d**, 121496-86-4; **6a**, 76822-72-5; **6b**, 107710-65-6; **6c**, 121496-87-5; **6d**, 121496-88-6; **7b**, 93355-82-9; **9a**, 101031-64-5; **9b**, 101031-66-7; **10**, 121497-01-6; **11a**, 78754-82-2; **11b**, 78754-83-3; **11c**, 78754-81-1; **12a**, 78754-86-6; **12b**, 121496-89-7; **12c**, 121496-90-0; **12d**, 121496-91-1; **13a**, 41632-04-6; **13b**, 19407-42-2; **13c**, 70625-65-9; **14a**, 118470-98-7; **14b**, 121496-92-2; **15a**, 101031-68-9; **15b**, 101031-70-3; **16**, 54166-95-9; **18**, 76822-74-7; **19**, 78754-85-5; **20**, 78754-87-7; 3-chloro-2-methylaniline, 87-60-5.

Excitatory Amino Acid Agonists. Enzymic Resolution, X-ray Structure, and Enantioselective Activities of (*R*)- and (*S*)-Bromohomoibotenic Acid

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The enantiomers of α-amino-4-bromo-3-hydroxy-5-isoxazolepropionic acid (4-bromohomoibotenic acid, Br-HIBO, 1), a selective and potent agonist at one class of the central (*S*)-glutamic acid receptors, were prepared with an enantiomeric excess higher than 98.8% via stereoselective enzymic hydrolysis of (*RS*)-α-(acetylamino)-4-bromo-3-methoxy-5-isoxazolepropionic acid (4) using immobilized aminoacylase. The absolute configuration of the enantiomers of Br-HIBO was established by X-ray crystallographic analysis, which confirmed the expected preference of the enzyme for the *S* form of the substrate 4. (*S*)- and (*RS*)-Br-HIBO were potent neuroexcitants on cat spinal neurones in vivo, while (*R*)-Br-HIBO was a very weak excitant. Correspondingly, the *S* enantiomer of Br-HIBO (IC_{50} = 0.34 μM) was considerably more potent than the *R* form (IC_{50} = 32 μM) as an inhibitor of [^{3}H]-(*RS*)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid ([^{3}H]AMPA) binding to rat brain synaptic membranes in vitro. In contrast, (*S*)- and (*R*)-Br-HIBO were approximately equipotent (IC_{50} values of 0.22 and 0.15 μM, respectively) as inhibitors of [^{3}H]-(*S*)-glutamic acid binding in the presence of $CaCl_2$. The enantiomers of Br-HIBO showed no significant affinity for those binding sites on rat brain membranes which are labeled by [^{3}H]kainic acid or [^{3}H]-(*R*)-aspartic acid.

(*S*)-Glutamic acid [(*S*)-Glu] and (*S*)-aspartic acid [(*S*)-Asp] are now widely recognized as excitatory neurotransmitters in the mammalian central nervous system (CNS).[1,2] In analogy to other neurotransmitters, multiple receptors seem to exist in the CNS for excitatory amino acids (EAA's), and on the basis of electrophysiological in vivo experiments and in vitro binding studies at least three receptor classes[3,4] for EAA's have been characterized by their relative sensitivity to a number of agonists and antagonists: NMDA receptors, where *N*-methyl-(*R*)-aspartic acid (NMDA) is a potent and selective agonist, and a number of compounds, notably (*R*)-2-amino-5-phosphonopentanoic acid [(*R*)-AP5] and (*RS*)-[3-(2-carboxypiperazin-4-yl)propyl]phosphonic acid (CPP), are potent and selective antagonists;[3] QUIS/AMPA receptors, where (*S*)-quisqualic acid (QUIS) is a potent but nonselective agonist,[4] (*RS*)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) is a potent and selective agonist,[5] and (*S*)-Glu diethyl ester [(*S*)-GDEE] is a weak but selective antagonist;[6] and KAIN receptors, where

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