Imidazodiazepinediones: A New Class of Adenosine Receptor Antagonists

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A series of imidazo[4,5-*e*][1-4]diazepine-5,8-diones were synthesized from hypoxanthines. Certain of these cyclic homologues of caffeine, theophylline, theobromine, 3-isobutyl-1-methylxanthine, and enprofylline were inhibitors of binding of adenosine analogues to rat brain A_1 and A_2 adenosine receptors and were antagonists of A_2 adenosine receptors stimulatory to adenylate cyclase in rat PC12 cell membranes. Activity at adenosine receptors was lower than the corresponding xanthines, perhaps because imidazodiazepinediones contain a boat-shaped seven-membered ring rather than the planar heteroaryl ring system of the xanthines. The imidazodiazepinediones had low affinity for brain benzodiazepine sites.

Adenosine receptors modulate a wide range of physiological functions.[1,2] The major class of antagonists for such receptors are xanthines, with alkyl substituents in the 1-, 3-, and 7-positions. The prototypic xanthines, theophylline and caffeine, are not particularly potent adenosine receptor antagonists, nor are they selective for either of the two major subclasses of adenosine receptors. Theophylline is widely used in treatment of asthma, but it now appears likely that its efficacy in that regard is due more to inhibition of phosphodiesterases rather than antagonism of adenosine receptors.[3,4] The diuretic, respiratory stimulant, and central stimulant activity of theophylline and caffeine, however, do probably involve antagonism of adenosine receptors.[1,2] In recent years considerable effort has been dedicated to the development of xanthines with potent and selective effects on the two major subclasses A_1 and A_2, of adenosine receptors.[5-15] In addition, a wide range of other heterocycles have been found to be antagonists at adenosine receptors. These include the following classes: pyrazolopyridines,[16-19] pyrazolopyrimidines,[20] pyrazolopyrimidin-7-ones,[21] pyrazoloquinolines,[19,22] imidazopyrazines,[23] triazoloquinazolines,[19,24,25] a triazolopyridazine,[16,19] benzodipyrazoles,[26] mesoionic analogues of xanthines,[19,27] pteridindiones and benzopteridindiones,[19,28,29] β-carbolines,[16,19,30] 9-methyladenines,[19,28,31] 9-phenyl-7-deazaadenines,[32] barbiturates,[33] and dibenzazepines.[19,34,35] Virtually, all of these heterocycles, with the exception of dibenzazepines, such as carbamazepine, have planar ring systems, suggesting the importance of such a planar system to binding at an antagonist recognition site on adenosine receptors.

In the present study imidazodiazepinediones, a further class of non-xanthine adenosine receptor antagonists are described. The imidazodiazepinedione **3a** represents the ring homologue of theobromine, **3b** the ring homologue of caffeine, **3h** the ring homologue of theophylline, **3j** the ring homologue of enprofylline, and **3l** the ring homologue of 3-isobutyl-1-methylxanthine. Certain of the homologues of caffeine with *N*-benzyl substituents (**3e**, **3f**, **3g**, **3m**) at what corresponds to the 7-position of caffeine are as potent as theophylline as inhibitors of binding of an adenosine agonist to a brain A_1 receptor, but are less potent than theophylline as inhibitors of binding of an adenosine agonist to a brain A_2 receptor or as antagonists of A_2-receptor-stimulated adenylate cyclase from PC12 cells.

Chemistry

The preparation of the caffeine homologue, **3b**, was first reported in 1980.[36] The method, which involved a xanthine ring opening step, was later adapted to the synthesis of **3e** starting from 7-benzyltheophylline.[37] The theophylline homologue, **3h**, was formed by removal of the

Scheme I. Synthetic Route to Imidazo[4,5-*e*][1,4]diazepine-5,8-diones from Hypoxanthines (Initial Reaction of Ethyl Bromoacetate with 7-Methyl- or 7-Benzylhypoxanthine Yields 1a or 1b)[a]

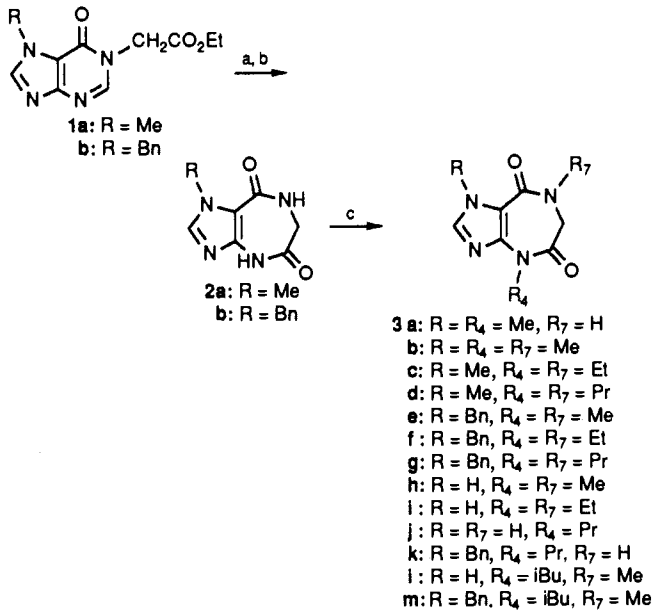

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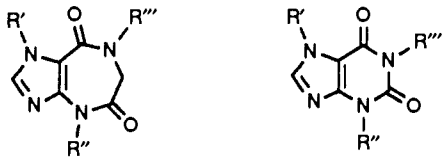
Table I. Biological Activity of Imidazodiazepinediones and Corresponding Xanthines



imidazodiazepinediones xanthines

compd	R′	R″	R‴	K_1 or K_B, μM: A_1 receptor[a] rat brain binding vs [^{3}H]PIA	A_2 receptor[c] rat striatum binding vs [^{3}H]NECA	A_2 receptor[b] PC12 cell adenylate cyclase vs NECA
				Imidazodiazepinediones		
3a	Me	Me	H	≫250 (10%)	≫250 (11%)	>300
3b	Me	Me	Me	≫250 (10%)	≫250 (9%)	>300
3c	Me	Et	Et	>250 (40%)	>250 (17%)	260 ± 37
3d	Me	*n*-Pr	*n*-Pr	>250 (40%)	>250 (23%)	170 ± 35
3e	Bn	Me	Me	30 ± 1.5	>250 (30%)	120 ± 18
3f	Bn	Et	Et	16 ± 6	81 ± 7	76 ± 14
3g	Bn	*n*-Pr	*n*-Pr	11 ± 3	52 ± 6	47 ± 7
3h	H	Me	Me	>250 (30%)	≫250 (9%)	>300
3i	H	Et	Et	>250 (40%)	>250 (20%)	>300
3j	H	*n*-Pr	H	236 ± 38	≫250 (11%)	>300
3k	Bn	*n*-Pr	H	32 ± 0.3	151 ± 15	163 ± 13
3l	H	*i*-Bu	Me	104 ± 7	≫250 (15%)	>300
3m	Bn	*i*-Bu	Me	11.3 ± 1.5	140 ± 5	116 ± 26
				Xanthines[d]		
theobromine	Me	Me	H	105 ± 6	>250 (40%)	250 ± 55
caffeine	Me	Me	Me	55 ± 11	48 ± 3	37 ± 9
7-benzyltheophylline	Bn	Me	Me	6 ± 1	46 ± 7	5.6 ± 1
7-benzyl-1,3-dipropylxanthine	Bn	*n*-Pr	*n*-Pr	1.0 ± 0.2	3.8 ± 1.3	0.88 ± 0.14
theophylline	H	Me	Me	14 ± 3	25 ± 2	17 ± 2
enprofylline	H	*n*-Pr	H	55 ± 6	137 ± 7	89 ± 4
3-isobutyl-1-methylxanthine (IBMX)	H	*i*-Bu	Me	6.7 ± 0.5	9.1 ± 0.7	6.3 ± 2.1
7-benzyl-IBMX	Bn	*i*-Bu	Me	6.9 ± 0.4	32 ± 4	7.5 ± 0.6

[a] Inhibition of binding of 1 nM [^{3}H]N^6-(phenylisopropyl)adenosine (PIA) to rat cerebral cortical membranes. Values are means ± SEM (n = 3-5). Values in parentheses are percent inhibition at the highest concentration tested. [b] Antagonism of *N*-ethylcarboxamidoadenosine-stimulated adenylate cyclase in rat PC12 membranes. Values are means ± SEM (n = 3). [c] Inhibition of binding of 1 nM [^{3}H]-N-ethylcarboxamidoadenosine (NECA) to rat striatal membranes. Values are means ±SEM (n = 3). Values in parentheses are percent inhibition at the highest concentration tested. [d] Certain values for xanthines have been published previously.

benzyl group by hydrogenolysis. A low overall yield and lack of versatility in this sequence led to development of an alternate approach to the preparation of imidazo[4,5-*e*][1,4]diazepine-5,8-diones from hypoxanthines.[37] This alternate method involved the preparation of 7-benzylhypoxanthine from inosine by benzylation, followed by deribosylation. Reaction with ethyl bromoacetate afforded **1b**, which through ring opening with base and cyclization with acetic acid yielded **2b** (Scheme I).[37] Dialkylation with ethyl bromide provided **3f**. Alkylation of **2b** with bromopropane provided **3k**, which was debenzylated to yield **3j**.[37] Dialkylation of **2b**, first with isobutyl bromide, then methyl iodide provided **3m**, which was debenzylated to **3l**.[37] The method has now been extended to the synthesis

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of **2a** and several di- and trialkyl derivatives, **3a**, **3c**, **3d**, **3g**, and **3i**.

Biological Results and Discussion

The imidazodiazepinediones were assayed for effects on adenosine receptors in three assays. Affinity for A_1 adenosine receptors was assessed in a binding assay with β-[^{3}H]N^6-(1-phenyl-2-propyl)adenosine and rat cerebral cortical membranes.[38] Such an assay has provided results for xanthines comparable to those obtained in antagonism of (*R*)-N^6-(1-phenyl-2-propyl)adenosine-elicited inhibition of adenylate cyclase in rat fat cell membranes, a classical A_1-receptor assay.[39] Affinity for A_2 adenosine receptors was assessed in two ways: First, affinity for brain A_2 receptor was assessed in a binding assay with [^{3}H]*N*-ethyladenosin-5'-uronamide and rat striatal membranes.[29] Second, activity at an A_2 receptor was assessed by antagonism of *N*-ethyladenosin-5'-uronamide-elicited stimulation of adenylate cyclase in rat pheochromocytoma cell membranes.[39] The results of these assays are presented in Table I along with comparative data on corresponding xanthines, where available. The ring system of imidazodiazepines are related closely in structures to benzodiazepines.[40] However, the IC_{50} values for inhibition of binding of [^{3}H]diazepam was 100 μM or less for all of the imidazodiazepines (see Experimental Section). Thus, imidazodiazepines are at least 100-fold less active than benzodiazepines at the GABA-receptor channel, but some are comparable in potency to caffeine and theophylline.[41]

The only imidazodiazepinediones with affinities towards A_1 adenosine receptors comparable to those of theophylline are **3e**, **3f**, **3g**, **3k**, and **3m** all of which contain a benzyl group at what corresponds to the 7-position of theophylline. 7-Benzyltheophylline itself is 2- to 3-fold more potent than theophylline at adenosine receptors (see Table I). The imidazodiazepinediones **3e**, **3f**, **3g**, and **3m** all had significantly lower activity in the A_2-receptor assays than in the A_1-receptor assay. Although the imidazodiazepinediones have low affinity for adenosine receptors, it would appear that increasing the size of alkyl substituents from methyl to ethyl to *n*-propyl increases affinity (see Table I) as is the case in xanthines. This suggests that imidazodiazepinediones and xanthines interact with the same site on the adenosine receptor. The much lower affinity of the imidazodiazepinediones could be the result of electronic or steric factors or both.

The structure of the imidazodiazepine ring system has been determined recently by a combination of NMR and computational methods.[40] The seven-membered ring is boat-shaped and the energy barrier to inversion for a dimethyl derivative was found to be 10.4 kcal/mol. Stereo views of the ring are shown in Figure 1 (for clarity only the hydrogen atoms of the methylene group are shown). The lack of planarity for the fused rings of the imidazodiazepinediones appears likely to be responsible for the marked reduction in activity, compared to corresponding xanthines at adenosine receptors. However, it is also possible that the orientation of the carbonyl dipoles are critical to activity and the orientation will be different in xanthines and imidazodiazepines.

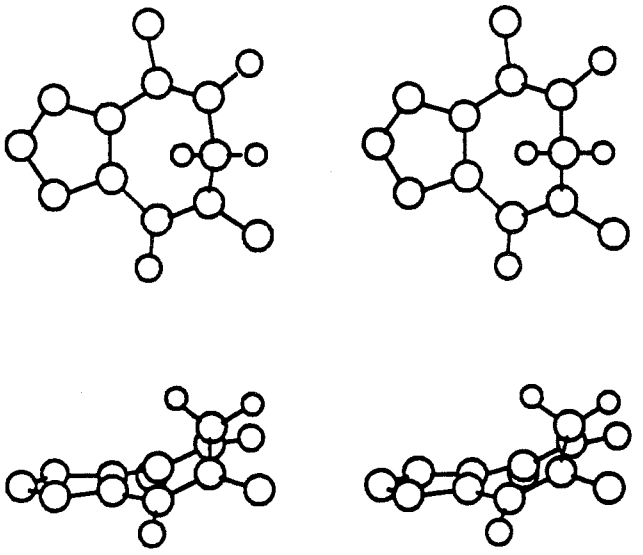

Figure 1. Stereodrawings of the imidazodiazepindione ring system.

Experimental Section

Melting points were determined on a Laboratory Devices Mel-Temp apparatus and are uncorrected. Proton and carbon NMR spectra were recorded on a Varian VXR-300 spectrometer in DMSO-d_6 and are referenced to the solvent. Microanalyses (C, H, N) were performed by Desert Analytics, Tucson, AZ, and were within ±0.4% of the theoretical values. Compounds **1b**, **2b**, 3b, **3e**, **3f**, **3h**, **3j**, **3k**, **3l**, and **3m** have been reported previously.[36,37]

Ethyl (7-Methylhypoxanthin-1-yl)acetate (1a). 7-Methylhypoxanthine (5.1 g, 34 mmol) and sodium hydride (60% dispersion in mineral oil, 1.6 g, 40 mmol) were suspended in anhydrous DMF (80 mL). After the mixture was stirred for 15 min, ethyl bromoacetate (4.4 mL, 40 mmol) was added, and the mixture was heated at 70 °C for 16 h. DMF was evaporated in vacuo, and the mineral oil was removed by trituration with hexane. The product was dissolved in dichloromethane, and crystalline sodium bromide was removed by filtration. The solvent was evaporated, and 1a was crystallized from ethanol, yielding 5.19 g (65%), mp 181–3 °C. ^{1}H NMR: 1.2 (t, 3 H, CH_2CH_3), 3.9 (s, 3 H, NCH_3), 4.1 (q, 2 H, OCH_2), 4.8 (s, 2 H, NCH_2CO), 8.15 (s, 1 H, H-2 or 8), 8.25 (s, 1 H, H-8 or 2).

1-Methyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (2a). Ethyl (7-methylhypoxanthin-1-yl)acetate (8.3 g, 35 mmol) was suspended in a mixture of ethanol (200 mL) and 6 M aqueous sodium hydroxide (17.5 mL). The solution was heated under reflux for 2 h, then cooled, and neutralized with concentrated hydrochloric acid. The solvents were evaporated in vacuo, and the residue was coevaporated twice with glacial acetic acid and then suspended in acetic acid (100 mL). The mixture was heated under reflux for 16 h. Acetic acid was evaporated in vacuo, and the residue was suspended in water. The solid was filtered and crystallized from water, yielding 4.95 g (78%), mp >320 °C dec. ^{1}H NMR: 3.7 (d, 2 H, NCH_2CO), 3.85 (s, 3 H, NCH_3), 7.75 (s, 1 H, H-2), 7.9 (t, 1 H, $CONHCH_2$), 10.7 (s, 1 H, $NHCOCH_2$).

1,4-Dimethyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (3a). 2a (0.9 g, 5 mmol) and sodium hydride (60%, 0.22 g, 5.2 mmol) were suspended in DMF (20 mL) at 70 °C. After 15 min, methyl iodide (0.32 mL, 5.2 mmol) was added, and heating was continued for 4 h. DMF was evaporated in vacuo, and the residue was dissolved in a minimum amount of water. Exhaustive extraction with chloroform and concentration of the extract gave 3a, which was crystallized from water, yielding 0.6 g (65%) of a monohydrate, mp 222–4 °C. ^{1}H NMR: 3.3 (s, 3 H, 4-CH_3), 3.75 (d, 2 H, $NHCH_2$), 3.8 (s, 3 H, 1-CH_3), 7.8 (s, 1 H, H-2), 8.15 (t, 1 H, $NHCH_2$).

General Procedure for Dialkylation. 2a or 2b was dissolved in DMF with 2.1 equiv of sodium hydride. Then 2.1 equiv of alkyl halide was added, and the mixture was stirred at 70 °C for 16

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h. DMF was evaporated in vacuo, and the residue was dissolved in water. The product was extracted into chloroform, and the extracts were dried and concentrated. Selective monoalkylation of compounds **2a** and **2b** occurs at N-4. This is clearly demonstrated by the NMR spectra of the products, in which the resonance for the remaining amide proton appears as a triplet due to coupling with the adjacent methylene group (see also ref 37).

4,7-Diethyl-1-methyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (3c). The monohydrochloride was crystallized from 2-propanol, mp 169–173 °C. ^{1}H NMR: 1.1 (t, 6 H, CH_2CH_3), 3.5 (q, 2 H, NCH_2CH_3), 3.8 (s, 3 H, NCH_3), 3.9 (q, 2 H, NCH_2CH_3), 4.0 (s, 2 H, NCH_2CO), 8.0 (s, 1 H, H-2).

4,7-Dipropyl-1-methyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (3d). The monohydrochloride was crystallized from ethanol, mp 161–3 °C. ^{1}H NMR: 0.8 (t, 6 H, CH_2CH_3), 1.5 (m, 4 h, $CH_2CH_2CH_3$), 3.5 (t, 2 H, NCH_2CH_2), 3.8 (s, 3 H, NCH_3), 3.9 (t, 2 H, NCH_2CH_2), 4.0 (s, 2 H, NCH_2CO), 8.0 (s, 1 H, H-2).

4,7-Dipropyl-1-benzyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (3g). Crystallized from aqueous ethanol, mp 112–114 °C. ^{1}H NMR: 0.8 (two t, 6 H, CH_2CH_3), 1.5 (m, 4 H, $CH_2CH_2CH_3$), 3.4 (t, 2 H, NCH_2CH_2), 3.8 (s, 2 H, NCH_2CO), 3.9 (t, 2 H, NCH_2CH_2), 5.5 (s, 2 H, NCH_2Ph), 7.2–7.4 (m, 5 H, Ph), 8.0 (s, 1 H, H-2).

4,7-Diethyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]-diazepine-5,8-dione (3i). The diethylbenzyl compound **3f** (0.32 g, 1 mmol)[37] was dissolved in glacial acetic acid (20 mL); 20% $Pd(OH)_2$ on carbon (Pearlman's catalyst, 0.1 g) was added, and the mixture was shaken under hydrogen (40 psi) for 14 h. The catalyst was separated by filtering through Celite, the filtrate was concentrated in vacuo, and the residue was crystallized from ethanol. The product (0.14 g, 61% yield) was recrystallized from ethanol–ether, mp 164–166 °C. ^{1}H NMR: 1.1 (two t, 6 H, NCH_2CH_3), 3.5 (q, 2 H, NCH_2CH_3), 4.0 (q and s, 4 H, NCH_2CH_3 and NCH_2CO), 7.8 (s, 1 H, H-2).

Binding of (*R*)-*N*^{6}-(1-Phenyl-2-propyl)[^{3}H]adenosine ([^{3}H]PIA) in Rat Brain Membranes. Membranes from rat cerebral cortex were prepared, and the binding of 1 nM [^{3}H]PIA to these membranes at 37 °C was assayed essentially as described;[38] IC_{50} values were transformed into K_i values by using a K_D for [^{3}H]PIA binding of 1.0 nM and the Cheng–Prusoff equation.[41]

Activity of Rat Pheochromocytoma PC12 Cell Adenylate Cyclase. PC12 cell membranes were prepared, and adenylate cyclase activity was determined essentially as described.[43] Briefly stated, the medium contained 0.1 mM [α^{32}P]ATP (0.9 μCi/tube), 10 μM GTP, 0.5 mM $MgCl_2$, 0.1 mM cyclic AMP, 2 μg/tube adenosine deaminase, 0.1 mM rolipram [4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone, ZK 62,711], 0.2 mM EGTA, 2 mM creatine phosphate as the Tris salt, 0.3 μg/tube creatine phosphokinase, 30 μg/tube bovine serum albumin, and 50 mM Tris-HCl, pH 7.4, in a total volume of 250 μL. Incubations were initiated by the addition of 10–15 μg of membrane protein and were conducted for 10 min at 37 °C. Incubations were stopped by the addition of 0.5 mL of 6% trichloroacetic acid. Cyclic AMP was purified as described.[44] EC_{50} values for *N*-ethyladenosin-5′-uronamide (NECA) were obtained from concentration–response curves in the absence or presence of the imidazodiazepinedione in three experiments. K_i values were then calculated by using the Schild equation.[45]

Binding of *N*-Ethyl[^{3}H]adenosin-5′-uronamide ([^{3}H]-NECA) in Rat Striatal Membranes. Membranes from rat striatum were prepared and the binding of 4 nM [^{3}H]NECA to these membranes was assayed essentially as described with 50 nM *N*^{6}-cyclopentyladenosine present to block A_1 adenosine receptors;[29] IC_{50} values were transformed into K_i values by using a K_D for [^{3}H]NECA binding to A_2 adenosine receptors of 8.5 nM and the Cheng–Prusoff equation.[42]

Binding of [^{3}H]Diazepam in Rat Cerebral Cortical Membranes. Membranes were prepared and inhibition of binding of 1 nM [^{3}H]diazepam was measured as described.[46] The benzyl analogues **3f**, **3g**, and **3l** at 100 μM inhibited [^{3}H]diazepam binding by 51 ± 3, 54 ± 3, and 34 ± 5%, respectively. Homologue **3c** inhibited binding at 100 μM by 38 ± 8%. All of the other imidazodiazepinediones caused less than 25% inhibition of binding of [^{3}H]diazepam at 100 μM. Thus, none of the imidazodiazepinediones are particularly potent at benzodiazepine receptors.

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