Statistical significance of the results was determined by the Mann-Whitney U-test.^{20,21} This is a nonparametric test because the null hypothesis is not concerned with specific parameters but only with the distribution of the variates. *P* values <0.05 were considered to indicate significant differences.

Determination of the Macroscopic pK_a Values. A glass electrode connected to a Philips PW 94149 ion activity meter was calibrated with buffers of pH 7.00 and 3.00. The ionic strength of the solution was 0.1635 (identical with the average ionic strength of the buffers used in the pharmacological experiments). Solutions of 2 mM mifentidine dihydrochloride, cimetidine dihydrochloride, and histamine dihydrochloride were titrated potentiometrically with 0.1 M KOH containing 63.5 mM NaCl, at 37.00 \pm 0.05 °C, under N₂, on a Mettler DV 10 micropipettor. Data (pH values and amounts of added KOH; about 40/titration) were analyzed with the scogs (stability constants of generated species) computer program,²²⁻²⁴ which was modified as follows: use of the

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Marquardt algorithm for minimalization;²⁵ iteration until optimium is obtained; calculation including 95% confidence intervals. The scogs computer program was used to obtain acid association constants making allowance for temperature, activity coefficients, volume of the solution, normality of the titrant, and added acid or base, following a nonlinear least-squares minimization of the added volumes of alkali. All titrations were in duplicate.

For calculation of the species distribution of the three compounds at the pH values used in the pharmacological experiments the computer program COMICS^{26} (concentrations of metal ions and complexing species) was applied. This program contains a method for calculating equilibrium concentrations of all species in multimetal-multiligand mixtures from the pH of the solution, the total concentration of each metal and each complexing agent, and the relevant equilibrium constants (p K_a values and stability constants).

Chemicals. Cimetidine was supplied by SK&F (U.K.). Mifentidine was a gift from Instituto de Angeli (Italy). Histamine dihydrochloride was derived from Janssen Pharmaceutica (Belgium). All other chemicals were of analytical grade.

Registry No. Cimetidine, 51481-61-9; mifentidine, 83184-43-4.

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Xanthine Functionalized Congeners as Potent Ligands at A₂-Adenosine Receptors^{†,‡}

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Amide derivatives of a carboxylic acid congener of 1,3-dialkylxanthine, having a 4-[(carboxymethyl)oxy]phenyl substituent at the 8-position, have been synthesized in order to identify potent antagonists at A_2 -adenosine receptors stimulatory to adenylate cyclase in platelets. Distal structural features of amide-linked chains and the size of the 1,3-dialkyl groups have been varied. 1,3-Diethyl groups, more than 1,3-dimethyl or 1,3-dipropyl groups, favor A_2 potency, even in the presence of extended chains attached at the 8-(p-substituted-phenyl) position. Polar groups, such as amines, on the chain simultaneously enhance water solubility and A_2 potency. Among the most potent A_2 ligands are an amine congener, 8-[4-[[[(2-aminoethyl)amino]carbonyl]methyl]oxy]phenyl]-1,3-diethylxanthine, and its D-lysyl conjugate, which have K_B values of 21 and 23 nM, respectively, for the antagonism of N-ethyl-adenosine-5'-uronamide-stimulated adenylate cyclase activity in human platelet membranes. Strategies for the selection and tritiation of new radioligands for use in competitive binding assays at A_2 -adenosine receptors have been considered.

The synthesis of potent and/or selective analogues of caffeine and theophylline as antagonists at extracellular adenosine receptors remains a challenge. Two adenosine receptor subtypes have been delineated on the basis of inhibition (A₁) or stimulation (A₂) of adenylate cyclase by adenosine and adenosine analogues. Numerous physiological functions have been shown to be regulated by either or both A₁- and A₂-adenosine receptor subtype has been found

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to occur. For example, in platelets and PC12 pheochromocytoma cells the existing adenosine receptors appear to be all of the A_2 subtype.² Fat cells are considered to contain only the A_1 -receptor subtype.

Characterization of adenosine receptors with reversibly-binding radioligands has been carried out mainly with brain membranes, due to the high density of A_1 receptors in that organ. A number of radioligands for A_1 receptors have been reported. Tritiated N⁶-cycloalkyladenosines^{3,4} and tritiated (*R*)-N⁶-(phenylisopropyl)adenosine⁵ (PIA)

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[†]Dedicated to Prof. B. Witkop on the occasion of his 70th birthday.

[‡]Abbreviations: DPX, 1,3-diethyl-8-phenylxanthine; NECA, N-ethyladenosine-5'-uronamide; XAC, xanthine amine congener (compound 6c); HOBt, 1-hydroxybenzotriazole; EDAC, 1ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride; PIA, N^{6} -(phenylisopropyl)adenosine.

[§]Laboratory of Bioorganic Chemistry.

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having high specific activity are used regularly in competitive-binding assays to determine affinity of new analogues at A₁ receptors. The choice of antagonist radioligands had been limited to [³H]-1,3-diethyl-8-phenylxanthine³ ([³H]-DPX, **1b**), which has a K_i value at A₁ receptors of about 60 nM. The recently introduced 8-[4-[[[[(2-aminoethyl)amino]carbonyl]methyl]oxy]phenyl]-1,3-dipropylxanthine ([³H]XAC, **6c**), a xanthine amine congener,^{6,7} has a higher affinity and specific activity than [³H]DPX, and its use overcomes a number of difficulties associated with the use of [³H]DPX as an antagonist radioligand for A₁ receptors.



Until recently the screening of analogues at A2 receptors has relied on biological assays of adenylate cyclase, platelet aggregation, or in vivo models such as coronary vasodilation.^{2,8,14} A competitive binding assay at A_2 receptors in striatal tissue using ³H-labeled N-ethyladenosine-5'uronamide (NECA) as a radiotracer has been introduced.⁹ Although NECA is one of the most potent A2 agonists reported, it is not selective for that subtype, and it in fact binds with approximately 5-50-fold greater affinity at A_1 -adenosine receptors.¹⁰ Thus, in the striatum, where both adenosine-receptor subtypes occur, it is necessary to block the A₁-receptor component of [³H]NECA binding by use of a selective A_1 ligand^{9b} or by pretreatment of the membranes with N-ethylmaleimide.^{9a} However, there also is evidence that NECA can bind to sites that have characteristics different from those expected of A2 receptors coupled to adenylate cyclase, particularly in peripheral tissue.^{13,14} With the goal of finding a more communication With the goal of finding a more convenient method for the study of A_2 receptors, we have applied the functionalized congener approach,^{6,11} previously used in the design of A_1 -receptor radioligands, such as $[^{3}H]XAC$, to the development of potential antagonist A_2 -receptor radioligands.

Results and Discussion

Although a number of moderately A_2 -selective antagonists have been reported,¹⁵ none are of sufficiently high

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Table I. Synthesis and Characterization^e of New Xanthine Derivatives (compound suffixes **a**, **b**, and **c** refer to $\mathbf{R} = \mathbf{Me}$, Et, and Pr, respectively)

no.	% yield	mp, °C	formula	anal.
2b	67ª	>310	$C_{17}H_{18}N_4O_5 \cdot H_2O_6$	C, H, N.
3a	61	294-296	$C_{17}H_{18}N_4O_5 \cdot 1/_4H_2O$	C, H, N
3b	86	267-269	$C_{19}H_{22}N_4O_5$	C, H, N
4b	71	275 - 277	$C_{20}H_{24}N_4O_5 \cdot 1/_2DMF$	C, H, N
5b	88	300-302	$C_{19}H_{23}N_5O_4\cdot^1/_2H_2O$	C, H, N
6a	99	255 - 258	$C_{17}H_{20}N_6O_4 \cdot 1/_4H_2O$	C, H, N
6b	92	233-235	C ₁₉ H ₂₄ N ₆ O ₄ ·H ₂ O·DMF	C; H, N^b
7b	58	>310	$C_{24}H_{25}N_5O_4\cdot^4/_5H_2O$	C, H, N
8a	60	>310	$C_{24}H_{23}N_5O_6$	H, N; C ^c
8b	92	310-313	$C_{26}H_{27}N_5O_6 \cdot 1/_2H_2O$	C, H, N
9a	94	280 dec	$C_{25}H_{27}N_7O_5$	H, N; C^d
9b	77	273–278d	$C_{27}H_{31}N_7O_5 \cdot {}^3/_4H_2O$	C, H, N
10b	79	215 - 219	$C_{38}H_{50}N_8O_{9}\cdot^1/_2H_2O$	C, H, N
10c	95	207 - 211	C ₄₀ H ₅₄ N ₈ O ₉	C, H, N
11b	100	270 - 275	$C_{25}H_{36}N_8O_5 \cdot 2HBr \cdot 2H_2O$	C, H, N
11c	83	dec begin 190	$C_{27}H_{40}N_8O_5 \cdot 3HBr$	C. H. N

^a Yield calculated from 6-amino-1,3-diethyl-5-nitrosouracil, which was treated with $Na_2S_2O_4$ and then condensed with [(4formylphenyl)oxy]acetic acid, and the benzylidene adduct was oxidized with NaIO₄ as in ref 12. ^bH calcd 6.77, found 6.25; N calcd 19.95, found 18.97. °C calcd 60.37, found 52.82. °C calcd 59.40, found 51.49. Proton NMR resonances (300 MHz) in ppm from Me₄Si for selected compounds in $(CD_3)_2SO$. 6b: δ 8.15 (t, 1 H, amide NH), 8.05 and 7.05 (each d, J = 8.7 Hz, 2 H, Ar), 4.54 (s, 2 H, CH₂O), 4.08 and 3.94 (each q, 2 H, Et methylene), 3.21 (m, 2 H, CH_2NHCO), 2.68 (t, J = 6.2 Hz, 2 H, CH_2NH_2), 1.26 and 1.13 (each t, 2 H, J = 6.8 Hz, CH₃). 8a: δ 8.10 (d, 2 H, Ar, meta to O), 7.58 (d, 2 H, Ar, ortho to NH), 7.23 (d, 2 H, Ar, ortho to CH₂), 7.13 (d, 2 H, Ar, ortho to O), 4.79 (s, 2 H, CH₂O), 3.63 (s, 2 H, CH₂Ar), 3.61 (s, 3 H, OCH₃), 3.49 and 3.27 (each s, 3 H, NCH₃). 9a: δ 8.06 (d, 2 H, Ar, meta to O), 8.02 (1 H, amide NH), 7.56 (d, 2 H, Ar, ortho to NH), 7.21 (d, 2 H, Ar, ortho to CH₂), 7.13 (d, 2 H, Ar, ortho to O), 4.75 (s, 2 H, CH₂O), 3.48 and 3.24 (each s, 3 H, NCH₃), 3.36 (s, 2 H, CH₂Ar), 3.07 (m, 2 H, CH₂NHCO), 2.60 (t, J = 6.7 Hz, 2 H, CH₂NH₂).

affinity to serve as radiotracer for competitive-binding studies. For this reason, we approached the development of an A₂-antagonist radioligand from the standpoint of maximizing A₂ potency regardless of the selectivity ratio. At that point a highly potent candidate should be radiolabeled and its binding properties examined in a membrane preparation such as human platelets in which A₂but not A₁-adenosine receptors are present. Subsequently, the platelet assay is to be used to study other potential A₂-adenosine ligands by measuring their inhibition of binding of a well-characterized radioligand.

The classical approach to developing new drugs has been to explore the effect of structural modifications at or around a primary pharmacophore. We have developed a "functionalized congener" approach for adenosine-receptor ligands, by which a chemically functionalized chain is incorporated at a point that does not reduce biological activity. The resulting active congener can be joined covalently to a variety of moieties, including amino acids and peptides¹¹ or solid supports for affinity chromatography, through a functional group such as an amine or a carboxylic acid. For xanthines as adenosine antagonists it has been shown⁶ that distal structural changes on a chain attached through the 8-(p-substituted-phenyl) position can modulate the potency and selectivity of the drugs, perhaps through interactions at sites on the receptor distal to the binding site for the pharmacophore. We now show the validity of this approach for xanthines as antagonists at A_2 -adenosine receptors.

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Table II. Potencies of Xanthine Derivatives at A_2 - and A_1 -Adenosine Receptors

no.	Rª	A_2 receptor: ^b K_B , nM	A_1 receptor: ^c K_i , nM
1a	Me	1900	70
1 b	\mathbf{Et}	210	65
1 c	\mathbf{Pr}	2100	13
2c	\mathbf{Pr}	2400 (1500-3900)	50
3b	\mathbf{Et}	170 (75-370)	140
3c	\mathbf{Pr}	135 (106-173)	13
4b	\mathbf{Et}	73 (54–98)	90
5b	\mathbf{Et}	48 (36-65)	57
6 a	Me	40 (30-54)	13
6b	\mathbf{Et}	21(18-23)	12
6 c	Pr	25 (21-30)	1.2
7a	Me	430 (260-720)	27
7b	\mathbf{Et}	100 (60-170)	9.3
8b	\mathbf{Et}	210 (190-230)	58
9a	Me	63 (57-68)	42
9b	\mathbf{Et}	28 (15-51)	25
10b	Et	230 (100-540)	180
11b	Et	23 (17-30)	9.4
11c	Pr	37 (35-40)	0.87

^aSubstituent at the 1,3-positions (see Figure 1). ^bAntagonism of NECA-induced stimulation of adenylate cyclase activity in human platelet membranes. Values are means with 95% confidence limits from three separate experiments. Values for 2c, 6c, and 11c from ref 2; value for 1b from ref 14. ^cInhibition of [³H]PIA binding to rat cerebral cortex membranes. Values are means from two separate experiments.

The K_i values for reversal of 2-chloroadenosine-stimulated cyclic AMP production in guinea pig brain slices for a carboxylic acid congener, 2c, an ethyl ester, 3c, an amine congener, 6c (all R = Pr), and a p-toluidine, 7a (R = Me) were 34, 30, 49, and 20 nM, respectively. Furthermore, within a series of amino acid conjugates of 6c, the D-lysyl conjugate 11c displayed high potency, high water solubility, and stability to enzymatic hydrolysis. Since a dissociation constant in the range of 10^{-8} M would be acceptable for a radiotracer, these compounds constituted suitable lead compounds. As modifications of these xanthines designed to increases A₂ potency we have explored changing the size of the 1,3-dialkyl groups and incorporating distal amino groups in the functionalized 8-phenyl moiety (see Table I for synthesis and characterization).

As reported previously,² the affinity of XAC (6c) for A_2 receptors of human platelets was in close agreement with the value in brain slices, but the potency of 2c showed a discrepancy between these two systems. Since we intended to study binding to A_2 receptors in platelets, the effect on platelet adenylate cyclase was adopted as the sole criterion of A_2 potency in this study.

In each case the potency of the 1,3-diethyl analogue at platelet A_2 receptors was greater than the 1,3-dimethyl analogue and at least as great as that of the 1,3-dipropyl analogue (Table II). The enhancement of A_2 affinity by ethyl substituents was more marked for the simple 8phenyl series, 1, than for the functionalized congeners. In contrast, Bruns et al.^{9b} reported 1,3-dipropyl-8-phenylxanthine to be 5-fold more potent than the diethyl analogue in inhibition of [³H]NECA binding to a striatal A_2 -adenosine receptor.

While the carboxylic acid congener 2c was not particularly potent, esterification to give compound 3c increased potency markedly at A_2 receptors, but not at A_1 receptors. A comparison of ethyl and isopropyl esters showed preference of the branched isopropyl group at A_2 receptors.

Compounds 7a and 7b, containing the *p*-toluidine group, were not as potent at A_2 receptors as expected on the basis of previous studies. However, when the [(2-aminoethyl)amino]carbonyl group was attached to the *p*-methyl group of the toluidine, as in 9, the potency rose. Thus, the potency-enhancing effect of a distal amino group, observed consistently with the A_1 receptor particularly with dipropyl analogues (e.g., 6c, 11c),^{6,11} now appears to apply as well to the A_2 receptor. The enhancement of A_2 potency by an amino group is also evident in comparing the ethyl amide 5 and the 2-aminoethyl amide 6b.

The potencies of XAC (6c) and the diethyl analogue 6b were nearly identical at A_2 receptors. The specific binding of a tritiated 1,3-dipropylxanthine amine congener (XAC) to A₂-adenosine receptors in platelets has been reported.¹³ However, a high degree of nonspecific binding of [3H]XAC will limit the usefulness of this radioligand in screening assays. For an A₂ radioligand it would be preferable to use the diethyl analogue, due to the likely lower levels of nonspecific binding with 1,3-diethylxanthines, in comparison to the corresponding 1,3-dipropyl analogues. Although not strictly indicative of the level of potential filter binding, the octanol-water partition coefficients (log p) are as follows: -0.63 (6a), -0.06 (6b), 0.81 (6c), -0.05(9a), and -1.20 (11b). Thus, there is a large difference in polarity between 1,3-diethyl (e.g., 6b) and 1,3-dipropyl (e.g., 6c) analogues, which is also reflected in maximum aqueous solubility (pH 7.2, 0.01 M phosphate) of 500 and 90 μ M, respectively. The lipophilic contribution of an additional ring and amide bond in the chain, as in 9a, is roughly equivalent to substituting 1,3-dimethyl with 1,3-diethyl substituents. Another potential A_2 radioligand is 11b, the polar conjugate of D-lysine and diethyl-XAC.

The synthesis of tritiated analogues of 1,3-dipropylxanthines through the catalytic tritiation of 1,3-diallyl precursors has been demonstrated.¹² To obtain the corresponding tritiated diethyl analogues in similar fashion would require starting with vinyl substituents. As an alternative we have explored coupling of the diethyl carboxylic congener 2b to ethylenediamine using the watersoluble carbodiimide 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride and 1-hydroxybenzotriazole as a catalyst. Coupling reactions using tritiated ethylenediamine to produce the desired radioligand are in progress.

Experimental Section

Xanthine analogues were synthesized as previously reported^{6,11,12} or by routes shown in Figure 1. HPLC-grade dimethylformamide (Aldrich Chemical Co., Milwaukee, WI) was used without further purification. New compounds were characterized by 300-MHz proton NMR on a Varian 300XL and gave spectra consistent with their structures. Except for compounds 10 and 11, chemicalionization mass spectra (CIMS) were obtained with a Finnigan 1015D spectrometer using ammonia gas with a Model 6000 data collection system. Samples for elemental analysis and biological testing were shown to be homogeneous by thin-layer chromatography (silica, CHCl₈/MeOH/HOAc, 85:10:5 and 10:10:1) and, if necessary, recrystallized from solvent mixtures including DMF/ether, DMF/water, or Me₂SO/ether.

Partition coefficients were determined by addition of a dimethyl sulfoxide solution (5 μ L) of the xanthine to an equivolume mixture (2 mL) of 1-octanol and aqueous sodium phosphate, pH 7.2, 0.1 M. After thorough mixing of phases and separation, the ratio of concentrations was determined by comparing absorption at 310 nm of aliquots diluted in methanol (aqueous was filtered). The ±SEM for six determinations corresponded to 0.01 log p unit.

Measurements of the potencies of the xanthines as antagonists of NECA-induced stimulation of adenylate cyclase activity in human platelet membranes and as inhibitors of [³H]PIA binding to rat cerebral cortex membranes were carried out as reported previously.^{2,3} The slopes of the inhibition curves had Hill coefficients of about 1.0, and all compounds completely inhibited the response to NECA or the specific binding of [³H]PIA.

8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-diethylxanthine 2-Propyl Ester (4b). Compound 2b (20 mg, 56 μmol) was



Boc-p-Lys(Cbz)-NH(CH₂)₂NHCO-X \xrightarrow{d} p-Lys-HN(CH₂)₂NHCO-X •2HBr 10 11

Figure 1. Synthesis of xanthine derivatives. Reagents: (a) EtOH/HCl,⁷ 50 °C (3) or R'OH/DMAP/EDAC (4); (b) 70% ethylamine, aqueous (5) or ethylenediamine, neat⁶ (6, 9); (c) DCC/HOBt; (d) HBr/HOAc. R = Me, Et, or *n*-Pr, corresponding to compound suffixes a, b, and c, respectively.

suspended in a solution of 4-(dimethylamino)pyridine (7 mg) and 2-propanol (0.1 mL) in dimethylformamide (1 mL) and the mixture treated with 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (24 mg, 110 μ mol). After several minutes a solution formed, followed by precipitation. After 2 h, water (3 mL) was added, and the white solid was collected, washed with water, and dried, giving 15.8 mg of compound 4; CIMS (NH₃), m/e 401 (M + 1)⁺.

8-[4-[[[((2-Aminoethyl)amino]carbonyl]methyl]oxy]phenyl]-1,3-diethylxanthine (6b). Compound 3b (70 mg, 0.18 mmol) was dissolved in ethylenediamine (2 mL) with stirring. The solvent was evaporated under a stream of nitrogen. The oily residue was triturated with methanol and ether to give compound **6b** (67 mg, 92% yield) as a solid; CIMS (NH₃), m/e 401 (M + 1)⁺.

Alternately, the carboxylic acid **2b** was preactivated with 1ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate in dimethylformamide, and this mixture was added slowly to a solution of 1 equiv of ethylenediamine. The product, **6b**, was isolated by thin-layer chromatography (CHCl₃/MeOH/HOAc, 10:10:1, on silica gel plates) in 44% yield (determined by UV).

8-[4-[[[[4-(Carboxymethyl)anilino]carbonyl]methyl]oxy]phenyl]-1,3-diethylxanthine Methyl Ester (8b). Compound 2b (80.8 mg, 0.23 mmol), methyl (p-aminophenyl)acetate hydrochloride (55 mg, 0.27 mmol), HOBt (31 mg, 0.23 mmol), and finally 1-ethyl-3-[3-(dimethylamino)propyl)carbodiimide hydrochloride (98 mg, 0.46 mmol) were combined with stirring in 8 mL of dimethylformamide. Diisopropylethylamine (39 μ L, 0.23 mmol) was added, and the mixture was stirred overnight. Water was added, and the product (60 mg) was collected, washed with water, and dried; CIMS (NH₃), m/e 506 (M + 1)⁺.

8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-diethylxanthine 2-(D-Lysylamino)ethylamide Dihydrobromide (11b). Compound 6b (50 mg, 0.13 mmol) was suspended in 2 mL of dimethylformamide and treated with N^{α} -Boc-N^{*}-Cbz-D-lysine (95 mg, 0.25 mmol), HOBt (17 mg, 0.13 mmol), and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (54 mg, 0.25 mmol). The mixture was stirred overnight. Aqueous workup, as above, followed by recrystallization from ethyl acetate/hexanes provided 75 mg of compound 10b. The protecting groups were removed with 30% HBr/acetic acid (2 mL), giving compound 11b (72 mg). An analytical sample was prepared by recrystallization from methanol/ether.

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Registry No. 1a, 961-45-5; 1b, 75922-48-4; 1c, 85872-53-3; 2a, 96865-82-6; 2b, 104576-44-5; 2c, 96865-83-7; 3a, 104576-45-6; 3b, 104576-46-7; 3c, 96865-87-1; 4b, 104576-47-8; 5b, 104576-48-9; 6a, 104576-49-0; 6b, 104598-39-2; 6c, 96865-92-8; 7a, 96865-84-8; 7b, 104576-50-3; 8a, 104576-51-4; 8b, 104576-52-5; 9a, 104576-53-6; 9b, 104576-54-7; 10b, 104576-55-8; 10c, 102255-74-3; 11b, 104576-56-9; 11c, 104576-57-0; 2-PrOH, 67-63-0; $H_2NCH_2CH_2NH_2$, 107-15-3; 4- $H_2NC_6H_4CH_2CO_2Me$ ·HCl, 83528-16-9; N^{α} -Boc- N^{ϵ} -Cbz-D-lysine, 55878-47-2; 4-MeC₆H₄NH₂, 106-49-0.

Dopamine Agonists: Effects of Charged and Uncharged Analogues of Dopamine

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Dopamine, at physiological pH, may exist as either an uncharged amine or a charged ammonium species. In order to gain insight as to which species is better suited for interaction with the dopamine receptor, we have synthesized dopamine analogues in which the nitrogen atom is replaced with a neutral methyl sulfide, a neutral methyl selenide, a charged dimethylsulfonium iodide, and a charged dimethylselenonium iodide. These analogues were tested for their ability to inhibit the K⁺-stimulated release of [³H]acetylcholine from striatal slices. At 30 μ M concentration, the charged sulfonium and selenonium salts possessed significant agonist activity while the corresponding neutral species were inactive, suggesting that a charged species is optimal for dopamine agonist activity. In addition, the methyl sulfide was converted into the corresponding sulfoxide and sulfone; however, neither of these oxidation products possessed significant activity as dopaminergic agonists.

An extensive number of structure-activity relationship studies have been carried out with dopamine agonists and antagonists.¹ Previous work in our laboratory has shown that the sulfonium analogue 4 has direct dopamine agonist