Substituted 1,3,4-Thiadiazoles with Anticonvulsant Activity. 3. Guanidines

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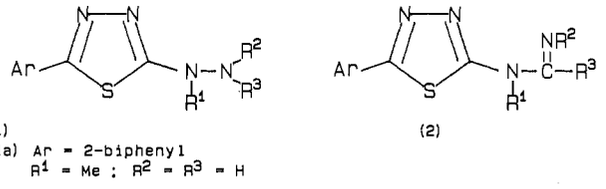
The synthesis and anticonvulsant activity of a number of 2-aryl-5-guanidino-1,3,4 thiadiazoles are described. The unsubstituted guanidine **2a** was found to possess potent anticonvulsant properties; considerable reduction or loss of activity however was observed with the majority of the substituted guanidines. Incorporation of the guanidine group into an imidazoline ring also resulted in a loss of activity. Secondary pharmacological evaluation confirmed the anticonvulsant properties of **2a** but also revealed that the compound exhibited a considerable degree of sedative activity.

A previous paper[1] described a series of 2-aryl-5-hydrazino-1,3,4-thiadiazoles **1** possessing anticonvulsant properties. The series of compounds had originally been designed as analogues of the antihypertensive agent hydralazine, but subsequent evaluation showed that some analogues possessed both antihypertensive and anticonvulsant activities. A similar situation was encountered in the corresponding 2-aryl-5-guanidine series **2**, the replacement of the hydrazine group by a guanidine moiety being prompted by the knowledge that hydrazine groups are associated with potential toxicological problems.[2] The guanidines synthesized[3] were generally found to possess antihypertensive properties (vasodilatation) as expected, but the 2-(trifluoromethyl)aryl derivative **2a** proved to have a significant level of anticonvulsant activity with a minimum of vasodilator activity. This paper describes the synthesis and pharmacological profile of **2a** together with a number of derivatives possessing substituents on the guanidine group.



(1) (2)

(1a) Ar = 2-biphenyl; R^1 = Me; R^2 = R^3 = H

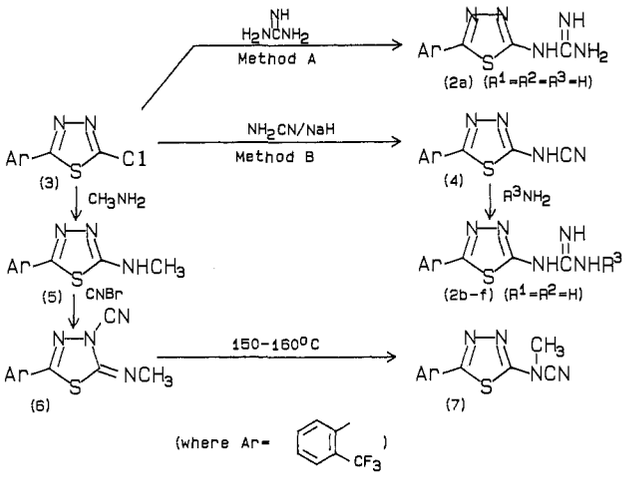
Chemistry

The key intermediate, 2-aryl-5-chloro-1,3,4-thiadiazole **3**, was synthesized by using the standard procedures already described.[1] The unsubstituted guanidine **2a** was prepared directly from the reaction of **3** with guanidine (method A, Scheme I). An alternative route to guanidines involving reaction of the corresponding 2-aryl-5-aminothiadiazole with cyanamide was unsuccessful.

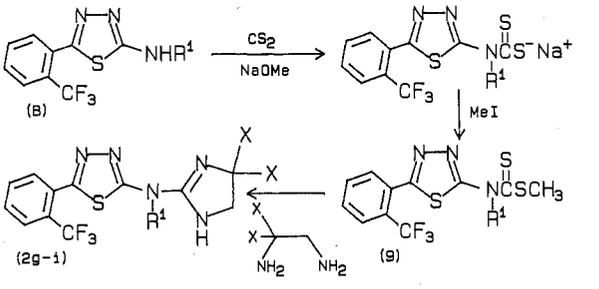
The method of choice for the synthesis of substituted guanidines **2b–f** utilized the 5-cyanamidothiadiazole **4**, which was prepared from **3** and sodium cyanamide; further reaction of **4** with amines furnished the required guanidines (method B, Scheme I).

An approach to the synthesis of guanidines substituted on the nitrogen atom adjacent to the thiadiazole ring (R^1, structure **2**) was investigated, which involved the reaction of cyanogen bromide with the appropriate N-alkylated 5-aminothiadiazole (Scheme I). However, the 5-methylamino compound **5** was converted to the ring N-cyanated product **6** rather than the required isomeric material **7**. In the mass spectrum a major fragmentation peak at 211 (M^+ – 73) was attributed to loss of a $SCNCH_3$ unit. Alkylation of aminothiadiazoles has also been observed to give ring alkylated products.[4] We have since shown that 5-cyanamidothiadiazoles are also alkylated on the ring nitrogen atom.[5] Subsequently it was found that **6** was thermally unstable and rearranged at 150–160 °C to the isomeric product **7**. The mass spectrum now revealed a significant loss of CH_3NCN. It is likely therefore that **6** is the kinetically favored product with **7** being the thermodynamically more stable entity. Unfortunately, the N-methylated cyanamide **7** on reaction with ammonia gave the starting 5-(methylamino)thiadiazole **5** rather than the required guanidine. This result together with other observations[5] indicates an inherent instability of substituted cyanamides of type **7** since nucleophilic displacement of the thiadiazole–amine portion appears to occur readily. It is possible that this could be related to the absence in the N-alkylated guanidine of tautomeric forms having conjugation between the functional group and the heterocyclic nucleus. Cyclic

Scheme I



Scheme II



(1) Chapleo, C. B.; Myers, M.; Myers, P. L.; Saville, J. F.; Smith, A. C. B.; Stillings, M. R.; Tulloch, I. F.; Walter, D. S.; Welbourn, A. P. *J. Med. Chem.* **1986**, *29*, 2273.
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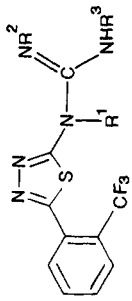
0022-2623/87/1830-0951$01.50/0

Table I



no.	R^1	R^2	R^3	method[a]	mp, °C	solvent recrystn	formula	ED_{50},[b] mg/kg (limits) MMS[c]	ED_{50},[b] mg/kg (limits) MES[d]	TD_{50},[b] mg/kg (limits), rotorod[e]
2a	H	H	H	A	215–218	MeOH/Et_2O	$C_{10}H_8F_3N_5S$·HCl	45 (17–70)	27 (17–43)	384 (171–inf)
2b	H	H	CH_3	B	160–162		$C_{11}H_{10}F_3N_5S$	44 (31–82)	49 (32–65)	>400
2c	H	H	^{n}Bu	B	147–149	$(Me)_2CO$	$C_{14}H_{16}F_3N_5S$·HCl	225 (inf)	142 (inf)	NT
2d	H	H	$PhCH_2$	B	120–121	EtOH	$C_{17}H_{14}F_3N_5S$	>100	>100	NT
2e	H	H	$(CH_2)_3N(CH_3)_2$	B	110–112	C_6H_6/c-C_6H_{12}	$C_{15}H_{19}F_3N_6S$	>100	>100	NT
2f	H	H	$(CH_2)_3OCH_3$	B	137–139	*i*-PrOH	$C_{14}H_{16}F_3N_5OS$	~78	>100	NT
2g	H		$(CH_2)_2$	C	229–230	EtOH	$C_{12}H_{10}F_3N_5S$	>100	>100	NT
2h	CH_3		$(CH_2)_2$	C	167–168		$C_{13}H_{12}F_3N_5S$	>100	>100	NT
2i	H		$C(CH_3)_2CH_2$	C	183–184	*i*-PrOH	$C_{14}H_{14}F_3N_5S$	>100	>100	NT

[a] Preparation methods referred to are as follows: A = guanidine + chlorothiadiazole **3**, B = amines + cyanamidothiadiazole **4**, C = diamines + dithiocarbamate **9**. [b] inf = infinity, NT = not tested. Limits obtained from a statistical analysis of the test result (Bliss computer assay[6]). [c] MMS = maximal metrazol seizures[7] (mouse); 1 h after dosing (po). [d] MES = maximum electroshock test[8] (mouse); 1 h after dosing (po). [e] Rotorod (mouse)[9] = rotating rod; 1 h after dosing (po).

Table II. Effects of **2a** on Maximal Electroshock Seizures in the Rat and Mouse and Maximal Metrazol Seizures in the Mouse Compared with Standards

	inhibn of hind limb tonus: ED_{50}, mg/kg po (t = 1 h)		
	mouse		rat,
compound	MES	MMS	MES
2a	27 (17–43)[a]	45 (17–70)	22 (11–34)
phenytoin	8 (4–12)	8 (6–11)	14 (6–23)
phenobarbital	12 (9–15)	4 (3–6)	9 (7–13)
carbamazepine	20 (17–23)	11 (2–16)	4 (2–7)
1a	18 (13–25)	27 (17–46)	16 (10–21)

[a] 95% confidence limits.

Table III. Effect of **2a** and Standards on Mouse Motor Performance in the Rotorod Test[9]

compound	TD_{50}, mg/kg (mouse),[a] at 1 h (po)
2a	384 (171–inf)[b]
phenytoin	216 (154–319)
phenobarbital	68 (52–92)
carbamazepine	166 (104–282)
1a	>1000 (800 at 2 h)

[a] Dose at which 50% of trained animals fall off the rotorod. [b] 95% confidence limits.

guanidines however with R^1 = alkyl have been isolated, albeit in low yield, by using a different approach (see below).

Attempts to prepare the cyclic guanidines (aminoimidazolines) **2g–i** via cyanamide **4** with a diamine were unsuccessful. Earlier work[3] indicated that N-substituted guanidines could be obtained from the corresponding aminothiadiazole via dithiocarbamates. This route was therefore adopted for the synthesis of derivatives **2g–i** as shown in Scheme II (method C). Competing nucleophilic displacements evidently occur during the reaction when R^1 = CH_3; compound **2h** was obtained together with ethylenethiourea (25%) and the methylamine **5**.

Results and Discussion

The compounds synthesized together with pharmacological evaluation results are summarized in Table I. The metrazol[7] and electroshock[8] tests are an assessment of the anticonvulsant activity; the rotorod test[9] was used to assess the neurotoxicity of the compounds. Only those compounds showing potent anticonvulsant activity were examined in this latter test situation. All test compounds were administered by the oral route. The parent compound **2a** was found to possess significant anticonvulsant activity. However, with the exception of the terminal methylated derivative **2b**, considerable reduction or complete loss of activity was observed with the substituted guanidines **2c–f**. Incorporation of the guanidine grouping into an imidazoline ring also produced compounds **2g–i** devoid of anticonvulsant activity.

From this guanidine series **2a** was considered to have a promising profile from the primary pharmacological program, and more detailed studies therefore were carried out. Compound **2a** was compared with some established

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anticonvulsant agents and with the lead compound **1a** from the thiadiazole hydrazine series.[1] Table II shows the ED_{50} values in the mouse maximum electroshock test (MES)[8] and maximum metrazol seizure test (MMS)[7] for **2a** as well as **1a** and some standard drugs after oral dosage; for comparison the corresponding ED_{50} values in the rat MES[8] test situation are also included. Table III shows TD_{50} values in the mouse motor impairment as observed in the rotorod test.[9] The results confirm that **2a** possesses reasonable potency as an anticonvulsant, inhibiting both electrically and chemically induced seizures, the best activity being observed in the rat MES test. Unfortunately, however, **2a** was found to be less potent in comparison to the standard drugs as well as being inferior to the lead compound, **1a**, from the related hydrazine series.[1] Although the level of neurotoxicity observed with **2a** in the rotorod test situation was at an acceptable level, the compound exhibited a considerable degree of sedative activity. In view of this neurotoxic profile, further work on this compound was discontinued.

Experimental Section

Melting points were determined in a Büchi apparatus in glass capillary tubes and are uncorrected. IR, NMR, and MS spectra were recorded on Perkin-Elmer 700, Varian Associates T-60, and LKB-2091 instruments, respectively, and were consistent with assigned structures. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values.

The chlorothiadiazole **3** was prepared following procedures already described.[1] Representative examples of the procedures used for methods B and C are given.

Method A. 2-Guanidino-5-[2-(trifluoromethyl)phenyl]-1,3,4-thiadiazole Hydrochloride (2a). A stirred mixture of sodium (4.34 g, 189 mmol) and anhydrous *t*-BuOH (250 mL) was heated at 80–90 °C under an atmosphere of nitrogen until the metal had dissolved. After cooling, guanidine hydrochloride (20.24 g, 213 mmol) was added with stirring. After 0.5 h a solution of **3** (16.5 g, 62.4 mmol) in *t*-BuOH (25 mL) was added and heating at 80–90 °C was continued for a further 24 h. Solvent was removed in vacuo and the residue was stirred with water (550 mL). The resultant solid was collected, washed with water, and dried to leave the free base of **2a** (15.94 g), which was converted to its hydrochloride salt with EtOH and ethereal HCl. Crystallization from MeOH/Et_2O gave **2a**: yield 13.2 g (65%); mp 164–165 °C. Anal. ($C_{10}H_8F_3N_5S$·HCl) C, H, N.

Method B. 2-Cyanamido-5-[2-(trifluoromethyl)-phenyl]-1,3,4-thiadiazole (4). A stirred mixture of sodium cyanamide (0.16 g, 2.5 mmol) and anhydrous DMF (3 mL) under a nitrogen atmosphere was treated with a solution of **3** (0.27 g, 1 mmol) in anhydrous DMF (2 mL). The mixture was stirred for 16 h at room temperature. Solvent was removed in vacuo and the residue was stirred with water (10 mL) during the addition of aqueous 2 N HCl until the pH was 2. Extraction with Et_2O followed by drying of the extracts and evaporation gave cyanamide **4**: yield 0.22 g (82%); MS, 270 (M^+) ($C_{10}H_5F_3N_4S$ requires M^+ 270). The product was used directly, without further purification, to prepare guanidines **2b–f**.

2-(3-Methylguanidino)-5-[2-(trifluoromethyl)phenyl]-1,3,4-thiadiazole (2b). A solution of **4** (3 g, 11.1 mmol) in methylamine (42 mL of 40% aqueous solution) was heated for 16 h at 110 °C in a sealed tube. On cooling, the contents were stirred with Et_2O (450 mL) to dissolve most of the solid that had precipitated. Any undissolved solid was removed by filtration. The organic layer was evaporated to dryness to leave 1.7 g of a solid, which was purified by chromatography on grade III alumina eluting with $CHCl_3$ to give pure **2b**: yield 1.02 g (30%); mp 160–162 °C. Anal. ($C_{11}H_{10}F_3N_5S$) C, H, N.

2-[3-[3-(Dimethylamino)-1-propyl]guanidino]-5-[2-(trifluoromethyl)phenyl]-1,3,4-thiadiazole (2e). A solution of **4** (2.22 g, 8.2 mmol) and 3-(dimethylamino)-1-propylamine (1.06 g, 10.4 mmol) in *n*-BuOH (10 mL) was heated with stirring at 110–120 °C for 16 h. The solvent was removed in vacuo and Et_2O was added. The precipitated solid was collected by filtration to give 2.37 g of impure product. Recrystallization from benzene/cyclohexane gave **2e**: yield 1.97 g (64%); mp 110–112 °C. Anal. ($C_{15}H_{19}F_3N_6S$) H, N; C: calcd, 48.38; found, 48.97.

The following compounds were also prepared by the method described above for **2e**: **2c** (66%), **2d** (25%), and **2f** (39%). **2f**: Anal. ($C_{12}H_{10}F_3N_5S$) H, N; C: calcd, 46.79; found, 47.31.

Attempt To Prepare Guanidines Substituted on the Nitrogen Atom Adjacent to the Thiadiazole Ring (R^1, Structure 2). 2-(Methylamino)-5-[2-(trifluoromethyl)phenyl]-1,3,4-thiadiazole (5). A mixture of **3** (4 g, 15.1 mmol), aqueous methylamine (16 mL of a 40% aqueous solution), dioxane (25 mL) was stirred at room temperature for 18 h. After removal of solvent in vacuo, the residue was treated with aqueous NH_3 solution and extracted with Et_2O. Drying and evaporation of the extracts gave **5**: yield 3.4 g (87%); mp 108–110 °C; MS, 259 (M^+) ($C_{10}H_8F_3N_3S$ requires M^+ 259).

3-Cyano-2,3-dihydro-2-(methylimino)-5-[2-(trifluoromethyl)phenyl]-1,3,4-thiadiazole (6). A mixture of **5** (4.67 g, 18 mmol), cyanogen bromide (3.25 g, 30.7 mmol), and sodium bicarbonate (3.33 g, 39.6 mmol) in $CHCl_3$ (60 mL) was heated under reflux with stirring for 4 h. Solvent and excess cyanogen bromide were removed by distillation, and the residue was partitioned between water and $CHCl_3$. The organic phase was dried and evaporated to give a solid (5.2 g), which was recrystallized from cyclohexane to afford **6**: yield 3.15 g (62%); mp 70–74 °C; MS, 284 (M^+), 211 ($M^+ - SCNCH_3$). Anal. ($C_{11}H_7F_3N_4S$) C, H; N: calcd, 19.71; found, 19.24.

2-(Methylcyanamido)-5-[2-(trifluoromethyl)phenyl]-1,3,4-thiadiazole (7). A sample of **6** (4.88 g, 17.2 mmol) was heated at 150–160 °C for 18 h. The resulting material was purified by chromatography using silica and eluting with $CHCl_3$ to give **7**: yield 1.8 g (37%); mp 59–60 °C; MS, 284 (M^+), 229 ($M^+ - CH_3NCN$). Anal. ($C_{11}H_7F_3N_4S$) C, H, N.

Reaction of Methylcyanamide 7 with Ammonia. This reaction was carried out by using the procedure described for the preparation of **2b**, and the product isolated was the 5-(methylamino)thiadiazole **5** identical with the sample of this amine already described.

Method C. Methyl *N*-[5-[2-(Trifluoromethyl)phenyl]-1,3,4-thiadiazol-2-yl]dithiocarbamate (9, R^1 = H). A stirred solution of aminothiadiazole **8** (R^1 = H) (6.2 g, 25.1 mmol) in anhydrous DMF (25 mL) was treated with sodium methoxide (1.43 g, 26.5 mmol) and carbon disulfide (2 mL, 32.9 mmol). After 5 days at room temperature, water (450 mL) was added and the mixture filtered to remove the solid (1.1 g). To the filtrate (pH 7) were added more water (50 mL) and methyl iodide (4.07 g, 28.7 mmol). After 3 h of stirring, the solid was collected, washed with water, and dried to leave the impure product (5.5 g). Crystallization from benzene gave the dithiocarbamate ester **9** (R^1 = H): yield 4.5 g (54%); mp 185–186 °C; MS, 335 (M^+) ($C_{11}H_8F_3N_3S_3$ requires M^+ 335).

The *N*-methyldithiocarbamate ester **9** (R^1 = CH_3) was prepared from **5** by using the same procedure as described above for the preparation of **9** (R^1 = H); mp 136 °C; MS, 349 (M^+) ($C_{12}H_{10}F_3N_3S_3$ requires M^+ 349).

2-(2-Imidazolinylamino)-5-[2-(trifluoromethyl)phenyl]-1,3,4-thiadiazole (2g). A mixture of the carbamate ester **9** (R^1 = H) (2.91 g, 8.7 mmol) and ethylenediamine (0.53 g, 8.8 mmol) in *n*-BuOH (20 mL) was stirred and heated under reflux for 16 h (solid dissolved slowly). On cooling the precipitated solid was collected and washed with a minimum amount of *n*-BuOH (5 mL) to leave 1.82 g of impure product. Recrystallization from EtOH gave **2g**: yield 1.48 g (54%); mp 229–230 °C. Anal. ($C_{12}H_{10}F_3N_5S$) C, H, N.

During the corresponding reaction between **9** (R^1 = H) and 1,2-diamino-2-methylpropane, the mixture (after 18 h reflux) was filtered hot to remove a solid. Washing of the solid with EtOH and Et_2O gave a small amount of 1-(2-amino-2-methylpropyl)-2-[5-[2-(trifluoromethyl)phenyl]-1,3,4-thiadiazol-2-yl]thiourea (an intermediate to the required imidazoline): mp 217–218 °C; MS, 375 (M^+). Anal. ($C_{14}H_{16}F_3N_5S_2$) C, H, N. The imidazoline **2i** was obtained in 25% yield.

N-Methylimidazoline **2h** was obtained in 50% yield. Two other products were also isolated and identified (by melting points, MS, IR, and TLC) as ethylenethiourea (25% yield) and methylamine **5**.

Pharmacology. The evaluation of compounds was carried out by using procedures described in part 1 of this series.[1]

Acknowledgment. We thank Colin Edwards and Colin Howes for their assistance in the synthetic work, members of the Pharmacology Department for their assistance, and Ginette Gray for typing the manuscript.

Registry No. **2a**, 107114-98-7; **2a**·HCl, 107114-83-0; **2b**, 107114-84-1; **2c**, 107114-99-8; **2c**·HCl, 107114-85-2; **2d**, 107114-86-3; **2e**, 107114-87-4; **2f**, 107114-88-5; **2g**, 107114-89-6; **2h**, 107114-90-9; **2i**, 107114-91-0; **3**, 107115-00-4; **4**, 107114-92-1; **5**, 107114-93-2; **6**, 107114-94-3; **7**, 107114-95-4; 8 (R^1 = H), 10445-00-8; **9** (R^1 = H), 107114-96-5; **9** (R^1 = CH_3), 107114-97-6; NH_2CN-Na, 17292-62-5; CH_3NH_2, 74-89-5; $(Me)_2N(CH_2)_3NH_2$, 109-55-7; $BuNH_2$, 109-73-9; $PhCH_2NH_2$, 100-46-9; $MeO(CH_2)_3NH_2$, 5332-73-0; cyanogen bromide, 506-68-3; ethylenediamine, 107-15-3; 1,2-diamino-2-methylpropane, 811-93-8; 1-(2-amino-2-methylpropyl)-2-[5-[2-(trifluoromethyl)phenyl]-1,3,4-thiadiazol-2-yl]-thiourea, 107115-01-5; guanidine hydrochloride, 50-01-1.

N^6-Phenyladenosines: Pronounced Effect of Phenyl Substituents on Affinity for A_2 Adenosine Receptors

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A number of N^6-phenyladenosines with various substitutions on the phenyl ring have been synthesized and tested for their affinities toward brain A_1 and A_2 adenosine receptors. Compounds with meta substituents, such as (*m*-hydroxy- and *m*-iodophenyl)adenosine, were found to have high A_1 selectivity. Meta substitution caused a selective decrease in the affinity of these compounds for A_2 receptors. The results suggest that, in contrast to what is commonly held, certain N^6-substituents have pronounced effects on affinity for brain A_2 adenosine receptors. Thus, brain A_2 receptors may have a well-defined region that recognizes N^6-substitutions.

Adenosine causes a number of physiological effects that are mediated by specific adenosine receptors termed A_1 (or R_i) and A_2 (or R_a) receptors.[1] In many cells, including neuronal cells, the activation of A_1 receptors causes the inhibition of adenylate cyclase activitiy, while the activation of A_2 receptors causes an increase in adenylate cyclase activity.[1-3] The two types of receptors differ in their selectivity toward various adenosine analogues (see Chart I for structures). For example, the potencies of N^6-(phenylisopropyl)adenosine (PIA) and cyclohexyladenosine (CHA) to inhibit adenylate cyclase (via A_1 receptors) are greater than that of 5′-(*N*-ethylcarbamoyl)adenosine (NECA), while the potency of NECA to stimulate adenylate cyclase (via A_2 receptors) is greater than that of PIA and CHA.[1-3]. The same A_2/A_1 selectivity is seen in ligand-binding assays conducted with PIA and CHA, although under these conditions NECA exhibits nearly equal affinity for A_1 and A_2 receptors[2-4] (and see Table I). These and other results have led to the hypothesis that A_1 receptors have a specialized region that interacts with the N^6 domain of the adenosine molecule, while A_2 receptors have a specific domain that interacts with 5′-substituents on the ribose ring.[5-7,16] However, both A_1 and A_2 receptors show selectivity for the two stereoisomers of PIA. While the stereoselectivity at A_1 receptors is greater than that at A_2 receptors,[2-4] the fact that A_2 receptors can discriminate between the *R* and *S* enantiomers of PIA suggests that the A_2 receptors also have specialized regions to interact with the N^6 domain. Recent studies have shown that apparent A_2 receptors in coronary artery recognize N^6-substitutions.[5-7] On the basis of these results, it was concluded that the coronary artery adenosine receptor might be a "hybrid" A_1/A_2 receptor.[5]

N^6-Phenyladenosine (Chart I) is a potent A_1 agonist with a moderate A_2/A_1 selectivity (Table II).[1] In this paper, we report on the synthesis of a number of phenyl-substituted analogues of this compound and their affinities for A_1 and A_2 receptors in brain preparations. Meta, but not para, substitution led to selective decreases in the affinities of these compounds for A_2 receptors. The results suggest that brain A_2 receptors, like those in coronary artery,[5-7] have a well-defined region to interact with the

Table I. Physical–Chemical Characteristics of Various N^6-Phenyladenosines

no.	phenyl substit	mp,[a] °C	(formula) anal.
1	H	199[b]	
2	*m*-OH	256–257	($C_{16}H_{17}N_5O_5$) C, H, N; C[c]
3	*m*-I	205–206	($C_{16}H_{16}N_5O_4I$) C, H, N; N[d]
4	*m*-C_2H_5	192–194	($C_{18}H_{21}N_5O_4$) C, H, N
5	*m*-NH_2	202–204	($C_{16}H_{18}N_6O_4$) C, H, N
6	*m*-$B(OH)_2$	280	($C_{16}H_{18}N_5O_6B$) C, H, N
7	*m*-F	207-208	($C_{16}H_{16}N_5O_4F$) C, H, N
8	*p*-F	231–232	($C_{16}H_{16}N_5O_4F$) C, H, N
9	*p*-I	220–221	($C_{16}H_{16}N_5O_4I$) C, H, N, I; N[e]
10	*p*-CH_3	214–216	($C_{17}H_{19}N_5O_4$) C, H, N; C[f]
11	*p*-C_2H_5	194–196	($C_{18}H_{21}N_5O_4$) C, H, N
12	*p*-OCH_3	207-208	($C_{17}H_{19}N_5O_5$) C, H, N

[a] Uncorrected. [b] Reference 8. [c] C: calcd, 53.48; found, 53.00. [d] N: calcd, 14.92; found, 14.04. [e] N: calcd, 14.92; found, 14.34. [f] C: calcd, 57.14; found, 56.68.

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