2-Aralkynyl and 2-Heteroalkynyl Derivatives of Adenosine-5′-*N*-ethyluronamide as Selective A_{2a} Adenosine Receptor Agonists

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A series of new 2-aralkynyl and 2-heteroaralkynyl derivatives of NECA were synthesized and studied in binding and functional assays to assess their potency for the A_{2a} compared to A_1 adenosine receptors. Compounds bearing an aromatic or heteroaromatic ring, conjugated to the triple bond, showed generally weaker activity at the A_{2a} receptor and lower selectivity (A_{2a} vs A_1) than the alkylalkynyl derivatives previously reported. However, the (4-formylphenyl)-ethynyl derivative **17** showed affinity in the low nanomolar range and high selectivity (about 160-fold) for the A_{2a} receptor. The presence of heteroatoms improved vasorelaxant activity, the 2-thiazolylethynyl derivative **30** being the most potent in the series. Introduction of methylene groups between the triple bond and the phenyl ring favored the A_{2a} binding affinity, and the 5-phenyl-1-pentynyl derivative **24** was found to be highly potent and selective (about 180-fold) at A_{2a} receptors. With regard to antiplatelet activity, the presence of aromatic or heteroaromatic rings decreased potency in comparison with that of NECA and of *N*-ethyl-1′-deoxy-1′-(6-amino-2-hexynyl-9*H*-purin-9-yl)-β-D-ribofuranuronamide (HENECA). Introduction of a methylene group was effective in increasing antiaggregatory potency only when this group is linked to a heteroatom (**31**–**35**). From these data and those previously reported, the structure–activity relationships derived for the 2-alkynyl-substituted ribose uronamides would indicate that potentiation of A_{2a} receptor affinity could be obtained by aromatic rings not conjugated with the triple bond or by heteroaromatic groups. As for A_{2a} receptors on platelets, the presence of aromatic rings, either conjugated or unconjugated to the triple bond, is detrimental for the antiaggregatory activity. However, the introduction of polar groups α to the triple bond strongly increases the potency when steric hindrance is avoided. Some of the compounds included in this series retain interesting vasodilating properties and merit further investigation for their potential in the treatment of cardiovascular disorders.

There is evidence that the purine nucleoside adenosine specifically modulates neurotransmission through the interaction with four cell surface receptors recently classified as A_1, A_{2a}, A_{2b}, and A_3.[1] These receptor types have been cloned and characterized as belonging to the superfamily of receptors with seven transmembrane helices that couple to G proteins.[2] Despite the data available from molecular biology and biochemical studies, the functional role of the A_{2b} and A_3 has not been clarified as yet. Conversely, the results of many studies indicate that adenosine acting through the A_{2a} receptors elicits a variety of physiological responses, including vasodilation,[3] inhibition of platelet aggregation,[4] and depression of central nervous system activity.[5]

Over the last few years there has been a considerable effort directed toward both characterization of the A_{2a} receptor and discovery of potent and selective agonists and antagonists.[6] A major advance in the search of A_{2a} adenosine agonists has been made with the introduction of C-2 substituents in the adenosine structure.[7] Selectivity and potency of the C-2 substituted adenosine analogs are greatly improved by replacing the 5′-hydroxyl group with other substituents, in particular the *N*-ethylcarboxamide group. For example, 2-[[4-(carboxyethyl)phenethyl]amino]adenosine-5′-*N*-ethylcarboxamide, CGS 21680, is a selective A_{2a} agonist which is widely used as a reference compound in biochemical and pharmacological studies.[7] More recently, the introduction of the 2-hexynyl group in the 5′-(*N*-ethylcarboxamido)adenosine (NECA) structure has been found to confer interesting pharmacological properties.[4b,8] HENECA, in addition to having good A_{2a} selectivity similar to that of CGS 21680, shows higher inhibitory activity on platelet aggregation,[9] a property of pharmacological interest considering the potential of these drugs for treatment of cardiovascular diseases, such as cardiac ischemia.[10] These data prompted us to perform the synthesis of a series of compounds bearing aliphatic alkynes, in which the C≡C bond was attached directly to the C-2 position of the adenine base. The pharmacological results, which are described in a previous report,[11] indicate that the 2-alkynyl-NECA derivatives are selective A_{2a} agonists possessing an interesting profile ranging from marked inhibitory actions on platelet aggregation to potent vasodilating properties. In the attempt to understand whether other substitutions on the C-2 acetylene group could modify the properties of such A_{2a} agonists, a series of compounds having aromatic and heteroaromatic groups directly attached to the triple bond or spaced by methylene group(s) were synthesized and tested in the biochemical and functional assays as previously reported.[12]

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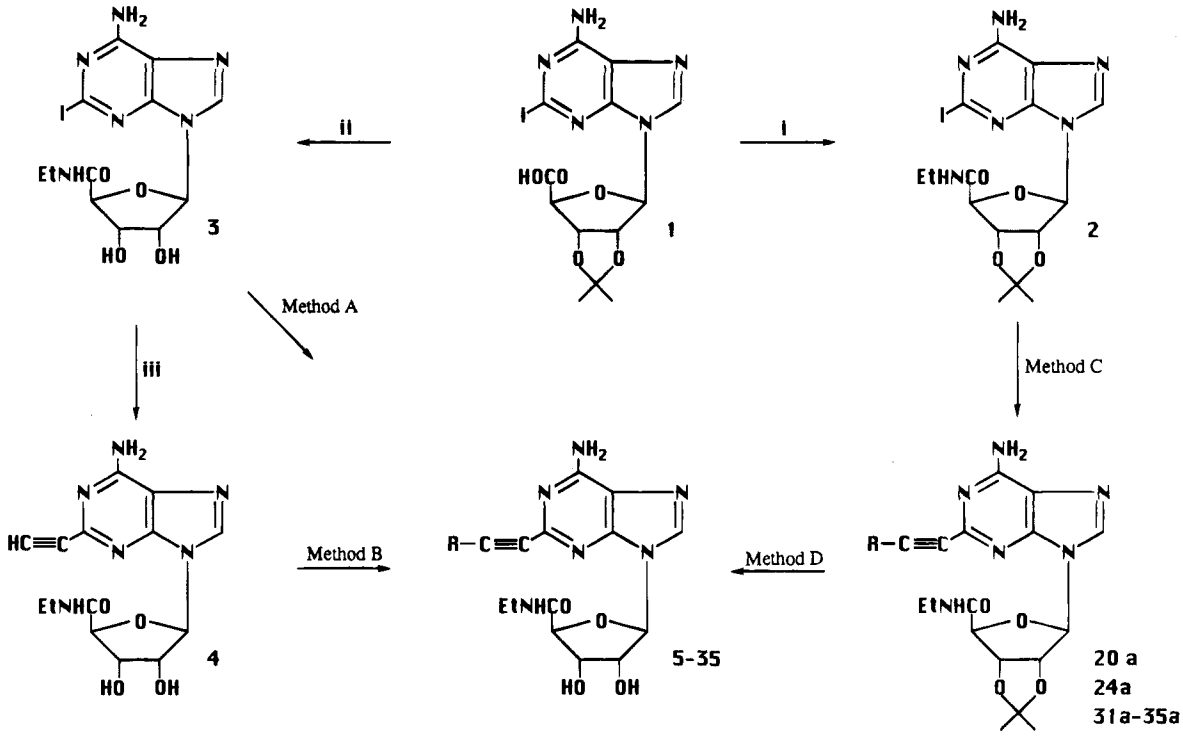
Scheme 1[a]



[a] Reagents: (i) $SOCl_2$, $EtHN_2$; (ii) (1) $SOCl_2$, EtOH, (2) $EtNH_2$; (iii) (1) (trimethylsilyl)acetylene, (2) KOH.

Chemistry

The synthesis of 2-aralkynyl and heteroaralkynyl derivatives of adenosine-5′-*N*-ethyluronamide **5**–**35** was accomplished by three general methods. As illustrated in Scheme 1, the appropriate terminal alkyne was added to a solution of *N*-ethyl-1′-deoxy-1′-(6-amino-2-iodo-9*H*-purin-9-yl)-β-D-ribofuranuronamide (**3**)[8] in dry acetonitrile, DMF, and triethylamine with cuprous iodide, $PdCl_2$, and triphenylphosphine as catalysts to provide compounds **5**–**7**, **10**, **13**–**15**, **17**–**19**, **21**–**23**, **25**, and **26** (method A). The terminal alkynes were commercially available or were synthesized following the procedure reported by Takahashi et al.[12]

As the synthesis of the selected terminal alkyne can be complicated by polymerization, for compounds **8**, **9**, **11**, **12**, **16**, and **27**–**30** an alternative method was used involving reaction of *N*-ethyl-1′-deoxy-1′-(6-amino-2-ethynyl-9*H*-purin-9-yl)-β-D-ribofuranuronamide (**4**)[11] with the suitable aromatic or heteroaromatic halide under the palladium-catalyzed cross-coupling reaction conditions (method B).

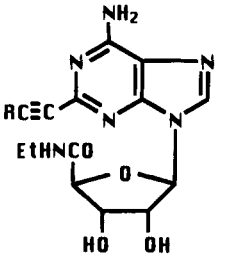
The third procedure was used to overcome separation problems, in the case of compounds **31**–**35**, or to avoid cross-reaction with the 2′- and 3′-hydroxyl groups, in the case of compounds **20** and **24**. The starting material of method C was *N*-ethyl-1′-deoxy-1′-(6-amino-2-iodo-9*H*-purin-9-yl)-2′,3′-*O*-isopropylidene-β-D-ribofuranuronamide (**2**), synthesized by reacting 1′-deoxy-1′-(6-amino-2-iodo-9*H*-purin-9-yl)-2′,3′-*O*-isopropylidene-β-D-ribofuranuronic acid (**1**)[12] with thionyl chloride at 50 °C for 2 h and then with ethylamine at −20 °C for 1 h. Compound **2** was coupled with the commercially available 5-phenyl-1-pentyne to give the derivative **24a** or with the terminal alkynes reported in Scheme 2 However or described elsewhere[13,14] to give compounds **20a** and **31a**–**35a**. Deprotection of the isopropylidene derivatives was carried out in 50% formic acid at 60 °C for 2 h, according to the general method D to give compounds **20**, **24**, and **31**–**35**.

The synthesis of *tert*-butyl 3-(4-ethynylphenyl)acrylate (**39**) was carried out starting from *p*-iodoaniline (**36**) and *tert*-butyl acrylate to give compound **37** by palladium-catalyzed cross-coupling reaction (Scheme 2). A deamination–halogenation procedure yielded *tert*-butyl 4-iodocinnamate (**38**), which was coupled to (trimethylsilyl)acetylene and then treated with 1 N KOH to give the desired compound **39**. *tert*-Butyl 4-aminocinnamate (**37**) was used as starting material for the synthesis of *tert*-butyl 3-(4-ethynylphenyl)propionate (**42**). Reduction of **37** with 10% Pd/C gave compound **40**, which was converted to the iodo derivative **41** by a deamination–halogenation procedure with isopentyl nitrite and methylene iodide. The palladium-catalyzed cross-coupling reaction of **41** with (trimethylsilyl)acetylene, followed by desilylation, gave compound **42** (Scheme 2). 1-(2-Propynyl)thiomorpholine (**44**) was obtained by reaction of the sodium salt of thiomorpholine with propargyl bromide in THF. Purification of the reaction mixture by flash chromatography gave compound **44** in high yield.

Receptor Binding Studies. Affinity of the new 2-aralkynyl and heteroalkynyl derivatives of NECA, **5**–**35**, at adenosine receptors were evaluated using radioligand binding technique. Competition assays for A_1 and A_{2a} receptors were determined in rat brain membranes using [^{3}H]CHA[15] and [^{3}H]CGS 21680[7b] as radioligands, respectively. NECA, HENECA,[11] and CCPA[4a] were used as reference compounds. The results are reported in Table 1.

Compounds **5**–**21** present an aromatic ring conjugated with the triple bond. Substitution of the acetylenic hydrogen atom of **4**, an adenosine receptor agonist substantially unselective,[11] with an aromatic ring led to a variety of A_2-selective derivatives. Selectivity might

Table I. *In vitro* Pharmacological Activity of 2-Alkynyl Derivatives of NECA



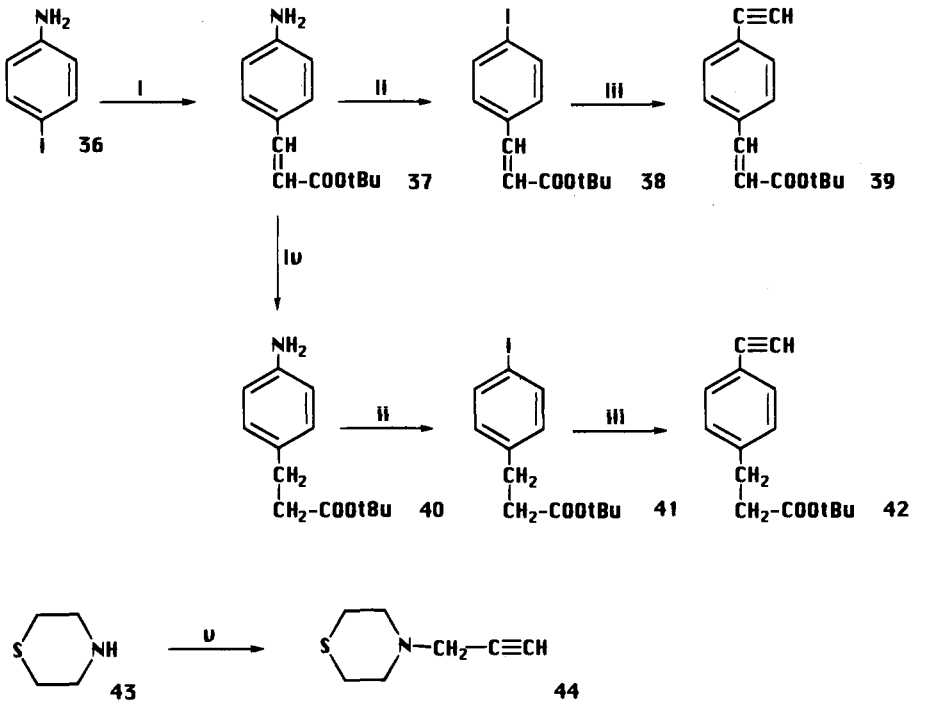
compound	R	binding assay[a] K_i (nM) rat brain (A_1)	rat striatum (A_{2a})	selectivity (A_1/A_{2a})	functional activity[b] EC_{50} (nM) rat atria (A_1)	rat aorta (A_{2a})	antiaggr activity:[c] potency ratio vs NECA for rabbit platelet A_{2a}	k' ⊥
HENECA	$(CH_2)_3CH_3$	130 (116–145)	2.2 (1.9-2.6)	59.1	>10 μM	596 (244–1460)	3.00	2.57
CGS 21680		569 (511–634)	11.0 (9.4–12.9)	51.7	>10 μM	115 (53–251)	0.1	0.24
NECA		10.4 (9.4–11.6)	7.8 (6.6–9.1)	1.3	54.8 (34.8–78.2)	394 (209–742)	1.00	0.19
CCPA		1.3 (1.1–1.4)	650 (555–762)	0.002	8.2 (4.4–15.3)	>10μM	0.003	2.76
4	H	35.4 (21.9–57.2)	57.8 (48.9–68.3)	0.6	167 (116–240)	440 (242–797)	0.300	0.25
5	Ph	698 (611–798)	120 (112–128)	5.8	>10 μM	1500 (920–2450)	0.010	2.04
6	*p*-$PhCH_3$	500 (421–594)	36.3 (30.7–42.8)	13.8	8530 (1890–35800)	3290 (746–14500)	0.013	3.59
7	*p*-$PhCH_2CN$	1603 (1522–1690)	54.8 (49.0–61.4)	29.3	>10 μM	6520 (2090–20400)	0.032	0.76
8	*p*-$PhOCH_3$	414 (404–425)	52.4 (34.2–80.4)	7.9	>10 μM	3480 (2380–51000)	0.004	2.15
9	*p*-PhOH	497 (412–599)	20.6 (18.6–22.7)	24.1	>10 μM	660 (65.8–6620)	0.006	0.66
10	*p*-$PhNH_2$	599 (522–687)	113 (104–123)	5.3	>10 μM	4070 (256–6480)	0.007	0.46
11	*p*-$PhCF_3$	2432 (2308–2563)	315 (173–575)	7.7	nd	2990 (33.7–26500)	0.01	5.79
12	*p*-PhF	3312 (3078–3563)	81.4 (63.5–104)	40.7	>10 μM	>10 μM	0.009	2.33
13	*p*-$PhCONH_2$	7498 (6752–8325)	1500 (1411–1596)	5.0	>10 μM	6420 (2090–19800)	0.003	0.32
14	*p*-$PhCOCH_3$	>10 μM	187 (165–213)	>53.5	>10 μM	1670 (109–25600)	0.019	1.18
15	*o*-PhCHO	6864 (6489–7261)	1158 (883–1518)	5.9	>10 μM	1300 (944–1780)	0.006	1.14
16	*m*-PhCHO	1435 (1127–1826)	176 (139–221)	8.2	>10 μM	3570 (811–15700)	0.004	1.06
17	*p*-PhCHO	1000 (911–1097)	6.3 (5.8–6.9)	158.7	>10 μM	110 (35.3–342)	0.110	1.02
18	*p*-$PhNO_2$	900 (815–993)	21.5 (21.2–29.7)	41.9	>10 μM	1210 (902–1620)	0.014	1.82
19	*p*-$Ph(CH)_2COOtBu$	>10 μM	743 (698–792)	>13.5	>10 μM	1350 (591–3080)	0.009	2.28
20	*p*-$Ph(CH_2)_2COOH$	>10 00	>1000	>10 μM	>10 μM	0.008	0.27	
21	1-naphthyl	4463 (4077–4885)	488 (448–530)	9.1	>10 μM	468 (73.8–2970)	0.003	5.49
22	CH_2Ph	27.4 (25.8–29.1)	1.6 (1.5–1.7)	17.1	164 (91–296)	406 (164–1010)	0.01	2.40
23	$(CH_2)_2Ph$	448 (373–537)	7.0 (4.4–11.1)	64	>10 μM	210 (63.4–731)	0.19	3.16
24	$(CH_2)_3Ph$	209 (194–226)	1.2 (1.1–1.4)	174.2	6480 (2490–9800)	497 (265–931)	0.35	5.82
25	2-pyridyl	114 (100–131)	89.8 (79.7–101)	1.3	840 (616–1150)	243 (129–458)	0.01	0.49
26	3-pyridyl	139 (116–167)	234 (175–311)	0.6	415 (219–787)	491 (257–936)	0.06	0.51
27	4-pyridyl	428 (372–492)	87 (67–113)	4.9	>10 μM	>10 μM	0.11	0.57
28	2-furyl	310 (267–359)	130 (118–144)	2.4	>10 μM	>10 μM	0.01	1.06
29	2-thienyl	597 (536–665)	19.5 (17.5–21.7)	30.6	>10 μM	227 (41.2–1250)	0.023	1.63
30	2-thiazolyl	85.4 (80.3–90.9)	41.3 (37.2–45.8)	2.1	7160 (1150–33100)	28.7 (14.7–56.1)	0.44	0.55
31	CH_2-N-imidazolyl	178 (166–191)	16.5 (9.1–29.8)	10.8	3140 (1530–6440)	753 (411–1380)	3.5	0.22
32	CH_2-N-piperidyl	27.5 (22.2–34.1)	4.3 (3.2–5.8)	6.4	322 (189–550)	302 (136–671)	4.7	1.11

Table I (Continued)

compound	R	binding assay[a] K_i (nM) rat brain (A_1)	rat striatum (A_{2a})	selectivity (A_1/A_{2a})	functional activity[b] EC_{50} (nM) rat atria (A_1)	rat aorta (A_{2a})	antiaggr activity:[c] potency ratio vs NECA for rabbit platelet A_{2a}	k' [d]
33	CH_2-*N*-piperazinyl-4-methyl	35.9 (32.3–40.0)	19.1 (15.4–23.7)	1.9	877 (666–1160)	408 (232–715)	nd	0.42
34	CH_2-*N*-morpholinyl	90.5 (77.7–105)	27.4 (15.5–48.2)	3.3	358 (265–484)	531 (194–1460)	2.6	0.28
35	CH_2-*N*-thiomorpholinyl	52.8 (44.1–63.3)	5.9 (4.4–7.9)	8.9	306 (174–538)	223 (164–303)	2.9	0.66

[a] Receptor binding affinity at A_1 and A_2 receptors was determined using [^{3}H]CHA and [^{3}H]CGS 21680 as radioligands, respectively. Data are geometrical means from at least three separate experiments; 95% confidence limits in parentheses. [b] Data are means from at least three separate experiments; 95% confidence limits in parentheses. [c] The potency ratio was calculated using the concentration of the test compound close to the IC_{50} value. In our experimental conditions the IC_{50} value for NECA was 0.2 μM. [d] Hydrophobicity index. Data are means from three separate experiments.

Scheme 2[a]



[a] Reagents: (i) *tert*-butyl acrylate; (ii) $S_5H_{11}ONO$, CH_2I_2; (iii) (1) (trimethylsilyl)acetylene, (2) KOH; (iv) H_2/Pd; (v) propargyl bromide.

be due to the fact that the C-2 binding region of the A_1 adenosine receptor, which easily accommodates α-hydroxyalkynyl groups,[11] is less tolerant toward conjugated aromatic rings. The introduction of an unsubstituted phenyl ring (**5**) produced a decrease in the affinity for both receptors with respect to compound **4**. The affinity was even more reduced by introducing the bulkier and more lipophilic naphthyl ring (**21**). Para substitution of the phenyl ring produced compounds with a wide variation in affinity and selectivity. The most interesting compound was the *p*-formyl derivative **17**, which showed low nanomolar binding affinity at A_{2a} receptor coupled with a 160-fold selectivity. Moving the formyl group from the para to the meta (**16**) and ortho (**15**) position markedly decreased both A_2 affinity and selectivity.

Introduction of methylene groups between the phenyl ring and the acetylenic bond (**22**–**24**) produced an increase in the A_{2a} affinity leading to a potent and selective compound in the series: the *N*-ethyl-1′-deoxy-1′-[6-amino-2-(5-phenyl-1-pentyn-1-yl)-9*H*-purin-9-yl]-β-D-ribofuranuronamide (**24**), bearing three methylene groups, showed a K_i = 1.2 nM and a 175-fold A_2 selectivity.

Replacing the phenyl ring by pyridyl (**25**–**27**) and 2-thiazolyl (**30**) produced rather nonselective compounds with slightly increased A_1 affinity. However, replacing of the phenyl ring by 2-thienyl (**29**) brought about an improvement both in A_{2a} affinity and selectivity.

Introduction of a methylene group between the acetylenic bond and heterocyclic rings (**31**–**35**) decreased binding affinity at both sites with low A_2 selectivity.

Functional Studies on Isolated Preparations. Negative chronotropic activity (A_1) in spontaneously beating rat atria, vasodilation (A_{2a}) in rat aorta, and antiaggregatory effect in rabbit platelets were tested according to methods described elsewhere.[9,11] Results are summarized in Table 1.

Compounds **5**–**21**, which present an aromatic ring conjugated with the triple bond, showed in general weaker vasorelaxant activity than NECA and little or no effect on heart rate. However, the *p*-formyl derivative **17** has high A_{2a} binding affinity and selectivity and

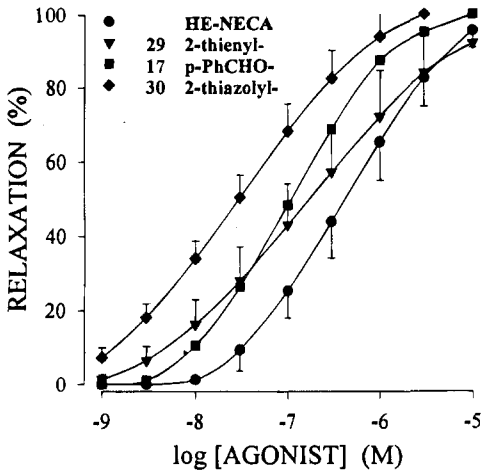


Figure 1. Mean dose–response curves for the vasorelaxant activity induced by HENECA and selected A_{2a} adenosine agonists (**17**, **29**, and **30**) in isolated rat aorta. Each response is expressed as the percentage of the maximum contraction induced by PGF2α (3 μM). Vertical bars represent 95% confidence limits.

vasodilating activity higher than HENECA, as reported in Figure 1. A change from para to ortho (**15**) and meta (**16**) substitution led to compounds with higher EC_{50} values in rat aorta. Replacement of the phenyl by heteroaromatic rings resulted in compounds with different pharmacological profiles. The presence of 4-pyridyl (**27**) or 2-furyl (**28**) was detrimental for the vasorelaxant activity, and the introduction of 2- (**25**) or 3-pyridyl (**26**) led to active but nonselective compounds. The presence of 2-thienyl group (**29**) increased the separation between the responses mediated by A_{2a} versus A_1 receptors as compared with the 2-pyridyl derivative **25**. However, the introduction of a 2-thiazolyl group (**30**) led to a compound with marked vasodilating activity among all the 2-alkynyl derivatives synthesized[11] (Figure 1).

Introduction of a methylene group between the acetylenic bond and the heterocyclic rings (**31**–**35**) led to derivatives with low selectivity. On the other hand, the lack of conjugation between the triple bond and the phenyl ring (**22**–**24**) increased vasorelaxant activity with less effect on heart rate.

The antiaggregatory effect of the new alkynyl derivatives of NECA on rabbit platelet aggregation induced by ADP is reported in Table 1 as the potency ratio calculated versus NECA. All the compounds which presented a ring conjugated to the triple bond showed an antiaggregatory activity lower than NECA, indicating that the introduction of C-2 aralkynyl substituents was not favorable for the interaction of these compounds with the platelet adenosine receptor. On the other hand, also spacing the phenyl ring by methylene groups resulted in compounds less potent than NECA (**22**–**24**). Conversely, the introduction of a methylene group between the acetylenic bond and heterocyclic rings (**31**–**35**) improved the antiaggregatory activity, the *N*-piperidyl derivative **32** being 5-fold more potent than NECA.

It is worth comparing compound **22** with the corresponding α-hydroxyl derivative, previously reported by Cristalli et al.[11] Their potency ratios vs NECA are 0.01 and 15.7, respectively, indicating that the presence of the hydroxyl group on the α-methylene is critical for the interaction with the adenosine platelet receptor.

Retention of nucleosides on a reverse-phase HPLC column is reported as a measure of the relative hydrophobicity[16] (*k'*, Table 1)., the hydrophobicity index of the new nucleosides barely correlated with the data obtained in both binding and functional studies.

Conclusions

We have reported a number of 2-aralalkynyl and heteroaralkynyl derivatives of NECA endowed with varying degrees of affinity and different selectivity at A_{2a} receptors in both binding assay and functional *in vitro* models. Specifically, compounds having an aromatic or heteroaromatic ring, conjugated to the triple bond, showed generally weaker activity and lower selectivity than the alkylalkynyl derivatives previously reported.[11] However, the presence of heteroatoms improved the vasorelaxant activity, the thiazolyl derivative **30** being the most potent in the series (Figure 1). Introduction of methylene groups between the triple bond and the phenyl ring markedly increased the A_{2a} binding affinity, resulting in about a 180-fold A_{2a}-selective compound (**24**). With regard to the antiaggregatory property, the presence of aromatic or heteroaromatic rings decreased the potency in comparison with that of NECA and HENECA. However, introduction of a methylene group is effective in increasing antiaggregatory potency at least when this group is linked to a heteroatom (**31**–**35**). From these data and those previously reported,[9,11] the structure–activity relationships derived for the 2-alkynyl-substituted ribose uronamides would indicate that selective potentiation of A_{2a} receptor affinity could be obtained by aromatic rings not conjugated to the triple bond or by heteroaromatic groups. The introduction of a polar group α to the triple bond increased affinity for both A_1 and A_{2a} receptors, indicating the presence of a polar subregion in both subtypes. However, this polar region is not critical for A_{2a} affinity, hence the possibility of obtaining selective A_2 agonists.

As for the platelet adenosine receptor, the presence of aromatic rings, conjugated or unconjugated to the triple bond, is detrimental for the antiaggregatory activity. However, the introduction of polar groups in α to the triple bond markedly increases the potency when steric hindrance is avoided, indicating that this polar subregion in platelets is not able to accommodate even additional methyl groups.

From this systematic investigation of the C-2 alkynyl derivatives of NECA, further insights into the SAR for A_{2a} adenosine receptor site have been gained and some compounds possessing interesting vasodilating properties have been identified. Additional *in vivo* studies are needed in order to evaluate the pharmacological profile and therapeutic potential for the treatment of cardiovascular diseases.

Experimental Section

Chemistry. Melting points were determined with a Buchi apparatus and are uncorrected. ^1H NMR spectra were obtained with a Varian VX 300 MHz spectrometer. TLC were carried out on precoated TLC plates with silica gel 60 F-254 (Merck). For column chromatography, silica gel 60 (Merck) was used. Microanalytical results are within 0.4% of theoretical values.

Preparation of 2-(Arylalkynyl)adenosine-5′-*N*-ethyluronamides. General Method A. To a solution of 250 mg (0.58 mmol) of *N*-ethyl-1′-deoxy-1′-(6-amino-2-iodo-9*H*-purin-9-yl)-β-D-ribofuranuronamide (**3**)[8] in 10 mL of dry acetonitrile, 5 mL of DMF, and 2.5 mL of triethylamine under an atmosphere of N_2 was added 8.1 mg (0.0115 mmol) of bis(triphenylphosphine)palladium dichloride and 0.58 mg (0.003 mmol) of cuprous iodide. To the mixture was added the appropriate terminal alkyne (2.9 mmol), and the reaction mixture was stirred under an atmosphere of N_2 at room temperature for several hours. The solvent was removed *in vacuo*, and the residue was chromatographed on a silica gel column, eluting with a suitable mixture of solvents to give compounds **5**–**7**, **10**, **13**–**15**, **17**–**19**, **21**–**23**, **25**, and **26** as chromatographically pure solids.

General Method B. To a solution of 200 mg (0.66 mmol) of *N*-ethyl-1′-deoxy-1′-(6-amino-2-ethynyl-9*H*-purin-9-yl)-β-D-ribofuranuronamide (**4**)[11] in 10 mL of dry acetonitrile, 5 mL of DMF, and 2.6 mL of triethylamine under an atmosphere of N_2 was added 9.24 mg (0.013 mmol) of bis(triphenylphosphine) palladium dichloride and 0.66 mg (0.0035 mmol) of cuprous iodide. To the mixture was added the appropriate aromatic or heteroaromatic halide (3.3 mmol), and the reaction mixture was stirred under an atmosphere of N_2 for several hours. The solvent was removed *in vacuo*, and the residue was chromatographed on a silica gel column, eluting with a suitable mixture of solvents to give compounds **8**, **9**, 11, **12**, **16**, and **27**–**30** as chromatographically pure solids.

General Method C. To a solution of 300 mg (0.63 mmol) of *N*-ethyl-1′-deoxy-1′-(6-amino-2-iodo-9*H*-purin-9-yl)-2′,3′-O-isopropylidene-β-D-ribofuranuronamide (**2**) in 15 mL of dry acetonitrile and 3 mL of triethylamine under an atmosphere of N_2 was added 10 mg (0.014 mmol) of bis(triphenylphosphine)palladium dichloride and 1.2 mg (6.3 μmol) of cuprous iodide. To the mixture was added the appropriate terminal alkyne (3.15 mmol), and the reaction mixture was stirred under an atmosphere of N_2 for 24 h. The solvent was removed *in vacuo*, and the residue was chromatographed on a silica gel column, eluting with a suitable mixture of solvents to give compounds **20a**, **24a**, and **31a**–**35a** as chromatographically pure solids.

General Method D. A 0.4 mmol sample of the isopropylidene derivatives in 10 mL of 50% formic acid was heated at 60 °C for 2 h. The solvent was removed *in vacuo*, and the residue coevaporated with water and then with ethanol. Purification of the reaction mixture was obtained by chromatography to give compounds **20**, **24**, and **31**–**35** as chromatographically pure solids.

***N*-Ethyl-1′-deoxy-1′-(6-amino-2-iodo-9*H*-purin-9-yl)-2′,3′-*O*-isopropylidene-β-D-ribofuranuronamide (2).** A mixture of 0.3 g (0.67 mmol) of 1′-deoxy-1′-(6-amino-2-iodo-9*H*-purin-9-yl)-2′,3′-*O*-isopropylidene-β-D-ribofuranuronic acid (**1**),[11] 1 mL of thionyl chloride, and 25 μL of DMF was heated at 50 °C for 2 h. After concentration *in vacuo*, the residue was coevaporated with dry toluene, then suspended in 20 mL of dry methylene chloride, cooled to −20 °C, and added dropwise of 1 mL of ethylamine. The mixture was allowed to warm to room temperature, stirred for 1 h, and then quenched with water and extracted with methylene chloride. The organic layer was dried over anhydrous Na_2SO_4, and the solvent removed *in vacuo*. The residue was flash chromatographed on a silica gel column eluting with chloroform–methanol (99:1) to give compound **2** (65%) as a chromatographically pure solid: ^{1}H NMR (Me_2SO-d_6) δ 0.68 (t, 3H, NCH_2CH_3), 1.36 and 1.54 (s, 3H each, $C(CH_3)_2$), 2.84 (m, 2H, NCH_2CH_3), 4.54 (d, 1H, J = 2.0 Hz, H-4′), 5.37 (m, 2H, H-2′ and H-3′), 6.29 (s, 1H, H-1′), 7.47 (t, 1H, NH), 7.71 (s, 2H, NH_2), 8.18 (s, 1H, H-8). Anal. ($C_{15}H_{17}IN_6O_4$) C, H, N.

***N*-Ethyl-1′-deoxy-1′-[6-amino-2-(phenylethynyl)-9*H*-purin-9-yl]-β-D-ribofuranuronamide (5).** The title compound was prepared according to general procedure A. Reaction of **3** with ethynylbenzene for 2 h, followed by chromatography on silica gel column eluting with chloroform–methanol–benzene (78:10:12), gave compound **5** (60%): mp 175–178 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.02 (t, 3H, NCH_2CH_3), 3.28 (m, 2H, NCH_2CH_3), 4.15 (m, 1H, H-3′), 4.31 (d, J = 1.2 Hz, 1H, H-4′), 4.62 (m, 1H, H-2′), 5.97 (d, 1H, J = 7.5 Hz, H-1′), 7.58 (d, J = 7.8 Hz, 2H, H-Ph), 7.46 (m, 2H, H-Ph), 7.66 (s, 2H, NH_2), 8.49 (s, 1H, H-8), 8.60 (t, 1H, NH). Anal. ($C_{20}H_{20}N_6O_4$·H_2O) C, H, N.

***N*-Ethyl-1′-deoxy-1′-[6-amino-2-(4-tolylethynyl)-9*H*-purin-9-yl]-β-D-ribofuranuronamide (6).** The title compound was prepared according to general procedure A. Reaction of **3** with 4-ethynyltoluene for 3 h, followed by chromatography on silica gel column eluting with chloroform–methanol (97:3), gave compound **6** (50%): mp 210–213 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.02 (t, 3H, NCH_2CH_3), 2.35 (s, 3H, CH_3Ph), 3.32 (m, 2H, NCH_2CH_3), 4.15 (m, 1H, H-3′), 4.32 (s, 1H, H-4′), 4.63 (m, 1H, H-2′), 5.97 (d, 1H, J = 7.5 Hz, H-1′), 7.28 (d, J = 8.4 Hz, 2H, H-Ph), 7.48 (d, J = 8.4 Hz, 2H, H-Ph), 7.62 (s, 2H, NH_2), 8.48 (s, 1H, H-8), 8.69 (t, 1H, NH). Anal. ($C_{21}H_{22}N_6O_4$·H_2O) C, H, N.

***N*-Ethyl-1′-deoxy-1′-{6-amino-2-[[4-(cyanomethyl)phenyl]ethynyl]-9*H*-purin-9-yl}-β-D-ribofuranuronamide (7).** The title compound was prepared according to general procedure A. Reaction of **3** with 4-ethynyl-1-phenylacetonitrile for 20 h, followed by chromatography on silica gel column eluting with chloroform–methanol (90:10), gave compound **7** (55%): mp 230–232 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.03 (t, 3H, NCH_2CH_3), 3.30 (m, 2H, NCH_2CH_3), 4.14 (s, 2H, CH_2CN), 4.16 (m, 1H, H-3′), 4.33 (s, 1H, H-4′), 4.63 (m, 1H, H-2′), 5.98 (d, 1H, J = 7.5 Hz, H-1′), 7.45 (d, J = 8.7 Hz, 2H, H-Ph), 7.63 (d, J = 8.7 Hz, 2H, H-Ph), 7.65 (s, 2H, NH_2), 8.51 (s, 1H, H-8), 8.66 (t, 1H, NH). Anal. ($C_{22}H_{21}N_7O_4$·H_2O) C, H, N.

***N*-Ethyl-1′-deoxy-1′-[6-amino-2-[(4-methoxyphenyl)ethynyl]-9*H*-purin-9-yl]-β-D-ribofuranuronamide (8).** The title compound was prepared according to general procedure B. Reaction of **4** with 4-iodoanisole at 30 °C for 3 h, followed by chromatography on silica gel column eluting with chloroform–methanol (94:6), gave compound **8** (49%, crystallized from methanol): mp 151–154 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.02 (t, 3H, NCH_2CH_3), 3.30 (m, 2H, NCH_2CH_3), 4.12 (m, 1H, H-3′), 4.30 (d, 1H, J = 1.2 Hz, H-4′), 4.60 (m, 1H, H-2′), 5.95 (d, 1H, J = 7.5 Hz, H-1′), 7.00 (d, 2H, H-Ph), 7.51 (d, 2H, H-Ph), 7.62 (s, 2H, NH_2), 8.46 (s, 1H, H-8), 8.68 (t, 1H, NH). Anal. ($C_{21}H_{22}N_6O_5$·H_2O) C, H, N.

***N*-Ethyl-1′-deoxy-1′-[6-amino-2-[(4-hydroxyphenyl)ethynyl]-9*H*-purin-9-yl]-β-D-ribofuranuronamide (9).** The title compound was prepared according to general procedure B. The reaction of **4** with 4-iodophenol for 16 h, followed by chromatography on silica gel column eluting with chloroform–methanol (85:15), gave compound **9** (63%, crystallized from methanol): mp 200–202 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.02 (t, 3H, NCH_2CH_3), 3.31 (m, 2H, NCH_2CH_3), 4.20 (m, 1H, H-3′), 4.30 (d, 1H, J = 1.2 Hz, H-4′), 4.62 (m, 1H, H-2′), 5.95 (d, 1H, J = 7.8 Hz, H-1′), 6.81 (d, 2H, J = 8.7 Hz, H-Ph), 7.39 (d, J = 8.7 Hz, 2H, H-Ph), 7.61 (s, 2H, NH_2), 8.45 (s, 1H, H-8), 8.69 (t, 1H, NH), 10.07 (s, 1H, PhOH). Anal. ($C_{20}H_{20}N_6O_5$·H_2O) C, H, N.

***N*-Ethyl-1′-deoxy-1′-[6-amino-2-[(4-aminophenyl)ethynyl]-9*H*-purin-9-yl]-β-D-ribofuranuronamide (10).** The title compound was prepared according to general procedure A. Reaction of **3** with 4-ethynylaniline for 4 h, followed by chromatography on silica gel column eluting with chloroform–methanol–benzene (80:10:10), gave compound **10** (60%): mp 225–228 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.04 (t, 3H, NCH_2CH_3), 3.33 (m, 2H, NCH_2CH_3), 4.12 (m, 1H, H-3′), 4.31 (s, 1H, H-4′), 4.60 (m, 1H, H-2′), 5.72 (s, 2H, $PhNH_2$), 5.96 (d, 1H, J = 7.8 Hz, H-1′), 6.57 (d, J = 8.7 Hz, 2H, H-Ph), 7.22 (d, J = 8.7 Hz, 2H, H-Ph), 7.56 (s, 2H, NH_2), 8.43 (s, 1H, H-8), 8.71 (t, 1H, NH). Anal. ($C_{20}H_{21}N_7O_4$·H_2O) C, H, N.

***N*-Ethyl-1′-deoxy-1′-{6-amino-2-[[4-(trifluoromethyl)phenyl]ethynyl]-9*H*-purin-9-yl}-β-D-ribofuranuronamide (11).** The title compound was prepared according to general procedure B. Reaction of **4** with 1-bromo-4-(trifluoromethyl)benzene at 50 °C for 1 h, followed by chromatography on silica gel column eluting with chloroform–methanol–benzene (80:10:10), gave compound 11 (65%): mp 224–227 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.01 (t, 3H, NCH_2CH_3), 3.26 (m, 2H, NCH_2CH_3), 4.14 (m, 1H, H-3′), 4.31 (s, 1H, H-4′), 4.61 (m, 1H, H-2′), 5.97 (d, 1H, J = 7.5 Hz, H-1′), 7.71 (s, 2H, NH_2),

7.81 (s, 4H, H-Ph), 8.52 (s, 1H, H-8), 8.58 (t, 1H, NH). Anal. ($C_{21}H_{19}F_3N_6O_4 \cdot H_2O$) C, H, N.

***N*-Ethyl-1′-deoxy-1′-[6-amino-2-[(4-fluorophenyl)ethynyl]-9*H*-purin-9-yl]-β-D-ribofuranuronamide (12).** The title compound was prepared according to general procedure B. Reaction of **4** with 1-fluoro-4-iodobenzene for 16 h, followed by chromatography on silica gel column eluting with chloroform–methanol (94:6), gave compound **12** (55%, crystallized from methanol–hexane): mp 184–185 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.04 (t, 3H, NCH_2CH_3), 3.30 (m, 2H, NCH_2CH_3), 4.16 (m, 1H, H-3′), 4.34 (s, 1H, H-4′), 4.63 (m, 1H, H-2′), 6.00 (d, 1H, J = 7.5 Hz, H-1′), 7.36 (t, 2H, H-Ph), 7.69 (m, 4H, NH_2 and H-Ph), 8.53 (s, 1H, H-8), 8.66 (t, 1H, NH). Anal. ($C_{20}H_{19}FN_6O_4 \cdot H_2O$) C, H, N.

***N*-Ethyl-1′-deoxy-1′-{6-amino-2-[(4-carboxamidophenyl)ethynyl]-9*H*-purin-9-yl}-β-D-ribofuranuronamide (13).** The title compound was prepared according to general procedure A. Reaction of **3** with 1-carboxamido-4-ethynylbenzene for 16 h, followed by chromatography on silica gel column eluting with chloroform–methanol–benzene (70:20:10), gave compound **13** (55%): mp 240–243 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.01 (t, 3H, NCH_2CH_3), 3.28 (m, 2H, NCH_2CH_3), 4.14 (m, 1H, H-3′), 4.31 (s, 1H, H-4′), 4.60 (m, 1H, H-2′), 5.97 (d, 1H, J = 7.8 Hz, H-1′), 7.50 and 8.08 (s, 1H each, $CONH_2$), 7.66 (d, J = 8.4 Hz, 4H, H-Ph and NH_2), 7.92 (d, J = 8.4 Hz, 2H, H-Ph), 8.51 (s, 1H, H-8), 8.61 (t, 1H, NH). Anal. ($C_{21}H_{21}N_7O_5 \cdot H_2O$) C, H, N.

***N*-Ethyl-1′-deoxy-1′-[6-amino-2-[(4-acetylphenyl)ethynyl]-9*H*-purin-9-yl]-β-D-ribofuranuronamide (14).** The title compound was prepared according to general procedure A. Reaction of **3** with 1-acetyl-4-ethynylbenzene for 20 h, followed by chromatography on silica gel column eluting with chloroform–methanol–benzene (80:10:10), gave compound **14** (60%): mp 185–188 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.04 (t, 3H, NCH_2CH_3), 2.62 (s, 3H, $COCH_3$), 3.28 (m, 2H, NCH_2CH_3), 4.17 (m, 1H, H-3′), 4.34 (s, 1H, H-4′), 4.63 (m, 1H, H-2′), 6.00 (d, 1H, J = 7.5 Hz, H-1′), 7.69 (s, 2H, NH_2), 7.74 (d, J = 8.4 Hz, 2H, H-Ph), 8.03 (d, J = 8.4 Hz, 2H, H-Ph), 8.53 (s, 1H, H-8), 8.61 (t, 1H, NH). Anal. ($C_{22}H_{22}N_6O_5 \cdot H_2O$) C, H, N.

***N*-Ethyl-1′-deoxy-1′-[6-amino-2-[(2-formylphenyl)ethynyl]-9*H*-purin-9-yl]-β-D-ribofuranuronamide (15).** The title compound was prepared according to general procedure B. Reaction of **4** with 2-bromobenzaldehyde at 60 °C for 5 h, followed by chromatography on silica gel column eluting with chloroform–methanol (92:8), gave compound **15** (23%, crystallized from ethanol): mp 189–191 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.02 (t, 3H, NCH_2CH_3), 3.24 (m, 2H, NCH_2CH_3), 4.18 (m, 1H, H-3′), 4.35 (d, 1H, J = 1.3 Hz, H-4′), 4.66 (m, 1H, H-2′), 6.03 (d, 1H, J = 7.5 Hz, H-1′), 7.74 (s, 2H, NH_2), 7.72 (m, 1H, H-Ph), 7.82 (m, 2H, H-Ph), 7.96 (d, 1H, J = 7.5 Hz, H-Ph), 8.56 (t, 1H, NH), 8.58 (s, 1H, H-8), 10.50 (s, 1H, CHO). Anal. ($C_{21}H_{20}N_6O_5 \cdot H_2O$) C, H, N.

***N*-Ethyl-1′-deoxy-1′-[6-amino-2-[(3-formylphenyl)ethynyl]-9*H*-purin-9-yl]-β-D-ribofuranuronamide (16).** The title compound was prepared according to general procedure A. Reaction of **3** with 3-ethynylbenzaldehyde at 40 °C for 36 h, followed by chromatography on silica gel column eluting with chloroform–methanol–benzene (80:10:10), gave compound **16** (50%, crystallized from ethanol): mp 164–165 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.05 (t, 3H, NCH_2CH_3), 3.29 (m, 2H, NCH_2CH_3), 4.17 (m, 1H, H-3′), 4.35 (d, 1H, J = 0.9 Hz, H-4′), 4.66 (m, 1H, H-2′), 6.01 (d, 1H, J = 7.5 Hz, H-1′), 7.72 (m, 3H, NH_2 and H-Ph), 7.98 (m, 2H, H-Ph), 8.12 (s, 1H, H-Ph), 8.54 (s, 1H, H-8), 8.64 (t, 1H, NH), 10.06 (s, 1H, CHO). Anal. ($C_{21}H_{20}N_6O_5 \cdot H_2O$) C, H, N.

***N*-Ethyl-1′-deoxy-1′-[6-amino-2-[(4-formylphenyl)ethynyl]-9*H*-purin-9-yl]-β-D-ribofuranuronamide (17).** The title compound was prepared according to general procedure A. Reaction of **3** with 1-ethynyl-4-formylbenzene for 6 h, followed by chromatography on silica gel column eluting with chloroform–methanol (92:8), gave compound **17** (80%): mp 210–213 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.00 (t, 3H, NCH_2CH_3), 3.26 (m, 2H, NCH_2CH_3), 4.13 (m, 1H, H-3′), 4.30 (d, 1H, J = 1.5 Hz, H-4′), 4.56 (m, 1H, H-2′), 5.97 (d, 1H, J = 7.5 Hz, H-1′), 7.70 (s, 2H, NH_2), 7.79 (d, J = 8.4 Hz, 2H, H-Ph), 7.96 (d, J = 8.4 Hz, 2H, H-Ph), 8.52 (s, 1H, H-8), 8.58 (t, 1H, NH), 10.02 (s, 1H, CHO). Anal. ($C_{21}H_{20}N_6O_5 \cdot H_2O$) C, H, N.

***N*-Ethyl-1′-deoxy-1′-[6-amino-2-[(4-nitrophenyl)ethynyl]-9*H*-purin-9-yl]-β-D-ribofuranuronamide (18).** The title compound was prepared according to general procedure A. Reaction of **3** with 1-ethynyl-4-nitrobenzene for 4 h, followed by chromatography on silica gel column eluting with chloroform–methanol–benzene (80:10:10), gave compound **18** (80%): mp 180–183 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.03 (t, 3H, NCH_2CH_3), 3.28 (m, 2H, NCH_2CH_3), 4.17 (m, 1H, H-3′), 4.33 (s, 1H, H-4′), 4.63 (m, 1H, H-2′), 6.00 (d, 1H, J = 7.5 Hz, H-1′), 7.88 (s, 2H, NH_2), 7.94 (d, J = 8.4 Hz, 2H, H-Ph), 8.30 (d, J = 8.4 Hz, 2H, H-Ph), 8.56 (s, 1H, H-8), 8.59 (t, 1H, NH). Anal. ($C_{20}H_{19}N_7O_6 \cdot H_2O$) C, H, N.

***N*-Ethyl-1′-deoxy-1′-{6-amino-2-[[4-(3-*tert*-butoxy-3-oxopropenyl)phenyl]ethynyl]-9*H*-purin-9-yl}-β-D-ribofuranuronamide (19).** The title compound was prepared according to general procedure A. Reaction of **3** with *tert*-butyl 3-(4-ethynylphenyl)acrylate (**39**) for 5 h, followed by chromatography on silica gel column eluting with chloroform–methanol–benzene (80:10:10), gave compound **19** (48%, crystallized from ethanol): mp 182–184 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.01 (t, 3H, NCH_2CH_3), 1.47 (s, 9H, $(CH_3)_3C$), 3.26 (m, 2H, NCH_2CH_3), 4.13 (m, 1H, H-3′), 4.30 (d, 1H, J = 1.5 Hz, H-4′), 4.60 (m, 1H, H-2′), 5.96 (d, 1H, J = 7.5 Hz, H-1′), 6.58 (d, 1H, J = 16.6 Hz, =CHPh), 7.57 (d, 1H, J = 16.6 Hz, =CHCO), 7.59 (d, J = 8.4 Hz, 2H, H-Ph), 7.66 (s, 2H, NH_2), 7.77 (d, J = 8.4 Hz, 2H, H-Ph), 8.50 (s, 1H, H-8), 8.60 (t, 1H, NH). Anal. ($C_{27}H_{30}N_6O_6 \cdot H_2O$) C, H, N.

***N*-Ethyl-1′-deoxy-1′-{6-amino-2-[[4-(*tert*-butoxycarbonyl)phenyl]ethynyl]-9*H*-purin-9-yl}-2′,3′-*O*-isopropylidene-β-D-ribofuranuronamide (20a).** The title compound was prepared according to general procedure C. Reaction of **2** with *tert*-butyl 3-(4-ethynylphenyl)propionate (**42**), followed by chromatography on silica gel column eluting with chloroform–cyclohexane–methanol (82:10:8), gave compound **20a** (65%): ^{1}H NMR (Me_2SO-d_6) δ 0.75 (t, 3H, NCH_2CH_3), 1.38 (s, 12H, $(CH_3)_3C$ and CH_3-isopropyl), 1.57 (s, 1H, CH_3-isopropyl.), 2.57 (t, 2H, CH_2Ph), 2.91 (m, 4H, NCH_2CH_3 and CH_2-CO), 4.57 (s, 1H, H-4′), 5.38 (s, 2H, H-2′ and H-3′), 6.32 (s, 1H, H-1′), 7.33 (d, 2H, J = 8.1 Hz, H-Ph), 7.53 (m, 4H, NH_2 and H-Ph), 7.69 (t, 1H, NH), 8.35 (s, 1H, H-8). Anal. ($C_{30}H_{36}N_6O_6 \cdot H_2O$) C, H, N.

***N*-Ethyl-1′-deoxy-1′-{6-amino-2-[[4-(2-carboxyethyl)phenyl]ethynyl]-9*H*-purin-9-yl}-β-D-ribofuranuronamide (20).** The title compound was prepared according to general procedure D. Reaction of **20a** with 50% formic acid, followed by chromatography on silica gel column eluting with chloroform–methanol (85:15), gave compound **20** (72%, crystallized from methanol): mp 205–207 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.04 (t, 3H, NCH_2CH_3), 2.58 (t, 2H, CH_2Ph), 2.84 (t, 2H, CH_2CO), 3.29 (m, 2H, NCH_2CH_3), 4.07 (m, 1H, H-3′), 4.30 (s, 1H, H-4′), 4.64 (m, 1H, H-2′), 5.99 (d, 1H, J = 7.7 Hz, H-1′), 7.33 (d, J = 8.2 Hz, 2H, H-Ph), 7.51 (d, J = 8.2 Hz, 2H, H-Ph), 7.68 (s, 2H, NH_2), 8.51 (s, 1H, H-8), 8.68 (t, 1H, NH). Anal. ($C_{23}H_{24}N_6O_6 \cdot H_2O$) C, H, N.

***N*-Ethyl-1′-deoxy-1′-[6-amino-2-[(1-naphthyl)ethynyl]-9*H*-purin-9-yl]-β-D-ribofuranuronamide (21).** The title compound was prepared according to general procedure A. Reaction of **3** with 1-ethynylnaphthalene for 20 h, followed by chromatography on silica gel column eluting with chloroform–methanol–benzene (80:10:10), gave compound **21** (45%): mp 225–228 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 0.97 (t, 3H, NCH_2CH_3), 3.14 (m, 2H, NCH_2CH_3), 4.17 (m, 1H, H-3′), 4.32 (d, J = 1.5 Hz, 1H, H-4′), 4.66 (m, 1H, H-2′), 6.01 (d, 1H, J = 7.5 Hz, H-1′), 7.55–7.73 (b m, 3H, H-naph), 7.69 (s, 2H, NH_2), 7.86, 8.05, 8.24 (4H, H-naph), 8.53 (s, 1H, H-8), 8.57 (t, 1H, NH). Anal. ($C_{24}H_{22}N_6O_4 \cdot H_2O$) C, H, N.

***N*-Ethyl-1′-deoxy-1′-[6-amino-2-(3-phenyl-1-propyn-1-yl)-9*H*-purin-9-yl]-β-D-ribofuranuronamide (22).** The title compound was prepared according to general procedure A. The reaction of **3** with 3-phenyl-1-propyne for 4 h, followed by chromatography on silica gel column eluting with chloroform–benzene–methanol (80:10:10), gave compound **22** (53%): mp 124–126 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.01 (m, 3H, NCH_2CH_3), 3.24 (m, 2H, NCH_2CH_3), 3.89 (s, 2H, CH_2), 4.14 (m, 1H, H-3′),

4.31 (d, 1H, J = 1.1 Hz, H-4'), 4.59 (m, 1H, H-2'), 5.94 (d, 1H, J = 7.9 Hz, H-1'), 7.32 (m, 2H, H-Ph), 7.39 (m, 3H, H-Ph), 7.59 (s, 2H, NH_2), 8.45 (s, 1H, H-8), 8.75 (t, 1H, NH). Anal. ($C_{21}H_{22}N_6O_4 \cdot H_2O$) C, H, N.

***N*-Ethyl-1'-deoxy-1'-[6-amino-2-(4-phenyl-1-butyn-1-yl)-9*H*-purin-9-yl]-β-D-ribofuranuronamide (23).** The title compound was prepared according to general procedure A. The reaction of **3** with 4-phenyl-1-butyne for 16 h, followed by chromatography on silica gel column eluting with chloroform–methanol (92:8), gave compound **23** (53%, crystallized from methanol): mp 143–145 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.06 (m, 3H, NCH_2CH_3), 2.72 (t, 2H, CH_2), 2.88 (t, 2H, CH_2), 3.26 (m, 2H, NCH_2CH_3), 4.12 (m, 1H, H-3'), 4.30 (s, 1H, H-4'), 4.57 (m, 1H, H-2'), 5.93 (d, 1H, J = 7.7 Hz, H-1'), 7.27 (m, 1H, H-Ph), 7.32 (d, 4H, H-Ph), 7.57 (s, 2H, NH_2), 8.44 (s, 1H, H-8), 8.76 (t, 1H, NH). Anal. ($C_{22}H_{24}N_6O_4 \cdot H_2O$) C, H, N.

***N*-Ethyl-1'-deoxy-1'-[6-amino-2-(5-phenyl-1-pentyn-1-yl)-9*H*-purin-9-yl]-2',3'-*O*-isopropylidene-β-D-ribofuranuronamide (24a).** The title compound was prepared according to general procedure C. Reaction of **2** with 5-phenyl-1-pentyne, followed by flash chromatography on silica gel column eluting with chloroform–cyclohexane–methanol (89:10:1), gave compound **24a** (92%): ^{1}H NMR (Me_2SO-d_6) δ 0.73 (m, 3H, NCH_2CH_3), 1.35 and 1.56 (s, 3H each, $C(CH_3)_2$), 1.86 (m, 2H, CH_2), 2.42 (t, 2H, CH_2), 2.79 (t, 2H, CH_2), 2.92 (m, 2H, NCH_2CH_3), 4.54 (s, 1H, H-4'), 5.36 (s, 2H, H-2' and H-3'), 6.29 (s, 1H, H-1'), 7.29 (m, 5H, H-Ph), 7.45 (s, 2H, NH_2), 7.67 (t, 1H, NH), 8.31 (s, 1H, H-8). Anal. ($C_{26}H_{30}N_6O_4 \cdot H_2O$) C, H, N.

***N*-Ethyl-1'-deoxy-1'-[6-amino-2-(5-phenyl-1-pentyn-1-yl)-9*H*-purin-9-yl]-β-D-ribofuranuronamide (24).** The title compound was prepared according to general procedure D. Reaction of **24a** with 50% formic acid, followed by chromatography on silica gel preparative TLC plate eluting with chloroform–methanol (85:15), gave compound **24** (71%): mp 128–130 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.05 (m, 3H, NCH_2CH_3), 1.86 (t, 2H, CH_2), 2.39 (t, 2H, CH_2), 2.69 (t, 2H, CH_2), 3.32 (m, 2H, NCH_2CH_3), 4.13 (m, 1H, H-3'), 4.31 (d, 1H, J = 1.1 Hz, H-4'), 4.58 (m, 1H, H-2'), 5.94 (d, 1H, J = 7.7 Hz, H-1'), 7.25 (m, 5H, H-Ph), 7.58 (s, 2H, NH_2), 8.44 (s, 1H, H-8), 8.79 (t, 1H, NH). Anal. ($C_{23}H_{26}N_6O_4 \cdot H_2O$) C, H, N.

***N*-Ethyl-1'-deoxy-1'-[6-amino-2-[(2-pyridyl)ethynyl]-9*H*-purin-9-yl]-β-D-ribofuranuronamide (25).** The title compound was prepared according to general procedure A. Reaction of **3** with 2-ethynylpyridine for 20 h, followed by chromatography on silica gel column eluting with chloroform–methanol (85:15), gave compound **25** (88%): mp 180–183 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.00 (t, 3H, NCH_2CH_3), 3.31 (m, 2H, NCH_2CH_3), 4.14 (m, 1H, H-3'), 4.31 (d, J = 1.5 Hz, 1H, H-4'), 4.62 (m, 1H, H-2'), 5.97 (d, 1H, J = 7.6 Hz, H-1'), 7.46 (m, 1H, H-pyridyl), 7.68 (m, 4H, H-pyridyl and NH_2), 7.89 (m, 1H, H-pyridyl), 8.51 (s, 1H, H-8), 8.63 (t, 1H, NH). Anal. ($C_{19}H_{19}N_7O_4 \cdot H_2O$) C, H, N.

***N*-Ethyl-1'-deoxy-1'-[6-amino-2-[(3-pyridyl)ethynyl]-9*H*-purin-9-yl]-β-D-ribofuranuronamide (26).** The title compound was prepared according to general procedure A. Reaction of **3** with 3-ethynylpyridine for 20 h, followed by chromatography on silica gel column eluting with chloroform–methanol (88:12), gave compound **26** (65%): mp 238–240 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.04 (t, 3H, NCH_2CH_3), 3.30 (m, 2H, NCH_2CH_3), 4.18 (m, 1H, H-3'), 4.34 (s, 1H, H-4'), 4.64 (m, 1H, H-2'), 6.01 (d, 1H, J = 7.5 Hz, H-1'), 7.53 (m, 1H, H-pyridyl), 7.73 (s, 2H, NH_2), 8.06 (m, 1, H-pyridyl), 8.56 (s, 1H, H-8), 8.64 (m, 2H, H-pyridyl and NH), 8.81 (d, 1H, J = 1.7 Hz, H-pyridyl). Anal. ($C_{19}H_{19}N_7O_4 \cdot H_2O$) C, H, N.

***N*-Ethyl-1'-deoxy-1'-[6-amino-2-[(4-pyridyl)ethynyl]-9*H*-purin-9-yl]-β-D-ribofuranuronamide (27).** The title compound was prepared according to general procedure B. Reaction of **4** with 4-bromopyridine hydrochloride for 24 h, followed by chromatography on silica gel preparative TLC plate eluting with chloroform–methanol–benzene (75:15:10), gave compound **27** (18%): mp 175–178 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.04 (t, 3H, NCH_2CH_3), 3.28 (m, 2H, NCH_2CH_3), 4.17 (m, 1H, H-3'), 4.35 (s, 1H, H-4'), 4.63 (m, 1H, H-2'), 6.01 (d, 1H, J = 7.5 Hz, H-1'), 7.59 (d, 2H, J = 5.0 Hz, H-pyridyl), 7.76 (s, 2H, NH_2), 8.58 (m, 2H, H-8 and NH), 8.69 (d, 2H, J = 5.0 Hz, H-pyridyl). Anal. ($C_{19}H_{19}N_7O_4 \cdot H_2O$) C, H, N.

***N*-Ethyl-1'-deoxy-1'-[6-amino-2-[(2-thienyl)ethynyl]-9*H*-purin-9-yl]-β-D-ribofuranuronamide (28).** The title compound was prepared according to general procedure B. Reaction of **4** with 2-iodothiophene for 16 h, followed by chromatography on silica gel column eluting with chloroform–methanol–benzene (80:10:10), gave compound **28** (82%): mp 245–248 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.05 (t, 3H, NCH_2CH_3), 3.31 (m, 2H, NCH_2CH_3), 4.13 (m, 1H, H-3'), 4.31 (d, J = 1.5 Hz, 1H, H-4'), 4.60 (m, 1H, H-2'), 5.95 (d, 1H, J = 7.8 Hz, H-1'), 7.16 (m, 1H, H-thienyl), 7.51 (d, J = 5.1 Hz, 1H, H-thienyl) 7.76 (d, J = 6.3 Hz, 1H, H-thienyl), 7.69 (s, 2H, NH_2), 8.49 (s, 1H, H-8), 8.67 (t, 1H, NH). Anal. ($C_{18}H_{18}N_6O_4S \cdot H_2O$) C, H, N.

***N*-Ethyl-1'-deoxy-1'-[6-amino-2-[(2-furyl)ethynyl]-9*H*-purin-9-yl]-β-D-ribofuranuronamide (29).** The title compound was prepared according to general procedure B. Reaction of **4** with 2-bromofurane for 24 h, followed by chromatography on silica gel column eluting with chloroform–methanol (92:8), gave compound **29** (30%): mp 180–183 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.08 (t, 3H, NCH_2CH_3), 3.31 (m, 2H, NCH_2CH_3), 4.16 (m, 1H, H-3'), 4.34 (d, J = 1.2 Hz, 1H, H-4'), 4.62 (m, 1H, H-2'), 5.99 (d, 1H, J = 7.5 Hz, H-1'), 6.68 (m, 1H, H-furyl), 7.07 (d, J = 3.5 Hz, 1H, H-furyl), 7.89 (d, J = 1.2 Hz, 1H, H-furyl), 7.73 (s, 2H, NH_2), 8.53 (s, 1H, H-8), 8.68 (t, 1H, NH). Anal. ($C_{18}H_{18}N_6O_5 \cdot H_2O$) C, H, N.

***N*-Ethyl-1'-deoxy-1'-[6-amino-2-[(2-thiazolyl)ethynyl]-9*H*-purin-9-yl]-β-D-ribofuranuronamide (30).** The title compound was prepared according to general procedure B. Reaction of **4** with 2-bromothiazole at 60 °C for 5 h, followed by chromatography on silica gel column eluting with chloroform–methanol (85:15), gave compound **30** (67%): mp 210–213 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.04 (t, 3H, NCH_2CH_3), 3.31 (m, 2H, NCH_2CH_3), 4.15 (m, 1H, H-3'), 4.31 (s, 1H, H-4'), 4.61 (m, 1H, H-2'), 5.97 (d, 1H, J = 7.5 Hz, H-1'), 7.77 (s, 2H, NH_2), 8.02 (d, 2H, H-thiazolyl), 8.54 (s, 1H, H-8), 8.60 (t, 1H, NH). Anal. ($C_{17}H_{17}N_7O_4S \cdot H_2O$) C, H, N.

***N*-Ethyl-1'-deoxy-1'-[6-amino-2-(3-*N*-imidazolyl-1-propyn-1-yl)-9*H*-purin-9-yl]-2',3'-*O*-isopropylidene-β-D-ribofuranuronamide (31a).** The title compound was prepared according to general procedure C. Reaction of **2** with 1-propargylimidazole,[14] followed by flash chromatography on silica gel column eluting with chloroform–cyclohexane–methanol (from 88:10:2 to 86:10:4), gave compound **31a** (60%): ^{1}H NMR (Me_2SO-d_6) δ 0.68 (m, 3H, NCH_2CH_3), 1.37 and 1.55 (s, 3H each, $C(CH_3)_2$), 2.87 (m, 2H, NCH_2CH_3), 4.55 (s, 1H, H-4'), 5.23 (s, 2H, $CH_2C{\equiv}C$), 5.37 (s, 2H, H-2' and H-3'), 6.31 (s, 1H, H-1'), 7.01 (s, 1H, H-4''), 7.35, (s, 1H, H-5''), 7.54 (s, 2H, NH_2), 7.61 (t, 1H, NH), 7.84 (s, 1H, H-2''), 8.33 (s, 1H, H-8). Anal. ($C_{21}H_{24}N_8O_4 \cdot H_2O$) C, H, N.

***N*-Ethyl-1'-deoxy-1'-[6-amino-2-(3-*N*-imidazolyl-1-propyn-1-yl)-9*H*-purin-9-yl]-β-D-ribofuranuronamide (31).** The title compound was prepared according to general procedure D. Reaction of **31a** with 50% formic acid, followed by chromatography on silica gel preparative TLC plate eluting with chloroform–methanol (80:20), gave compound **31** (63%): mp 215–218 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.02 (m, 3H, NCH_2CH_3), 3.18 (m, 2H, NCH_2CH_3), 4.14 (s, 1H, H-3'), 4.31 (s, 1H, H-4'), 4.58 (m, 1H, H-2'), 5.22 (s, 2H, $CH_2C{\equiv}C$), 5.95 (d, 1H, J = 7.4 Hz, H-1'), 6.98 (s, 1H, H-4''), 7.30 (s, 1H, H-5''), 7.66 (s, 2H, NH_2), 7.77 (s, 1H, H-2''), 8.50 (s, 1H, H-8), 8.60 (t, 1H, NH). Anal. ($C_{18}H_{20}N_8O_4 \cdot H_2O$) C, H, N.

***N*-Ethyl-1'-deoxy-1'-[6-amino-2-(3-*N*-piperidyl-1-propyn-1-yl)-9*H*-purin-9-yl]-2',3'-*O*-isopropylidene-β-D-ribofuranuronamide (32a).** The title compound was prepared according to general procedure C. Reaction of **2** with 1-(2-propynyl)piperidine,[15] followed by flash chromatography on silica gel column eluting with chloroform–cyclohexane–methanol (88:10:2), gave compound **32a** (95%): ^{1}H NMR (Me_2SO-d_6) δ 0.71 (m, 3H, NCH_2CH_3), 1.30–1.65 (m, 12H, H-piperidyl and $C(CH_3)_2$), 2.52 (m, 4H, H-piperidyl), 2.89 (m, 2H, NCH_2CH_3), 3.52 (s, 2H, $CH_2C{\equiv}C$), 4.55 (s, 1H, H-4'), 5.38 (s, 2H, H-2' and H-3'), 6.31 (s, 1H, H-1'), 7.48 (s, 2H, NH_2), 7.81 (t, 1H, NH), 8.32 (s, 1H, H-8). Anal. ($C_{23}H_{31}N_7O_4 \cdot H_2O$) C, H, N.

***N*-Ethyl-1'-deoxy-1'-[6-amino-2-(3-*N*-piperidyl-1-propyn-1-yl)-9*H*-purin-9-yl]-β-D-ribofuranuronamide (32).** The

title compound was prepared according to general procedure D. Reaction of **32a** with 50% formic acid, followed by chromatography on silica gel preparative TLC plate eluting with chloroform–methanol (85:15), gave compound **32** (40%): mp 201–204 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.08 (m, 3H, NCH_2CH_3), 1.42 (m, 2H, H-piperidyl), 1.55 (m, 4H, H-piperidyl), 2.49 (m, 4H, H-piperidyl), 3.31 (m, 2H, NCH_2CH_3), 3.47 (s, 2H, $CH_2C{\equiv}C$), 4.14 (s, 1H, H-3′), 4.32 (d, 1H, J = 1.5 Hz, H-4′), 4.59 (m, 1H, H-2′), 5.96 (d, 1H, J = 7.5, H-1′), 7.60 (s, 2H, NH_2), 8.32 (s, 1H, H-8), 8.71 (t, 1H, NH). Anal. ($C_{20}H_{27}N_7O_4{\cdot}H_2O$) C, H, N.

***N*-Ethyl-1′-deoxy-1′-{6-amino-2-[3-(4-methyl-*N*-piperazinyl-1-propyn-1-yl]-9*H*-purin-9-yl}-2′,3′-*O*-isopropylidene-β-D-ribofuranuronamide (33a).** The title compound was prepared according to general procedure C. Reaction of **2** with 1-(2-propynyl)-*N*-methyl-4-methylpiperazine,[15] followed by flash chromatography on silica gel column eluting with chloroform–cyclohexane–methanol (from 85:13:2 to 82:13:5), gave compound **33a** (67%): ^{1}H NMR (Me_2SO-d_6) δ 0.73 (m, 3H, NCH_2CH_3), 1.36 and 1.57 (s, 3H each, $C(CH_3)_2$), 2.17 (s, 3H, NCH_3), 2.28 (m, 4H, H-piperazinyl), 2.51 (m, 4H, H-piperazinyl), 2.91 (m, 2H, NCH_2CH_3), 3.50 (s, 2H, $CH_2C{\equiv}C$), 4.55 (s, 1H, H-4′), 5.36 (s, 2H, H-2′ and H-3′), 6.29 (s, 1H, H-1′), 7.49 (s, 2H, NH_2), 7.66 (t, 1H, NH), 8.31 (s, 1H, H-8). Anal. ($C_{23}H_{32}N_8O_4{\cdot}H_2O$) C, H, N.

***N*-Ethyl-1′-deoxy-1′-{6-amino-2-[3-(4-methyl-N-piperazinyl)-1-propyn-1-yl]-9*H*-purin-9-yl}-β-D-ribofuranuronamide (33).** The title compound was prepared according to general procedure D. Reaction of **33a** with 50% formic acid followed by crystallization from acetonitrile–methanol (90:10) gave compound **33** (30%) as formiate salt: mp 158–161 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.08 (m, 3H, NCH_2CH_3), 2.20 (s, 3H, NCH_3), 2.40 (m, 4H, H-piperazinyl), 2.51 (m, 4H, H-piperazinyl), 3.30 (m, 2H, NCH_2CH_3), 3.51 (s, 2H, $CH_2C{\equiv}C$),4.14 (s, 1H, H-3′), 4.32 (s, 1H, H-4′), 4.59 (m, 1H, H-2′), 5.96 (d, 1H, J = 7.4 Hz, H-1′), 7.62 (s, 2H, NH_2), 8.18 (s, 1H, HCO), 8.47 (s, 1H, H-8), 8.68 (t, 1H, NH). Anal. ($C_{20}H_{28}N_8O_4{\cdot}H_2O{\cdot}H_2$-COO) C, H, N.

***N*-Ethyl-1′-deoxy-1′-[6-amino-2-(3-N-morpholinyl-1-propyn-1-yl)-9*H*-purin-9-yl]-2′,3′-*O*-isopropylidene-β-D-ribofuranuronamide (34a).** The title compound was prepared according to general procedure C. Reaction of **2** with 1-(2-propynyl)morpholine,[15] followed by flash chromatography on silica gel column eluting with chloroform–cyclohexane–methanol (88:10:2), gave compound **34a** (88%): ^{1}H NMR (Me_2-SO-d_6) δ 0.72 (m, 3H, NCH_2CH_3), 1.36 and 1.56 (s, 3H each, $C(CH_3)_2$), 2.51 (m, 4H, H-morpholinyl), 2.90 (m, 2H, NCH_2-CH_3), 3.52 (s, 2H, $CH_2C{\equiv}C$), 3.62 (m, 4H, H-morpholinyl), 4.55 (s, 1H, H-4′), 5.37 (s, 2H, H-2′ and H-3′), 6.30 (s, 1H, H-1′), 7.49 (s, 2H, NH_2), 7.63 (t, 1H, NH), 8.32 (s, 1H, H-8). Anal. ($C_{22}H_{29}N_7O_5{\cdot}H_2O$) C, H, N.

***N*-Ethyl-1′-deoxy-1′-[6-amino-2-(3-*N*-morpholinyl-1-propyn-1-yl)-9*H*-purin-9-yl]-β-D-ribofuranuronamide (34).** The title compound was prepared according to general procedure D. Reaction of **34a** with 50% formic acid, followed by chromatography on silica gel preparative TLC plate eluting with chloroform–methanol (85:15), gave compound **34** (41%): mp 238–241 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.09 (m, 3H, NCH_2CH_3), 2.20 (s, 3H, NCH_3), 2.52 (m, 4H, H-morpholinyl), 3.31 (m, 2H, NCH_2CH_3), 3.53 (s, 2H, $CH_2C{\equiv}C$), 3.63 (m, 4H, H-morpholinyl), 4.14 (s, 1H, H-3′), 4.32 (d, 1H, J = 1.5 Hz, H-4′), 4.59 (m, 1H, H-2′), 5.96 (d, 1H, J = 7.7 Hz, H-1′), 7.62 (s, 2H, NH_2), 8.47 (s, 1H, H-8), 8.68 (t, 1H, NH). Anal. ($C_{19}H_{25}N_7O_5{\cdot}H_2O$) C, H, N.

***N*-Ethyl-1′-deoxy-1′-[6-amino-2-(3-*N*-thiomorpholinyl-1-propyn-1-yl)-9*H*-purin-9-yl]-2′,3′-*O*-isopropylidene-β-D-ribofuranuronamide (35a).** The title compound was prepared according to general procedure C. Reaction of **2** with 1-(2-propynyl)thiomorpholine (**44**), followed by flash chromatography on silica gel column eluting with chloroform–cyclohexane–methanol (88:10:2), gave compound **35a** (82%): ^{1}H NMR (Me_2SO-d_6) δ 0.73 (m, 3H, NCH_2CH_3), 1.37 and 1.56 (s, 3H each, $C(CH_3)_2$), 2.67 (m, 4H, H-thiomorpholinyl), 2.81 (m, 4H, H-thiomorpholinyl), 2.93 (m, 2H, NCH_2CH_3), 3.55 (s, 2H, $CH_2C{\equiv}C$), 4.56 (s, 1H, H-4′), 5.37 (s, 2H, H-2′ and H-3′), 6.30 (s, 1H, H-1′), 7.51 (s, 2H, NH_2), 7.63 (t, 1H, NH), 8.32 (s, 1H, H-8). Anal. ($C_{22}H_{29}N_7O_4S{\cdot}H_2O$) C, H, N.

***N*-Ethyl-1′-deoxy-1′-[6-amino-2-(3-*N*-thiomorpholinyl-1-propyn-1-yl)-9*H*-purin-9-yl]-β-D-ribofuranuronamide (35).** The title compound was prepared according to general procedure D. Reaction of **35a** with 50% formic acid, followed by chromatography on silica gel preparative TLC plate eluting with chloroform–methanol (85:15), gave compound **35** (87%): mp 198–201 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.08 (m, 3H, NCH_2CH_3), 2.66 (m, 4H, H-thiomorpholinyl), 2.81 (m, 4H, H-thiomorpholinyl), 3.26 (m, 2H, NCH_2CH_3), 3.55 (s, 2H, $CH_2C{\equiv}C$), 4.14 (s, 1H, H-3′), 4.32 (d, 1H, J = 1.5 Hz, H-4′), 4.60 (m, 1H, H-2′), 5.96 (d, 1H, J = 7.5 Hz, H-1′), 7.63 (s, 2H, NH_2), 8.48 (s, 1H, H-8), 8.68 (t, 1H, NH). Anal. ($C_{19}H_{25}$-$N_7O_4S{\cdot}H_2O$) C, H, N.

***tert*-Butyl 4-Aminocinnamate (37).** A mixture of 2 g (9.13 mmol) of *p*-iodoaniline (**36**), 2.13 mL (14.7 mmol) of *tert*-butyl acrylate, 20 mg (0.09 mmol) of Pd $(OAc)_2$, and 110 mg (0.36 mmol) of tri-*O*-tolylphosphine in 5 mL of triethylamine was refluxed for 0.5 h.

The reaction mixture was poured into ice and extracted with chloroform. The organic layers were dried over Na_2SO_4 and then the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel column eluting with cyclohexane–ethyl acetate (90:10) to give **37** (67%) as a chromatographically pure oil: ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 9*H*, $C(CH_3)_3$), 3.90 (s, 2H, NH_2), 6.17 (d, 1H, J = 15.9 Hz, CHPh), 6.63 (d, 2H, J = 5.1 Hz, H-Ph), 7.32 (d, 2H, J = 5.1 Hz, H-Ph), 7.49 (d, 1H, J = 15.9 Hz, CHCO). Anal. ($C_{13}H_{17}NO_2$) C, H, N.

***tert*-Butyl 4-Iodocinnamate (38).** A mixture of 1.3 g (5.93 mmol) of **37**, 4 mL of isopentyl nitrite, and 35 mL of methylene iodide was stirred at 85 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure (oil pomp, 60 °C), and the residue was chromatographed on silica gel column eluting with cyclohexane–ethyl acetate (98:2) to give **38** (55%) as a chromatographically pure oil: ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 9*H*, $C(CH_3)_3$), 6.37 (d, 1H, CHPh), 7.24 (d, 2H, H-Ph), 7.49 (d, 1H, J = 15.9 Hz, CHCO), 7.73 (d, 2H, H-Ph). Anal. ($C_{13}H_{15}$-IO_2) C, H.

***tert*-Butyl 3-(4-Ethynylphenyl)acrylate (39).** To a solution of 1 g (3.0 mmol) of **38** in 20 mL of dry acetonitrile and 12 mL of triethylamine under an atmosphere of N_2 was added 42 mg (0.060 mmol) of bis(triphenylphosphine)palladium dichloride, 3 mg (15.5 μmol) of cuprous iodide, and 0.51 mL (3.6 mmol) of (trimethylsilyl)acetylene, and the reaction mixture was stirred under an atmosphere of N_2 for 24 h. The solvent was removed *in vacuo* and the residue taken up in chloroform, dried over Na_2SO_4, and then concentrated to dryness. The crude silylated alkyne was dissolved in methanol, treated with 3 mL of 1 N KOH, and allowed to stir at room temperature for 0.5 h. The solvent was removed *in vacuo* and the residue extracted with chloroform. The organic layers were dried over Na_2SO_4, and then the solvent was removed *in vacuo*. The residue was purified by chromatography on silica gel column eluting with cyclohexane–benzene–ethyl acetate (76:20:4) to give **39** (78%) as a chromatographically pure oil: ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 9*H*, $C(CH_3)_3$), 3.17 (s, 1H, C≡CH), 6.37 (d, 1H, J = 16.0 Hz, CHPh), 7.47 (m, 4H, H-Ph), 7.55 (d, 1H, J = 16.0 Hz, CHCO). Anal. ($C_{11}H_{16}O_2$) C, H.

***tert*-Butyl-3-(4-Aminophenyl)propionate (40).** To a solution of 3.2 g (14.6 mmol) of **37** in 15 mL of ethanol was added 0.3 g of 10% Pd/C, and the mixture was shaken with hydrogen at 35 psi for 1 h. After the catalyst was removed by filtration, the filtrate was evaporated and the residue was flash chromatographed on a silica gel column. Elution with chloroform–ethyl acetate (90:10) gave **40** (80%) as a chromatographically pure oil: ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9*H*, $C(CH_3)_3$), 2.46 (t, 2H, CH_2Ph), 2.78 (t, 2H, CH_2CO), 3.55 (s, 2H, NH_2), 6.62 (d, 2H, J = 8.4 Hz, H-Ph), 6.99 (d, 2H, J = 8.4 Hz, H-Ph). Anal. ($C_{13}H_{19}$-NO_2) C, H, N.

***tert*-Butyl 3-(4-Iodophenyl)propionate (41).** A mixture of 2 g (9.12 mmol) of **40**, 7.6 mL of isopentyl nitrite, and 66 mL of methylene iodide was stirred at 85 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure (oil pomp, 60 °C), and the residue was flash chromatographed on silica gel column eluting with cyclohexane to give **41** (53%) as a chromatographically pure oil: ^{1}H NMR ($CDCl_3$) δ 1.41 (s,

9*H*, $C(CH_3)_3$), 2.51 (t, 2H, CH_2Ph), 2.85 (t, 2H, CH_2CO), 6.96 (d, 2H, J = 8.3 Hz, H-Ph), 7.60 (d, 2H, J = 8.3 Hz, H-Ph). Anal. ($C_{13}H_{17}IO_2$) C, H.

***tert*-Butyl 3-(4-Ethynylphenyl)propionate (42).** To a solution of 1.5 g (4.52 mmol) of **41** in 30 mL of dry acetonitrile and 18 mL of triethylamine under an atmosphere of N_2 was added 53 mg (0.076 mmol) of bis(triphenylphosphine)palladium dichloride, 4.5 mg (23.3 μmol) of cuprous iodide, and 0.75 mL (5.3 mmol) of (trimethylsilyl)acetylene, and the reaction mixture was stirred under an atmosphere of N_2 for 3 h. The solvent was removed *in vacuo* and the residue taken up in chloroform, dried over Na_2SO_4, and then concentrated to dryness. The crude silylated alkyne was dissolved in methanol, treated with 3 mL of 1 N KOH, and allowed to stir at room temperature for 0.5 h. The solvent was removed *in vacuo* and the residue extracted with chloroform. The organic layers were dried over Na_2SO_4, and then the solvent was removed *in vacuo*. The residue was purified by chromatography on silica gel column eluting with cyclohexane–benzene–ethyl acetate (75:20:5) to give **42** (72%) as a chromatographically pure oil: ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9*H*, $C(CH_3)_3$), 2.53 (t, 2H, CH_2Ph), 2.91 (t, 2H, CH_2CO), 3.05 (s, 1H, C≡CH), 7.19 (d, 2H, J = 8.2 Hz, H-Ph), 7.42 (d, 2H, J = 8.2 Hz, H-Ph). Anal. ($C_{15}H_{18}O_2$) C, H.

1-(2-Propynyl)thiomorpholine (44). To a suspension of 0.25 g (6.27 mmol) of 60% NaH in 20 mL of dry THF, cooled at 0 °C, was added 0.59 g (9.57 mmol) of thiomorpholine, and the mixture was stirred at 0 °C for 1 h. To the ice-cooled suspension was added 0.6 mL of propargyl bromide, and the mixture was stirred at 0 °C for 0.5 h and then at room temperature overnight. The reaction mixture was treated with 50% acetic acid, poured onto ice, and extracted several times with chloroform. The organic layers were dried over Na_2SO_4 and then the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel column eluting with chloroform to give **44** (90%) as a chromatographically pure oil: ^{1}H NMR ($CDCl_3$) δ 2.26 (t, 1H, C≡CH), 2.79 and 2.84 (m, 4H each, CH_2 thiomorphol.), 3.31 (d, 2H, J = 2.4 Hz, CH_2N). Anal. ($C_7H_{11}NS$) C, H, N.

Biological Studies. Receptor Binding Assay. Cerebral membranes were obtained from male Sprague–Dawley rats (Charles River, Calco, Italy) weighing 150–200 g. Tissue preparation was carried out according to Jarvis et al.[7b] Adenosine A_1 and A_{2a} receptor binding assay were performed according to Bruns et al.[15] and Jarvis et al.[7b] using [^{3}H–N^6-cyclohexyladenosine ([^{3}H]CHA) and [^{3}H]-2-[[*p*-(2-carboxyethyl)-phenethyl]amino]-5′-(*N*-ethylcarboxamido)adenosine ([^{3}H]CGS 21680). The IC_{50} values were estimated by probit models.[17] K_i values were calculated from the Cheng–Prusoff equation[18] using 1 nM as the K_d for [^{3}H]CHA and 18.5 nM for [^{3}H]CGS 21680 in A_1 and A_{2a} binding studies, respectively.

Isolated Tissue Preparations. Rats were sacrificed by decapitation and both heart and thoracic aorta were removed and placed in Krebs Henseleit's solution according to a method described elsewhere.[3] Briefly, isolated spontaneously beating rat atria were used to measure drug interaction with A_1 receptors. The decrease in beating rate evoked by cumulative addition of agonist was measured. Vascular tissue is specific to measure the interaction of adenosine analogues with A_{2a} receptors. Specimens of vessel were cleaned of connective tissue, cut into rings and allowed to equilibrate in an organ bath. Submaximal contractions of vascular rings were obtained by PGF2α (3 μM). The compounds were then added cumulatively, and the evoked relaxation was measured isometrically. The relationship between the contractile response (y) and the log dose was modeled by a straight line after arcsin transformation of dependent variable in order to obtain least square estimates of EC_{50} values for each preparation.[19] The average dose–response function was computed as a mean constant curve (i.e., a curve whose constants are the mean of those estimated from each preparation). The effective dose of each compound was expressed as mean EC_{50} with 95% confidence limits. The analysis was carried out by PROC GLM.[20]

Platelet Aggregation Assay. Platelet aggregation assay was performed according to the Born turbidimetric technique,[21] as previously described.[9] Compounds were dissolved in saline containing 10% of dimethyl sulfoxide (DMSO), which was present in the platelet-rich plasma at a final concentration of 0.3%. The maximal amplitude of aggregation, recordered 5 min after the addition of 5 μM ADP, was used for quantitative evaluation of the aggregation process. Percentage of inhibition was calculated in relation to control values. The potency ratio was calculated versus NECA, a reference adenosine analogue, after logit–log transformation, and fitted by weighted least square method.[17] The antiaggregatory activity was evaluated using a concentration of the test compound close to the IC_{50} value. The resulting single dose potency ratio is only a rough estimate because the dose–response relationship and the deviation from parallelism could not be evaluated.

Hydrophobicity Index *k′*. Retention of nucleosides on a reverse-phase HPLC column is reported to be a useful measure of the relative hydrophobicity.[16] This hydrophobicity index, k', is calculated by the formula $k' = (t - t_0)/t_0$, where t_0 represents the transit time of the solvent and t the retention time of each compound. The present measurements employed a column Supelcosil (150 × 4.6 mm) LC-8-DB 3u, eluted with a mixture of CH_3OH and 0.1 M $HCOONH_4$, pH 7.5 (56:44).

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