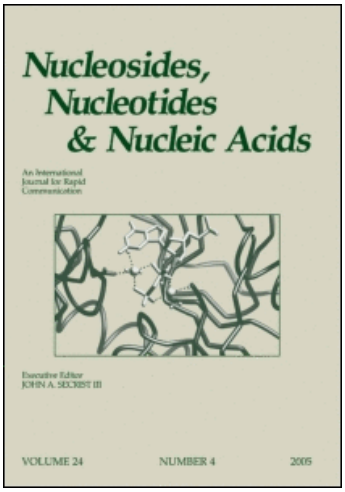

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2-Substituted 5'-N-Methylcarboxamidoadenosine (MECA) Derivatives as A_3 Adenosine Receptor Ligands

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2-SUBSTITUTED 5′-N-METHYLCARBOXAMIDOADENOSINE (MECA) DERIVATIVES AS A_3 ADENOSINE RECEPTOR LIGANDS

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INTRODUCTION

The introduction of various substituents in the 2-position of adenosine (Ado) (**1**–**3**, Figure 1) and 5′-N-ethylcarboxamidoadenosine (NECA) led to compounds endowed with high affinity for all the adenosine receptor subtypes (AdoRs).[1–3] Among them, NECA derivatives bearing a 2-hexynyl, 2-phenylethynyl, and 2-phenylhydroxypropynyl chains in the 2-position (**4**–**6**, Figure 1) showed high affinity and different degree of selectivity for human A_3 subtype.[4,5] In this work we have substituted the 5′-ethylcarboxamido groups of these latter compounds with methylcarboxamido substituents, since this modification seems to favor the interaction of the adenosine derivatives with the A_3 AdoR.[6,7]

CHEMISTRY

The synthesis of the new 2-alkynyl-5′-N-methylcarboxamido adenosines (**7**–**9**, Scheme 1) was carried out starting from 2-iodoadenosine-4′-ethylester (**10**),[8] prepared from the commercially available guanosine in eight steps. Reaction of this intermediate with methylamine gave the 2-iodo-5′-N-methylcarboxamidoadenosine (2-IMECA, **11**), which was treated with the appropriate terminal alkyne, using a modification of the classical palladium catalyzed cross-coupling reaction to obtain the desired 2-alkynyl-5′-N-methylcarboxamidoadenosines (**7**–**9**).[1,8,9]

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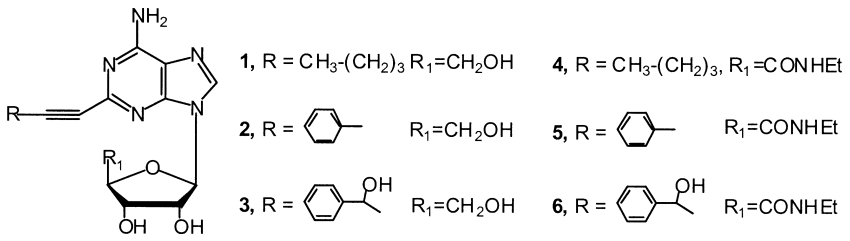
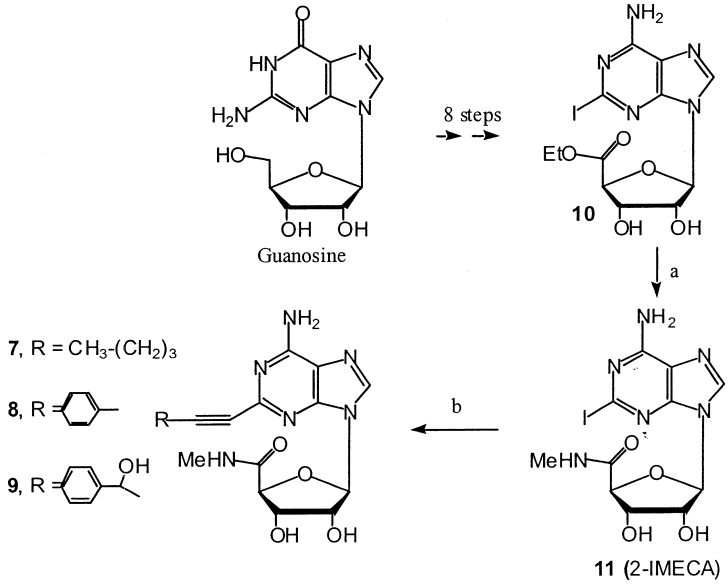


FIGURE 1 Structures of 2-alkynyl-Ado (**1**–**3**) and -NECA (**4**–**6**) derivatives reported in Table 1.

BIOLOGICAL RESULTS

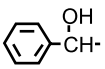
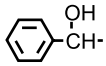
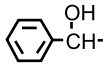
The new compounds were evaluated at the human recombinant adenosine receptors, stably transfected into Chinese hamster ovary (CHO) cells, utilizing radioligand binding studies (A_1, A_{2A}, A_3) or adenylyl cyclase activity assay (A_{2B}). Receptor binding affinity was determined using [^{3}H]CCPA (2-chloro-N^6-cyclopentyladenosine) as radioligand for A_1 receptors, whereas [^{3}H]NECA was used for the A_{2A} and A_3 subtypes (K_i; nM).[10] The results are shown in Table 1. NECA, the alkynyl-adenosines (**1**–**3**) and -NECA (**4**–**6**) derivatives have been reported as reference compounds.

The relative potencies of these compounds for the A_{2B} subtype were measured by evaluating the receptor-stimulated adenylyl cyclase activity expressed as EC_{50}, nM. Data reported in Table 1 show that the 2-alkynyl Ado derivatives **1**–**3** possess high affinity at A_1, A_{2A}, and A_3 AdoRs, but do not activate the A_{2B} subtype. In particular, the 2-phenylethynylAdo, with a K_i A_3=16 nM and a selectivity of 24 and



SCHEME 1 Synthesis of 2-alkynylMECA derivatives. a) $MeNH_2$; b) R–C ≡ CH, $(Pn_3P)_2PdCl_2$, CuI, Et_3N.

TABLE 1 Affinity (A_1, A_{2A}, and A_3) and Potency (A_{2B}) of the AdoR Ligands **1–9**

Cpd	R[a]	R_1[a]	A_1	A_{2A}	A_{2B}	A_3	A_1/A_3	A_{2A}/A_3
NECA			14	20	2,400	6.2	2	3
1	$CH_3(CH_2)_3$	CH_2OH	18	5.7	>10,000	4.7	4	1
4	$CH_3(CH_2)_3$	CONHEt	60	6.4	6,100	2.4	25	3
7	$CH_3(CH_2)_3$	CONHMe	711	25	>100,000	1.4	508	18
2		CH_2OH	391	363	>100,000	16	24	23
5		CONHEt	560	620	>100,000	6.2	90	100
8		CONHMe	3,920	1,760	>100,000	7.3	536	241
3		CH_2OH	0.67	7.0	2,400	3.3	0.2	2
6		CONHEt	2.7	3.1	1,100	0.42	6	7
9		CONHMe	14	3.0	5,030	1.7	8	2

[a]See Figure 1.

23 versus A_i and A_{2A}, respectively, resulted A_3 selective. The presence of an ethylcarboxamido substituent in the 4′ position of the three adenosine derivatives led to compounds **4–6**, which possessed decreased affinity at A_1 receptor, showed different profile at A_{2A}, and increased their affinity for the A_3 subtype, in comparison with the parent compounds **1–3**.

On the other hand, substitution of the 4′-ethylcarboxamide with a methylcarboxamido group resulted in compounds **7–9**, which, while maintaining a similar affinity for the A_3 AdoR subtype, showed in general a decrease in A_1 and A_{2A} affinity, resulting more A_3 selective.

Among them, the 2-phenylethynylMECA (**8**, K_i A_3=7.3 nM, selectivity A_1/A_3=537 and A_{2A}/A_3=241) resulted in one of the nucleoside derivatives with the highest selectivity for the human A_3 subtype reported so far.

REFERENCES

1. Cristalli, G.; Elcuteri, A.; Vittori, S.; Volpini, R.; Lohse, M.J.; Klotz, K.-N. J. Med. Chem. **1992**, *35*, 2363–2368.
2. Volpini, R.; Costanzi, S.; Lambertucci, C.; Vittori, S.; Cristalli, G. Curr. Pharm. Des. **2002**, *3*(26), 2285–2298.
3. Cristalli, G.; Lambertucci, C.; Taffi, S.; Vittori, S.; Volpini, R. Curr. Top. Med. Chem. **2003**, *3*(4), 387–402.
4. Cristalli, G.; Camaioni, E.; Costanzi, S.; Vittori, S.; Volpini, R.; Klotz, K.-N. Drug. Dev. Res. **1998**, *45*, 176–181.
5. Vlpini, R.; Costanzi, S.; Lambertucci, C.; Taffi, S.; Vittori, S.; Klotz, K.-N.; Cristalli, G. J. Med. Chem. **2002**, *45*, 3271–3279.
6. Kim, H.O.; Ji, X.-D.; Siddiqui, S.M.; Olah, M.E.; Stiles, G.; Jacobson, K.A. J. Med. Chem. **1994**, *37*, 3614–3621.

7. Mueller, C. Curr. Top. Med. Chem. **2003**, *3*(4), 445–462.
8. Cristalli, G.; Volpiny, R.; Vittori, S.; Camaioni, E.; Conti, A.; Dionisotti, S.; Zocchi, C.; Ongini, E. J. Med. Chem. **1994**, *37*, 1720–1726.
9. Cristalli, G.; Volpini, R.; Vittori, S.; Camaioni, E.; Monopoli, A.; Conti, A.; Dionisotti, S.; Zocchi, C.; Ongini, E. J. Med. Chem. **1995**, *38*, 1462–1472.
10. Klotz, K.N.; Hessling, J.; Hegler, J.; Owman, B.; Kull, B.; Fredholm, B.B.; Lohse, M.J. Arch. Phamacol. **1998**, *357*, 1–9.