Communications to the Editor

[Chem. Pharm. Bull. 33(4)1766—1769(1985)]

PALLADIUM-CATALYZED CROSS-COUPLING OF 2-IODOADENOSINE WITH TERMINAL ALKYNES: SYNTHESIS AND BIOLOGICAL ACTIVITIES OF 2-ALKYNYLADENOSINES

Akira Matsuda,[a] Misao Shinozaki,[a] Tadashi Miyasaka,*[,a] Haruhiko Machida,[b] and Toh-ichi Abiru[b]

School of Pharmaceutical Sciences, Showa University,[a] Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142, Japan and Research Laboratories, Yamasa Shoyu Co., Ltd.,[b] 2-10-1 Araoicho, Choshi-shi, Chiba 288, Japan

Reaction of 2-iodoadenosine (2) with terminal alkynes in the presence of bis(triphenylphosphine)palladium dichloride and cuprous iodide in triethylamine and N,N,-dimethylformamide gave 2-alkynyladenosines (3a-h) in excellent yields. Several compounds showed high activity as inhibitors in rat passive cutaneous anaphylaxis (PCA) reaction. Among them, 2-(3-hydroxypropynyl)- and 2-(3-hydroxybutynyl)-adenosines (3d,f) are much more potent than disodium cromoglycate (DSCG).

KEYWORDS——palladium-catalyzed cross-coupling; terminal alkyne; 2-iodoadenosine; 2-alkynyladenosine; bis(triphenylphosphine)palladium dichloride; passive cutaneous anaphylaxis; disodium cromoglycate

Adenosine plays an important role in initiating numerous metabolic actions in a variety of cells.[1] These include coronary vasodilation,[2] increased steroid production,[3] potentiation of histamine release from mast cell,[4] inhibition of lipolysis in fat cell,[5] inhibition of platelet aggregation,[6] and inhibition of vas deferens contraction.[7] Externally added adenosine is, however, of short duration in its action due to its rapid uptake into cells, deamination by adenosine deaminase, and phosphorylation by adenosine kinase. Also its disadvantage is that it is not orally effective.

Among the large number of adenosine derivatives tested on coronary vasodilatory action, some of the C-2 substituted derivatives have shown activity with higher potency and longer duration of action than the parent compound.[2,8,9] In contrast to the development of methods of introducing hetero-atoms to the C-2 position of adenosine, only few studies have reported on the carbon-carbon bond formation reactions. These so far involve the cyclization of appropriately substituted imidazole nucleosides,[9,10] homolytic methylation,[11] and nucleophilic substitution of the methanesulfonyl group with cyanide.[12] In the present communication we wish to describe a convenient method for the introduction of terminal alkynes into the C-2 position of adenosine *via* organopalladium intermediates. We also report on their cytotoxicity against mouse leukemic L5178Y cells and inhibitory activity on passive cutaneous anaphylaxis (PCA) reaction in the rat, which has been considered

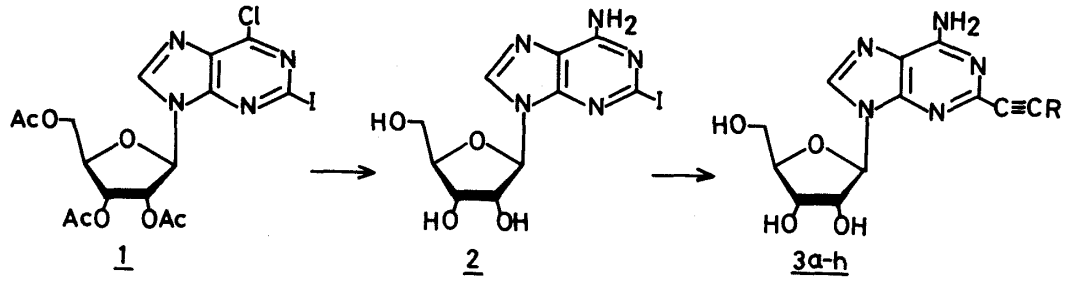

Table I. Synthesis of 2-Alkynyladenosines (3a-h)[a]

Product No.	R	Isolated yield (%)	mp(°C)	IR(KBr)(cm^{-1}) νC≡C
3a	$Si(CH_3)_3$	97	168-170	2160
3b	H	93[b]	205-207(dec.)	2110
3c	Ph	97	146-147	2210
3d	CH_2OH	96	212-215	c)
3e	CH_2CH_2OH	85[d]	151-153	2230
3f	$CH(OH)CH_3$	80[d]	173-176(dec.)	c)
3g	$(CH_2)_2CH_3$	90[e]	129-132	2230
3h	$(CH_2)_3CH_3$	81[d]	121-125	2230

a) The cross-coupling reactions were completed within 1 h at 80°C.
b) Deblocking yield from 3a. c) νC≡C band was not observed.
d) Isolated as a hydrate. e) Isolated as a hemihydrate.

Table II. Biological Activities of 2-Alkynyladenosines (3a-h)

Compound No.	Cytotoxicity ID_{50}[a] (μg/ml)	% inhibition of 48 h-PCA in rat[b] (mg/kg, i.v.) 0.12	0.4	1.2	4.0
3a	3.2	20	48	76	75
3b	1.6	0	10	50	100
3c	32	0	0	0	0
3d	85	0	100	100	100
3e	>100	0	0	100	100
3f	>100	0	100	100	100
3g	>100	0	30	100	100
3h	43	0	0	0	0
Adenosine	—	0	0	25	21
DSCG	—	—	30	37	63

a) ID_{50} indicates the concentration necessary for 50% inhibition of growth of mouse leukemic L5178Y cell line.
b) Compounds 3a-h, adenosine, and DSCG were given 1 min before antigen challenge.[17]

a primary screening test for antiallergy agents.

As a starting material of palladium-catalyzed cross-coupling reactions, 2-iodoadenosine (2, 90%, mp 141-144°C, M^+ m/z 397)[13] was synthesized by treatment of 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-6-chloro-2-iodopurine (1)[14] with methanolic ammonia in a sealed tube at 60°C for 17 h. For the palladium-catalyzed cross-coupling reaction of 2 with terminal alkynes, the modified method by Sonogashira,[15] which was originally developed by Heck,[16] was employed with a slight modification in this study.

When 2 was treated with a slight molar excess of (trimethylsilyl)acetylene in the presence of catalytic amounts of bis(triphenylphosphine)palladium dichloride and cuprous iodide in triethylamine and N,N-dimethylformamide as a cosolvent at 80°C for 1 h under argon atmosphere, 2-[2-(trimethylsilyl)ethynyl]adenosine (3a) was isolated in a crystalline form after treatment with H_2S and subsequent purification on silica gel column chromatography. It should be noted that H_2S treatment of the reaction mixture prior to further purifications is necessary since without H_2S treatment, the cross-coupled compound is found to be contaminated with metals. In such a case, the absorption corresponding to the H-8 (δ 8.45 in DMSO-d_6) of 3a is shown to be a broad singlet with a half-width of ca. 15 Hz presumably due to the chelation of metals between the 6-NH_2 and N^7 groups. Similar reactions starting from 2 with several terminal alkynes proceeded analogously with the formation of 2-alkynyladenosines (3c-h) in uniformly high isolated yields (Table I). Desilylation of 3a was accomplished by treatment with methanolic ammonia at room temperature to afford 2-ethynyladenosine (3b, δ 3.93: C≡CH in DMSO-d_6). Thus, the palladium-catalyzed cross-coupling reaction of 2 with terminal alkynes takes place smoothly under mild conditions in high isolated yields and tolerates hydroxyl and amino functional groups. This method would provide a general and versatile route to the C-2 carbon substituted adenosines since an acetylene group appears to be easily functionalizable.

The preliminary in vitro data in Table II indicate that 3a and 3b have moderate growth inhibitory activity against mouse leukemic L5178Y cells in culture. The inhibitory effect of 3a-h including adenosine and disodium cromoglycate (DSCG) as a positive control on the 48 h-PCA was examined by i.v. route in rat sensitized with rat anti-dinitrophenylated-ascaris extract antiserum[17] (Table II). Clearly, 3d and 3f are the most potent compounds of the series. These are much more potent than the parent adenosine and DSCG. However, increase or decrease in the number of carbon atoms in the R substituent resulted in a reduced or a loss of the PCA inhibitory activity. Furthermore, the R substituent's increasing in size (R = trimethylsilyl or phenyl) also reduced or eliminated the inhibitory activity. As was shown by Marquardt,[4] adenosine as well as 2-chloroadenosine were able to potentiate the histamine release from rat mast cells. Since the PCA reaction is shown by the action of histamine and other mediators, the inhibitory mechanism of action of 2-alkynyladenosines in this report might be different from that of adenosine and 2-chloroadenosine. Thus, although no well-defined mechanism of action has been elucidated at present it should be emphasized that we have found a new class of antiallergic compounds which is more potent than the widely used DSCG.[18] Synthesizing other analogues of 3 to examine the structure-activity relationships further and investigation of their detailed mechanism of action are currently under way.

REFERENCES AND NOTES

1) For recent reviews, see J. R. S. Arch and E. A. Newsholme, Essays Biochem., 14, 82 (1978); I. H. Fox and W. N. Kelley, Annu. Rev. Biochem., 47, 655 (1978).
2) R. A. Olsson, J. A. Snow, M. K. Gentry, and G. P. Erick, Circ. Res., 31, 767 (1972).
3) J. Wolff and G. H. Cook, J. Biol. Chem., 252,687 (1977).
4) D. L. Marquardt, C. E. Parker, and T. J. Sullivan, J. Immunol., 120, 871 (1978).
5) J. N. Fain and C. C. Malbon, Mol. Cell. Biochem., 23, 1 (1979).
6) R. J. Haslam and G. M. Rosson, Mol. Pharmacol., 11, 528 (1975).
7) M. J. Muller and D. M. Paton, Arch. Pharmacol., 306, 23 (1979).
8) J. A. Angus, L. B. Cobbin, R. Einstein, and M. H. Maguire, Br. J. Pharmacol., 41, 592 (1971); L. B. Cobbin, R. Einstein, and H. Maguire, Br. J. Pharmacol., 50, 25 (1974); K. Kawazoe, N. Matsumoto, M. Tanabe, S. Fujiwara, M. Yanagimoto, M. Hirata, and K. Kikuchi, Arzneim. Forsch., 30, 1083 (1980).
9) R. Marumoto, Y. Yoshioka, O. Miyashita, S. Shima, K. Imai, K. Kawazoe, and M. Honjo, Chem. Pharm. Bull., 23, 759 (1975).
10) A. Yamazaki, I. Kumashiro, and T. Takenishi, J. Org. Chem., 32, 3258 (1967); T. Murakami, M. Otsuka, S. Kobayashi, and M. Ohno, Heterocycles, 16, 1315 (1981).
11) M. Maeda, K. Nushi, and Y. Kawazoe, Tetrahedron, 30, 2677 (1974).
12) A. Matsuda, Y. Nomoto, and T. Ueda, Chem. Pharm. Bull., 27, 183 (1979).
13) The compounds 2 and 3a-h showed acceptable ^{1}H-NMR spectra and gave satisfactory elemental analyses.
14) V. Nair and S. G. Richardson, Synthesis, 1982, 670.
15) K. Sonogashira, Y. Tohda, and N. Hagihara, Tetrahedron Lett., 1975, 4467. Recently this modified method has been utilized for synthesizing a variety of alkynylated nucleosides. M. J. Robins and P. J. Barr, Tetrahedron Lett., 22, 421 (1981); S. Koyama, Z. Kumazawa, and N. Kashimura, Nucleic Acids Res. Sympodium Series 11, 41 (1982); E. De Clercq, J. Descamps, J. Balzarini, J. Giziewicz, P. J. Barr, and M. J. Robins, J. Med. Chem., 26, 661 (1983); M. J. Robins and P. J. Barr, J. Org. Chem., 48, 1854 (1983).
16) R. F. Heck, Acc. Chem. Res., 12, 146 (1979) and references therein.
17) T. Tada and K. Okumura, J. Immunol., 106, 1002 (1971).
18) Recently it was found that 1-methylisoguanosine and 2-methoxyadenosine had antiallergic activities through examination of the inhibition of passive paw anaphylaxis in rats (55% and 57% inhibition at 10 mg/kg i.v., respectively) by R. T. Bartlett, A. F. Cook, M. J. Holman, W. W. McComs, E. F. Nowoswait, M. S. Poonian, J. A. Baird-Lambert, B. A. Baldo, and J. F. Marwood in J. Med. Chem., 24, 947 (1981).

(Received February 21, 1985)