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Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

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To cite this Article Saito, Yoshio, Kato, Kuniki and Umezawa, Kazuo(1999) 'Synthesis and Inhibitory Activity Against Phosphatidylinositol 4-Kinase of Echiguanine Analogs', *Nucleosides, Nucleotides and Nucleic Acids*, 18: 4, 713 — 714

To link to this Article: DOI: 10.1080/15257779908041550

URL: <http://dx.doi.org/10.1080/15257779908041550>

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SYNTHESIS AND INHIBITORY ACTIVITY AGAINST PHOSPHATIDYLINOSITOL 4-KINASE OF ECHIGUANINE ANALOGS

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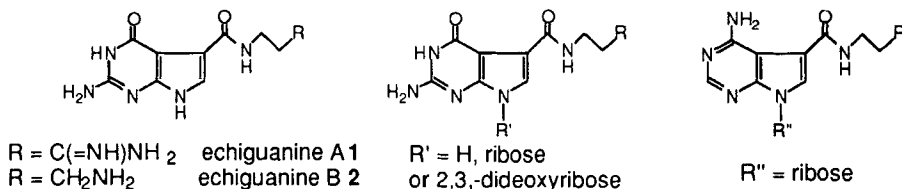
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ABSTRACT: *N*-Substituted-2-amino-4(3*H*)-7*H*-oxopyrrolo[2,3-*d*]pyrimidine-5-carboxamides and their ribofuranosyl and 2',3'-dideoxyribofuranosyl derivatives were prepared as membrane permeable echiguanine analogs and tested for their ability to inhibit phosphatidylinositol (PI) 4-kinase. The ethylamide **5** and the corresponding ribofuranosyl compound **11** inhibited PI 4-kinase with IC₅₀ values of 0.02 and 2.4 µg/ml, respectively.

The signaling pathways associated with activation of cell growth are considered to be new targets for cancer chemotherapy. Phosphatidylinositol (PI) 4-kinase is an enzyme involved in PI turnover, which turnover often regulates the growth of cells. PI 4-kinase activity was reported to be elevated in rat hepatomas¹ and human ovarian carcinoma cells. One of us previously isolated novel PI 4-kinase inhibitors, echiguanine A and B, from *Streptomyces*², but they did not show any cellular effect, possibly because of poor permeation of the membrane. To prepare effective and permeable inhibitors of PI 4-kinase, we became interested in modification of the terminal amidine moiety of echiguanine A.

Echiguanine analogs and ribosylated ones were synthesized by using similar reactions. Cyanoethylamide-deazaguanine, which served as a starting material, was prepared from 7-iodo-7-deazaguanine with or without ribose and 3-aminopropionitrile



under a carbon monoxide atmosphere in the presence of bis-(triphenylphosphine)palladium (II) chloride according to the protocol of Shih and Hu.³

We examined the PI 4-kinase activity⁴ of the newly synthesized echiguanine analogs. As shown in Table 1, compounds **5** and **6** were found to inhibit the enzyme approximately at the same level as echiguanines A and B. Although ribofuranosyl echiguanines **7** and **8** did not inhibit the enzyme, ribofuranosides **11**, **12**, and **13** and dideoxyribofuranoside **17** effectively inhibited PI 4-kinase. Thus, compounds having a terminal amide inhibited PI 4-kinase, even when they are ribosylated or dideoxyribosylated. In one hand, 7-deazaadenine analog **18** was also synthesized, but it did not show any significant activity. Thus, the guanine base structure may be essential for the inhibitory activity. Echiguanines A and B did not inhibit the growth of A431 cells, even at 200 µg/ml. Interestingly, **11** and **13** were shown to inhibit the growth with IC₅₀ values of 41 and 82 µg/ml, respectively, suggesting that both compounds are permeable to the membrane. Inhibition of PI 4-kinase by ribosylated or dideoxyribosylated echiguanines in cultured mammalian cells remains to be studied.

TABLE 1. Inhibitory activity of echiguanine analogs on PI 4-kinase

		IC ₅₀ µg/ml				
R	R' = H	R' = ribose	R' = dideoxyribose	R'' = ribose		
C(=NH)NH ₂	1 0.03	7 100	n. p.	n. p.		
CH ₂ NH ₂	2 0.18	8 >100	14 12	n. p.		
CN	3 0.45	9 >100	15 >100	n. p.		
COOMe	4 0.30	10 25	16 10	n. p.		
CONH ₂	5 0.02	11 2.4	17 3.8	18 >100		
CH ₂ NHC(=NH)NH ₂	6 0.15	12 7.5	n. p.	n. p.		
CH ₂ NHCONH ₂	n. p.	13 1.0	n. p.	n. p.		

n. p. : not prepared

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