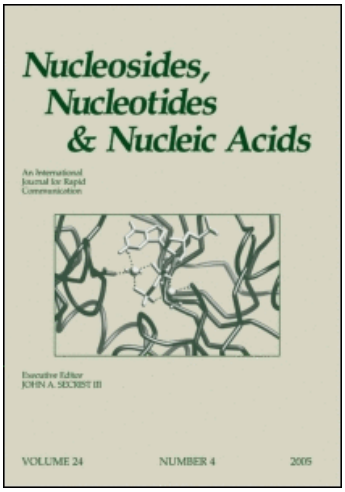

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis and Inhibitory Activity Against Phosphatidylinositol 4-Kinase of Echiguanine Analogs

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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

NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 713–714 (1999)

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

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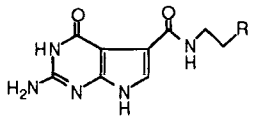
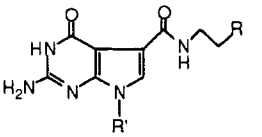
ABSTRACT: *N*-Substituted-2-amino-4(3*H*)-7*H*-oxopyrrolo[2,3-*d*]pyrimidine-5-carboxamides and their ribofuranosyl and 2',3'-dideoxyribofuranosyl derivatives were prepared as membrane permeable echiguanine analogs and tested for their ability to inhibit phosphatidylinositol (PI) 4-kinase. The ethylamide **5** and the corresponding ribofuranosyl compound **11** inhibited PI 4-kinase with IC_{50} 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 hepatomas[1] 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.

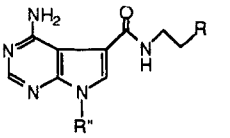
Echiguanine analogs and ribosylated ones were synthesized by using similar reactions. Cyanoethylamide-deazaguanine, which served as a starting material, was prepared from 7-iodo-7-deazaguanine with or without ribose and 3-aminopropionitrile



R = C(=NH)NH 2 echiguanine A **1**
R = CH_2NH_2 echiguanine B **2**



R' = H, ribose
or 2,3,-dideoxyribose

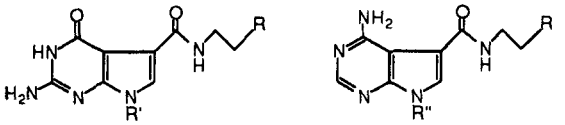


R" = ribose

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 activity[4] 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 IC_{50} 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_2NH_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
$CH_2NHC(=NH)NH_2$	**6**	0.15	**12**	7.5	n. p.		n. p.	
$CH_2NHCONH_2$	n. p.		**13**	1.0	n. p.		n. p.	

n. p. : not prepared

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