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A Short and Efficient Synthesis of Echiguanines A and B: Potent Inhibitors of Phosphatidylinositol-4-kinase

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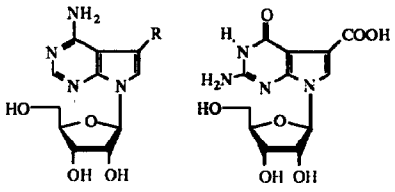
Abstract: An efficient synthesis which utilizes a palladium catalyzed carbonylation reaction between 2-pivaloyl-7-iodo-7-deazaguanine and 3-aminopropionitrile as a key step was developed for the preparation of a new class of pyrrolopyrimidine based PI 4-Kinase inhibitors: Echiguanines A and B.

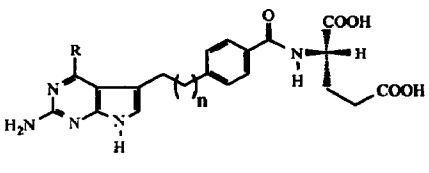
Deazaguanines, especially the pyrrolo[2,3-d]pyrimidine based compounds, represent a class of agents with broad and diversified biological activity. This includes the naturally occurring nucleoside antitumor antibiotics such as tubercidin (**1**), toyocamycin (**2**), sangivamycin (**3**), cadeguomycin (**4**)[1] and the non-naturally occurring antifolate antimetabolites that were discovered recently such as LY231514 (**5**)[2] and TNP-351 (**6**).[3] In 1991, yet another interesting series of pyrrolo[2,3-d]pyrimidine based agents, Echiguanines A (**7**) and B (**8**), were isolated from *Streptomyces* and were found to be selective and potent inhibitors of phosphatidylinositol-4-kinase (PI 4-kinase) derived from the A-431 cell membrane.[4] Inhibitors with specific inhibition of the PI kinases of the phosphotidylinositol turnover pathway can serve as important tools that may provide key information in the understanding of signal transduction in cell regulation and differentiation processes. Our earlier work and experience on the pyrrolo[2,3-d]pyrimidine based antifolate antimetabolite LY231514[2,5] has led us to a very short and efficient synthesis of these naturally occurring Echiguanines and thus reasonable quantity of these agents can be obtained for various biological evaluations.

Similar to the earlier Heck based synthetic approach of LY231514, a palladium catalyzed carbonylation reaction between 2-pivaloyl-7-iodo-7-deazaguanine (**9**)[2] and 3-aminopropionitrile was developed as a key step for the synthesis of Echiguanines (Scheme 1). This coupling reaction went very efficiently under one atmosphere of carbon monoxide using bis(triphenylphosphine)palladium (II) chloride as the catalyst.

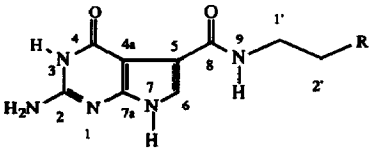


1, R=H
2, R=CN
3, R=$CONH_2$

4



5, R=OH, n=1 (**LY231514**)
6, R=NH_2, n=2 (**TNP-351**)



7, R = $\overset{3'}{\underset{\underset{NH}{\|}}{C}}-NH_2$, Echiguanine A

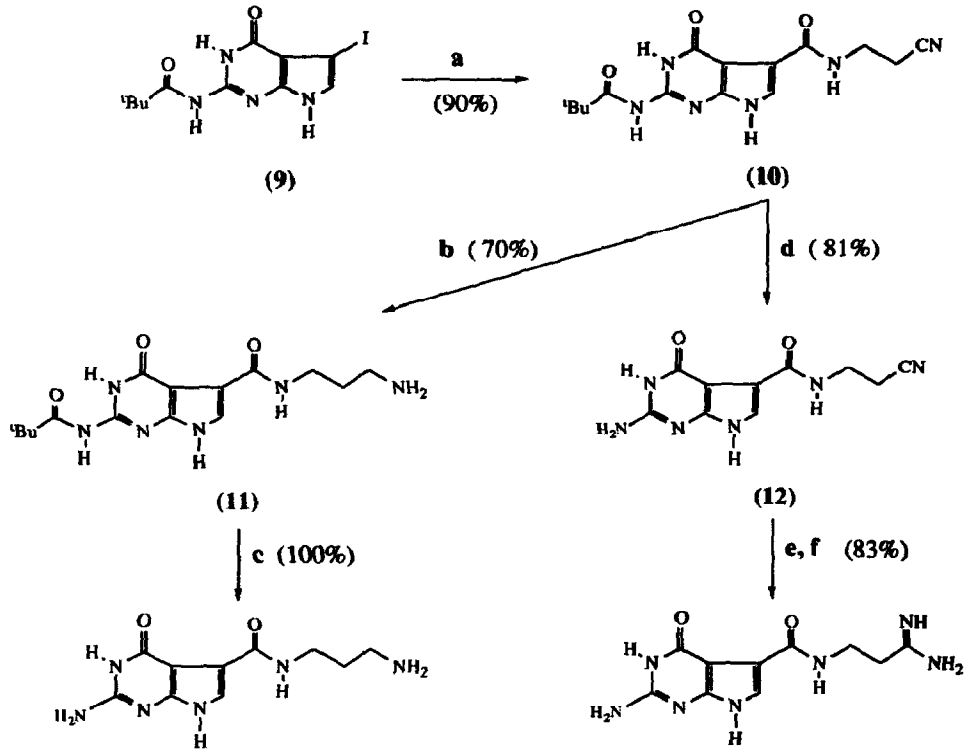
8, R = CH_2NH_2, Echiguanine B

A typical reaction condition involves reacting 0.52 g (1.46 mmol) of 2-pivaloyl-7-iodo-7-deazaguanine and 0.20 g (2.92 mmol, 2.0 eq) of 3-aminopropionitrile, 50 mg (0.07 mmol, 4.5 mol %) of bis-(triphenylphosphine)palladium (II) chloride in 10 ml of dry DMF. The reaction was let stir at 80 °C under one atmospheric carbon monoxide (balloon) and was homogeneous. The color of the reaction mixture changed gradually from bright yellow to red and the reaction was completed in 5 hours at 80 °C. The coupled product (**10**) was isolated after flash column chromatography on silica gel (10 % methanol/chloroform) in greater than 90 % yield as a white solid, mp 284-286 °C.[6] Compound (**10**) then serves as a common intermediate for the preparation of both Echiguanines A and B.

For the preparation of Echiguanine B, the cyano group of compound (**10**) was first reduced catalytically (PtO_2, CH_3COOH, 48 h) to the corresponding 3-aminopropyl side chain of compound (**11**). Removal of the 2-pivaloyl group of (**11**) in methanolic ammonia in a sealed tube (70°C, 5h) then gave Echiguanine B (**8**) as a white solid in quantitative yield, mp 270 °C (dec) (lit.,[4] 270-280 °C, dec). In the preparation of Echiguanine A, the 2-pivaloyl group of compound (**10**) was first removed (NH_3, CH_3OH, 70 °C, 7h, 81%) to give compound (**12**). The cyano group of (**12**) was then converted to the amidinoethyl side chain via a two step sequence: first by reacting (**12**) with anhydrous methanolic hydrogen chloride at 0 °C (1h) and giving the corresponding imino methyl ester (imidate), which was then treated with methanolic ammonia (RT, 24h) to give Echiguanine A (**7**, 83 %) as a white solid, mp 217-219 °C (purified by reversed phase HPLC, 10-15 % H_2O/CH_3CN, lit.,[4] 215-220 °C). The physical and spectroscopic data of these synthetic Echiguanines A and B are identical to those isolated from the natural sources.[7] Preliminary enzymatic study has also indicated that these synthetic Echiguanines exerted similar level of inhibition on the other phosphatidylinositol kinase of the phosphotidylinositol turnover pathway (PI 3-kinase) when compared to that of the natural Echiguanines.[8]

This palladium catalyzed carbonylation approach has thus provided a quick entry to the pyrrolo-[2,3-d]pyrimidine-5-carboxamide class of compounds; it can also in principle be expanded to other heterocyclic and amine systems and thus may prove to be useful tool in the structure-activity relationship studies of the effects of other structure variations on phosphatidylinositol kinases.

SCHEME 1



(a) $H_2NCH_2CH_2CN$, CO, $PdCl_2(Ph_3P)_2$, DMF, 80 °C; (b) PtO_2, H_2, AcOH;
(c) NH_3, MeOH, 70 °C; (d) NH_3, MeOH, 70 °C; (e) HCl, MeOH, (f) NH_3, MeOH.

References and Notes:

(1) (a) Suhadolnik, R. J. In *Nucleoside Antibiotics*; Wiley-Interscience: New York, **1970**; Chapter 8, p 315. (b) Suhadolnik, R. J. In *Nucleosides As Biological Probes*; Wiley-Interscience: New York, **1979**; Chapter 3, p 158.

(2) Taylor, E. C.; Kuhnt, D.; Shih, C.; Rinzel, S.; Grindey, G. B.; Barredo, J.; Jannatipour, M.; Moran, R. G.; *J. Med. Chem.*, **1992**, 35, 4450.

(3) (a) Akimoto, H.; Hitika,T.; Miwa, T.; Yukishige, K.; Kusanagi, T.; Ootus, K., *Proceedings of American Association of Cancer Research*, **1991**, 32, 327. (b) Miwa, T.; Hitaka, T.; Akimoto, H., *J. Med. Chem.*, **1991**, 34, 555.

(4) (a) Nishioka, H.; Sawa, T.; Nakamura, H.; Iinuma, H.; Ikeda, D.; Sawa, R.; Naganawa, H.; Hayashi, C; Hamada, M.; Takeuchi, T; Iitaka, Y.; Umezawa, K., *J. Natural Products*, **1991**, 54, 5, 1321. (b) Nishioka, H.; Sawa, T.; Iinuma, H.; Naganawa, H.; Hamada, M.; Takeuchi, T; Umezawa, K., *Japanese Patent* 04217681.

(5) Shih, C.; Gossett, L. S., *Heterocycles*, **1993**, 35, 825.

(6) For compound (**10**): mp 284-286°C; IR (KBr) 3373, 3139, 2978, 2255, 1645, 1560, 1422, 1329, 1264, 1160 cm^{-1}; UV (EtOH, λ_{max}) nm 216 (ε=12,700), 281 (ε=12,800), 300 (sh, ε= 11,300); ^1H NMR (DMSO-d6, 300 MHz) δ 1.22 (s, 9 H, $(CH_3)_3C$), 2.74 (t, 2 H, J=6.4 Hz, 2'-CH_2), 3.51 (dd, 2 H, J=6.1, J=12.2 Hz, 1'-CH_2), 7.60 (s, 1 H, 6-CH), 10.27 (t, 1 H, J=5.4 Hz, 9-NH), 11.02 (br s, 1 H, 3-NH), 12.26 (br s, 2 H, 2-NH and 7-NH); ^{13}C NMR (DMSO-d6, 75 MHz) δ 18.3 (q, $(CH_3)_3C$), 26.8 (s, $(CH_3)_3C$), 35.3 (t, 1'-CH_2), 79.6 (t, 2'-CH_2), 100.4 (s, 4a-C), 114.9 (s, 5-C), 119.7 (d, 6-CH), 126.1 (s, CN), 147.7 (s, 7a-C), 149.7 (s, 2-C), 159.2 (s, 4-CO), 163.0 (s, 8-CO), 181.5 (s, $(CH_3)_3CCO$); mass (FAB) m/z 331 (M^++1); Calcd for $C_{15}H_{18}N_6O_3$: 331.1519, obsd 331.1560.

(7) The physical and spectroscopic data of the synthetic Echiguanines A and B are summarized as follows:
Echiguanine A: mp 217-219°C; IR (KBr) 3500-2600 (br), 1700, 1665, 1643, 1611, 1514, 1420, 1384, 1362, 1344, 1230, 1163, 1100, 840, 783, 743, 724, 684 cm^{-1}; UV (H_2O, λ_{max}) nm 220 (ε=15,200), 227 (ε=15,100), 252 (ε=9,600), 296 (ε=8,700); ^1H NMR (DMSO-d6, 300MHz) δ 2.61 (t, 2 H, J=6.4 Hz, 2'-CH_2), 3.54-3.60 (dd, J= 6.4 Hz, J=12.0 Hz, 2 H, 1'-CH_2), 6.65 (s, 2 H, 2-NH_2), 7.22 (s, 1 H, 6-CH), 8.72 (s, 2 H, 3-NH and 7-NH), 9.05 (s, 2 H, 3'-NH_2), 10.39 (t, 1 H, J=5.5 Hz, 9-NH), 11.68 (s, 1 H, 3'-NH); ^{13}C NMR (DMSO-d6, 75 MHz) δ 33.2 (t, 2'-CH_2), 36.0 (t, 1'-CH_2), 96.3 (s, 4a-C), 114.5 (s, 5-C), 123.2 (d, 6-CH), 152.9 (s, 7a-C), 153.5 (s, 2-C), 160.7 (s, 4-CO), 163.4 (s, 8-CO), 169.5 (s, 3'-C); mass (FAB) m/z 264 (M^++1); Calcd for $C_{10}H_{13}N_7O_2$: 264.1209, obsd 264.1230.
Echiguanine B (as free amine form): mp 270°C (dec); IR (KBr) 3438, 3380, 3119, 2941, 2340, 1680, 1632, 1562, 1533, 1507, 1468, 1392, 1350, 1327, 1168, 832, 748, 686 cm^{-1}; UV (H_2O, λ_{max}) nm 219 (ε=13,200), 229 (ε=12,400), 254 (ε=8,000), 296 (ε=7,000); ^1H NMR (DMSO-d6, 300 MHz) δ 1.57-1.66 (m, 2 H, 2'-CH_2), 2.67 (t, 2 H, J=6.9 Hz, 3'-CH_2), 3.25-3.31 (dd, 2 H, J=6.0 Hz, J=12.0 Hz, 1'-CH_2), 6.70 (s, 2 H, 2-NH_2), 7.19 (s, 1 H, 6-CH), 6.50-7.50 (br s, 4 H, 3-NH, 7-NH and 3'-NH_2), 10.32 (t, 1 H, J = 4.9 Hz, 9-NH); ^{13}C NMR (DMSO-d6, 75 MHz) δ 31.9 (t, 2'-CH_2)[9], 36.2 (t, 1'-CH_2), 38.8 (t, 3'-CH_2)[9], 96.3 (s, 4a-C), 115.0 (s, 5-C), 122.8 (d, 6-CH), 153.2 (s, 7a-C), 153.8 (s, 2-C), 161.5 (s, 4-CO), 163.3 (s, 8-CO); mass (FAB) m/z 251 (M^++1); Calcd for $C_{10}H_{14}N_6O_2$: 251.1257, obsd 251.1267.

(8) Vlahos, C., Lilly Research Laboratories (unpublished data).

(9) Some of the discrepancy between the ^{13}C chemical shifts (especially the 2'C and 3'C) of the synthetic and the natural Echiguanine B may be due to the protonation of the 3' NH_2 group in the natural product. It has been reported that protonation of the aliphatic amines can cause higher field shift of the carbon signals three and four bonds from the positive nitrogen atom: Stothers, J. B. in *Carbon-13 NMR Spectroscopy*: Academic Press: New York, **1972**; Chapter 5, Section D, page 153 and references therein.

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