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Synthesis of (±)-10H-Phenothiazine-10-propanoyl-1′-myo-inositol

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SYNTHESIS OF (±)-10*H*-PHENOTHIAZINE-10-PROPANOYL-1'-*myo*-INOSITOL

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Abstract: The synthesis of (±)10*H*-phenothiazine-10-propanoyl-1'-*myo*-inositol was accomplished in order to test it as inhibitor of phosphatidylinositol specfic phospholipase C (PI-PLC).

Recently it has been found that agonist stimulation of a number of receptors results in the hydrolysis of phosphatidylinositol-4,5-biphosphate [(Ptd)Ins(4,5)P_2] to give diacylglycerol[1] and D-*myo*-inositol-1,4,5-triphosphate [1,4,5-IP_3][2] by a G-protein-activated phospholipase C (PLC)[3]. The two species released in this way by receptor-initiated cleavage may function as second messengers. Thus diacylglycerol was found[1] to be involved in the activation of protein kinase C, and [1,4,5-IP_3] in binding to a receptor, presumably a component of the endoplasmic reticulum, resulting in the discharge of calcium from intracellular stores into the cytosol.

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The inhibition of PLC is an ambitious target because the possibility of elucidation of complex mechanisms that are activated by this enzyme. At the date only aspecific inhibitors of this enzyme like ethylendiaminosuccinic acid[4], some aminoglycosilic antibiotics[5] and chloroquine[6] are known. Some years ago, Wightman *et al.*[6] described a PI-PLC activity in homogenates of purified resident mouse peritoneal macrophages and showed that certain phenothiazines are potent inhibitors of this activity, but the mechanism of this inhibition has not been cleared.

In order to study the structure-activity relationships of these compounds we have synthesised (±) 10*H*-phenothiazine-10-propanoyl-1'-*myo*-inositol (**5**). The alkaline hydrolysis of 10*H*-phenothiazine-10-propanenitrile[8] (**2**) yielded the corresponding acid that was converted without purification to 10*H*-phenothiazine-10-propanoyl chloride (**3**) by phosphorus pentachloride

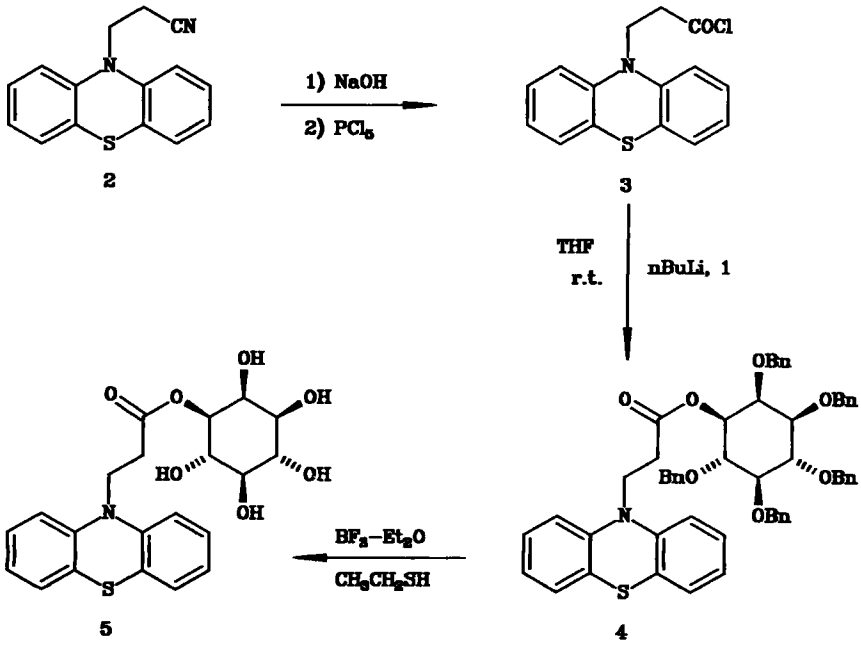

Table I

Compounds	Conc. (mM)	% inhib.
5	0.19	19.51
Chlorpromazine	0.03	40.70

in 92% yield. This was reacted with (±) 2,3,4,5,6 penta-*O*-benzyl-*myo*-inositol (**1**)[10] (n-BuLi, THF, r.t.) to give a 68% yield of **4**[9], and debenzylation with boron trifluoride etherate in ethanethiol[11] afforded a 41% yield of **5**[12].

The inhibiting activity on PI-PLC from human platelets was tested. Compound **5** showed an inhibiting actity lower than the phenothiazine chlorpromazine (Table I).

This result must be developed and it needs an eventual investigation; notwithstanding, it suggests a phenothiazine inhibition mechanism due to aspecific interaction with PI-PLC not involving enzyme active site.

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9) Compound **4**: ^{1}H-NMR ($CDCl_3$) δ 7.23 (m, 33 H), 4.65 (m, 12 H), 4.01 (t, 2 H, J = 9 Hz, $\underline{CH_2}N$), 3.45 (m, 4 H), 2.24 (t, 2 H, J = 6 Hz, $\underline{CH_2}COO$).

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11)Compound **5**: ^{1}H-NMR (DMSO D6) δ 7.10 (m, 8 H), 4.45 (dd, 1 H, $J_{1,2}$ = 2, $J_{1,6}$ = 9 Hz, H-1), 4.16 (t, 2 H, J = 6 Hz, $\underline{CH_2}N$), 3.82 (t, 1 H, $J_{2,3}$ = 2 Hz, H-2), 3.50 (m, 1 H, H-4, under H_2O), 3.37 (t, 1 H, $J_{5,6}$ = 9 Hz, H-6), 3.19 (dd, 1 H, $J_{2,3}$ = 2, $J_{1,3}$ = 9 Hz, H-3), 3.00 (t, 1 H, $J_{1,6}$ = 9 Hz, H-5), 2.79 (t, 2 H, J = 6 Hz, $\underline{CH_2}CO$); ^{13}C-NMR (DMSO D6) δ 170.87 ($\underline{CO}$), 144.28, 127.71, 127.31, 123.41, 122.67, 115.53, 79.16, 75.30, 74.95, 72.32, 71.22, 69.80, 42.21 ($\underline{CH_2}N$), 32.16 ($\underline{CH_2}CO$).

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