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IMIDAZOLE AND TRIAZOLE SUBSTITUTED ETHER PHOSPHOLIPIDS: POTENT ANTITUMOR AGENTS

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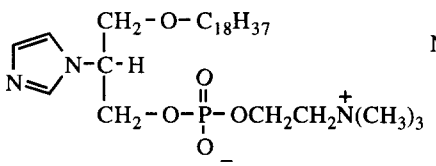
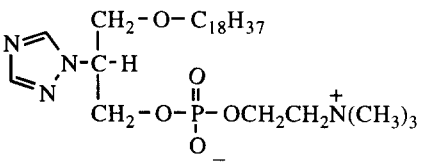
Abstract. Two novel ether phospholipids containing an imidazole and a triazole at the C-2 position of the glyceryl chain, respectively, were synthesized and evaluated as antitumor agents. Both compounds inhibited the growth of a number of tumor cell lines in vitro; IC_{50} values ranged from 1 to 6 μM for MCF-7, MDA-MB-231, HT-29 and HL-60 tumor cell lines. © 1997 Elsevier Science Ltd.

A number of ether phospholipids have been synthesized and evaluated as antitumor agents.[1] *rac-1*-O-n-Octadecyl-2-O-methyl-3-glycerophosphocholine (ET-18-OCH_3, edelfosine), first introduced by Arnold et al.,[2] has served as the prototype for the development of ether phospholipids as a novel class of antitumor agents.[1] It has been demonstrated that *in vivo* administration of ether phospholipids results in their preferential localization in tumor tissues.[3] Although the exact mechanism of action of ether lipids is not fully understood at present, they do not induce DNA damage and are not mutagenic, in contrast to most antitumor agents currently available.[1,4] Thus, the synthesis and study of new analogs of ether phospholipids may aid the development of therapeutically useful compounds to treat various types of cancer. As part of our program to develop potent antitumor agents, we sought to study ether phospholipids that feature a heterocylic group attached directly to the C-2 carbon atom of the glycerol backbone, which are currently unknown to our knowledge. In this communication, we report the synthesis of two novel ether phospholipids, *rac*-CPR 1006 and *rac*-CPR 1007 (Chart I), and provide a preliminary account of their antitumor activity.

Chart I



CPR 1006

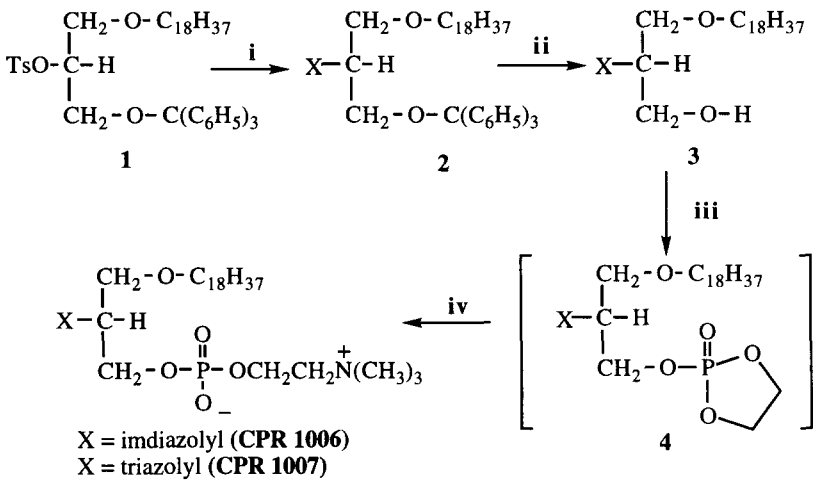


CPR 1007

The synthesis of CPR 1006 and CPR 1007 was accomplished as depicted in Scheme I, below. Starting material *rac*-1-O-n-octadecyl-2-*p*-toluenesulfonyl-3-O-tritylglycerol (**1**) was prepared by tosylation of *rac*-1-O-n-octadecyl-3-O-tritylglycerol by a reported procedure.[5] Introduction of imidazole or triazole group was achieved by

the reaction of the appropriate commercially available sodium derivative, respectively, with compound **1** in DMSO. Removal of trityl group from **2** was effected by treatment with *p*-toluenesulfonic acid [6] or $BF_3 \cdot Et_2O$.[7] Compound **3** on treatment with 2-chloro-2-oxo-1,3,2-dioxaphospholane[8] furnished the requisite intermediate **4** which on treatment with trimethylamine in acetonitrile at 65 °C afforded target compounds. Column chromatography of the crude material afforded pure CPR 1006/CPR 1007; the yields ranged from 45% to 57%, based on the intermediate alcohol, **3**. Both CPR 1006 and CPR 1007 are hygroscopic and should be stored in the absence of moisture.

Scheme I



(**i**) imidazole or triazole sodium derivative, anhyd. DMSO, ~100 °C, 48 h (**ii**) *p*-CH_3-C_6H_4-SO_3H, CH_3OH, reflux, 8 h (**iii**) 2-chloro-2-oxo-1,3,2-dioxaphospholane, anhyd. $C_6H_5CH_3$, 48 h (**iv**) $(CH_3)_3N$, CH_3CN, 65 °C, 48 h.

CPR 1006 and CPR 1007 were fully characterized by spectral (^1H NMR, ^{31}P NMR, ^{13}C NMR, and FAB/MS) analyses.[9] Purity was ascertained by thin-layer chromatography (TLC).[9]

Both CPR 1006 and CPR 1007 were evaluated for antitumor activity by reported procedure of Skehan et al.[10] These compounds inhibit the growth of a number of tumor cell lines (see Table I, below). The antitumor activity of these compounds was further confirmed by tests conducted at the National Cancer Institute. Although the IC_{50} values (average of 3 sets) of CPR 1006 and CPR 1007 are similar to ET-18-OMe, they do not exhibit the undesirable platelet activating factor (PAF) agonism associated with ET-18-OMe.[11]

Table I: Antitumor Activity (in vitro) of CPR 1006 and CPR 1007

Compound	IC_{50} values in μM				
	MCF-7[a]	MDA-MB-231[b]	HL-60[c]	HT-29[d]	FHC[e]
CPR 1006	3	4.5	2	2	50
CPR 1007	3	6	3	undetermined	undetermined
ET-18-OMe	undetermined	5	2	2	45

[a] Estrogen responsive human breast cancer cell line. [b] Estrogen receptor negative human breast cancer cell line. [c] Human promyelocytic leukemia cell line. [d] Transformed human colon cell line. [e] Normal human colon cell line.

Our work continues with investigations of various heterocycle containing ether phospholipids and their isomers as anti-tumor agents.

Acknowledgment

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9. All ^{1}H and $^{13}C\{^{1}H\}$ NMR chemical shifts reported are referenced against internal TMS; $^{31}P\{^{1}H\}$ NMR chemical shifts are referenced against external 85% H_3PO_4. **CPR 1006** FABMS (low resolution, positive ion mode, 3-NBA alcohol matrix): *m/z* (% relative intensity) 560.3 (100%) for $(MH)^+$; ^{1}H NMR ($CDCl_3$+CD_3OD, 2:1 v/v): 0.88 (t, 3H, J = 7 Hz), 1.27 (br s, 30H), 1.55 (m, 2H), 3.15 (s, 9H), 3.46–3.49 (m, 5H), 3.75–4.00 (m, 4H), 4.19 (t, 2H, J = 6 Hz), 4.52 (m, 1H), 6.98 (s, 1H), 7.23 (s, 1H), and 7.74 (s, 1H) ppm; $^{31}P\{^{1}H\}$ NMR ($CDCl_3$+CD_3OD, 2:1 v/v): 0.03 (s) ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$+CD_3OD, 2:1, v/v): 14.1, 22.9, 26.3, 29.6, 29.7, 30.7, 32.2, 54.2, 58.7 (d, J = 7 Hz), 58.9 (d, J = 5 Hz), 65.6 (d, J = 5 Hz), 70.3, 72.1, 119.2, 127.9, and 137.3 ppm. **CPR 1007** FABMS (low resolution, positive ion mode, 3-NBA alcohol matrix): *m/z* (% relative intensity) 561.4 (100%) for $(MH)^+$; ^{1}H NMR ($CDCl_3$+CD_3OD, 2:1 v/v): 0.88 (t, 3H, J = 7 Hz), 1.27 (br s, 30H), 1.49 (m, 2H), 3.15 (s, 9H), 3.35–3.52 (m, 5H), 3.82 (m, 2H), 4.02 (br m, 1H), 4.24 (m, 2H), 4.80 (m, 1H), 7.95 (s, 1H), and 8.42 (s, 1H) ppm; $^{31}P\{^{1}H\}$ NMR ($CDCl_3$+CD_3OD, 2:1 v/v): 0.04 (s) ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$+CD_3OD, 2:1 v/v): 14.2, 22.9, 26.1, 29.6, 29.8, 29.9, 32.1, 54.3, 59.1, 61.3 (d, J = 5 Hz), 64.3, 66.5, 68.9, 71.9, 144.4 and 151.1 ppm. TLC data: R_F values for **CPR 1006** and **CPR 1007** are 0.4 and 0.5, respectively [4x8 mm Silica gel TLC plate; eluent: $CHCl_3$+CH_3OH+30% aq.NH_4OH, 65+25+5 v/v/v].
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11. Unpublished work of Dr. P.T. Yazdi, Clarion Pharmaceuticals, Inc.

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