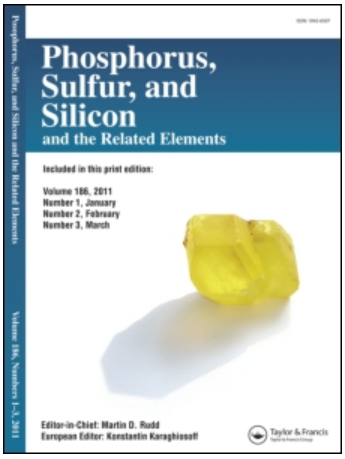

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Phosphoryl Substituted 3,5-*Bis*(Arylidene)-4-Piperidones Posessing High Antitumor Activity

I. L. Odinets,[1] M. V. Makarov,[1] O. I. Artyushin,[1] E. Yu. Rybalkina,[2] K. A. Lyssenko,[1] T. V. Timofeeva,[3] and M. Yu. Antipin[1]

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Keywords N-(phosphoryl)-3,5-bis(arylidene)-4-piperidones; N-(phosphorylalkyl)-3,5-bis(arylidene)-4-piperidones; alkylation; phosphorylation; cytotoxity

3,5-Bis(arylidene)-4-piperidones and related compounds **1** possess anticancer and antioxidant activity (Scheme 1).[1,2] Some of these compounds are also fluorescent, which makes possible to use them as dyes for tracing their cellular pathways during chemotherapy and as agents for photodynamic therapy.[3] The important way to regulate the bioavailability and drug delivery of these compounds to target organs is an introduction of different substitutes R^1 to the N-atom of a piperidone moiety. Phosphorus-containing groups are prospective as such modifiers and may contribute to the biological activity. Therefore, we investigated synthetic approaches to phosphorylated arylidenepiperidones and "structure-activity-fluorescence properties" relationship in this series.

Direct phosphorylation of NH-precursor **2** by phosphorus(IV) acid chlorides afforded N-phosphorylated compounds **3**. Derivatives **4** with elongated alkylene-phosphoryl linker could be synthesized only by condensation of aldehydes with phosphorylated N-alkylpiperidones as

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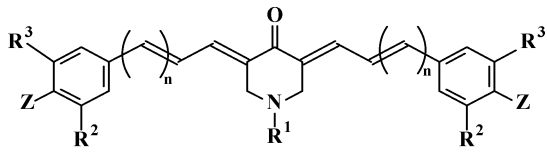
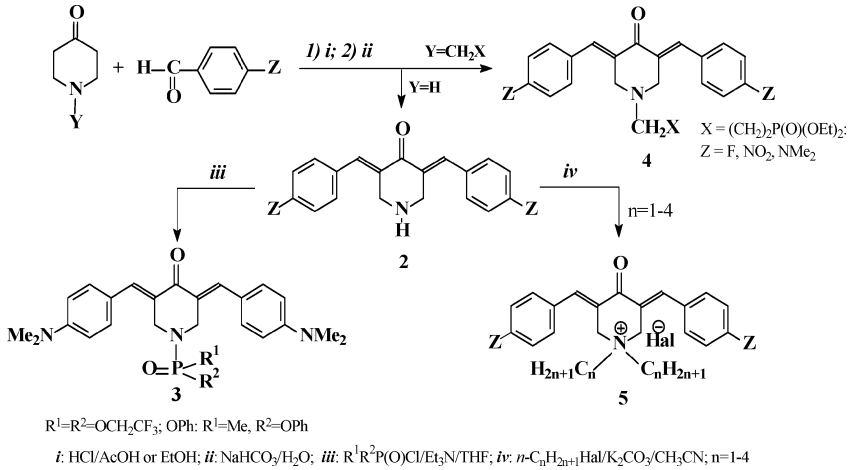


1, R^1 = alkyl, R^2, R^3=H, OH; n = 0, 1;
Z = NMe_2, NO_2

SCHEME 1

alkylation of the NH-precursor **2** with alkyl halides surprisingly resulted in quaternary salts **5** as the only reaction products (Scheme 2).



i: HCl/AcOH or EtOH; *ii*: $NaHCO_3/H_2O$; *iii*: $R^1R^2P(O)Cl/Et_3N/THF$; *iv*: *n*-$C_nH_{2n+1}Hal/K_2CO_3/CH_3CN$; n=1-4

SCHEME 2

Compounds **3–5** demonstrate high antitumor activity against a number of human cancer cell lines with IC_{50} values in the range of 0.3–$50 \cdot 10^{-6}$ M including resistant lung carcinoma cell line A549 (compounds **5**).

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