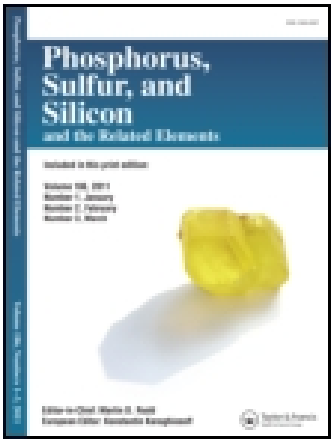

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Synthetic Approaches to Cytotoxic Amidophosphates, Aminophosphonates, and Aminobisphosphonates with 3,5-Bis(arylidene)piperid-4-one Framework

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SYNTHETIC APPROACHES TO CYTOTOXIC AMIDOPHOSPHATES, AMINOPHOSPHONATES, AND AMINOBISPHOSPHONATES WITH 3,5-BIS(ARYLIDENE)PIPERID-4-ONE FRAMEWORK

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Abstract *Facile synthetic approaches to a few novel classes of amidophosphates, ω-aminophosphonates, and bisphosphonates having a 3,5-bis(arylidene)piperid-4-one backbone have been elaborated starting from piperid-4-ones functionalized with phosphorus motives followed by aldol-crotonic condensation with a range of (hetero)aromatic aldehydes or via introduction of the corresponding phosphorus function into the preformed NH-3,5-bis(arylidene)piperid-4-ones. Combination of phosphorus-containing moieties possessing inherent bioactivity and cytotoxic 3,5-bis(arylidene)piperid-4-one moiety resulted in the compounds with high antitumor activity towards human carcinoma cell lines Caov3, A549, Scov3, PC3, KB 3-1, and KB 8–5 (IC_{50} in the range of 1–80 μM).*

Keywords Aminobisphosphonates; aminophosphates; aminophosphonates; 3,5-bis(arylidene) piperid-4-ones; cytotoxic properties; synthesis

INTRODUCTION

3,5-bis(Arylidene)piperid-4-ones (and the related bis(arylidene)cycloalkanones) possessing the general structure **I** and bearing in the molecule 1,5-diaryl-3-oxo-1,4-pentadienyl (dienone) pharmacophore moiety have been intensively studied over last decades. The above pharmacophore group has been shown to be responsible for different types of biological activity, including free radical scavenging,[1] α-glucosidase inhibitory,[2] antimycobacterial,[3]

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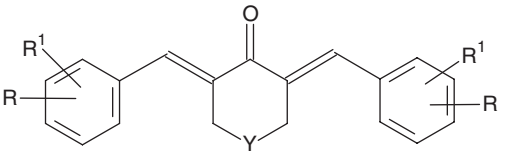
and antineoplastic properties.[4,5] According to the proposed mechanism of antineoplastic action, these compounds are capable of alkylating the biogenic cellular thiols (via the SH-nucleophile addition to vinyl bonds), whereas the nitrogen-containing intracellular nucleophiles, such as proteins and nucleic acids, are not affected by them. Therefore, 3,5-bis(arylidene)-piperid-4-ones are considered as promising potential drug-candidates that may be free of mutagenic properties of known alkylating anticancer agents used in current medicine practice,[6] especially taking into account their very low general toxicity.[7] Moreover, recently N-alkylated 3,5-bis(arylidene)piperid-4-ones were found to have potential as two-photon sensitizers useful for two-photon photodynamic therapy, which is more advantageous than one-photon one due to deeper tissue penetration and being highly localized in the effect.[8]

Antineoplastic properties of these compounds may be adjusted, for example, by variation of aromatic substituents in their structure. Thus, increase of the electron-withdrawing properties of these substituents usually results in more pronounced cytotoxicity apparently due to the more electrophilic character of unsaturated carbon atoms in the pharmacophore group. Furthermore, the introduction of different groups to the piperidone nitrogen atom may influence bioactivity of the compound via their interactions with additional binding sites of a biological target. In general, these groups can either increase the cytotoxic properties by facilitating the approach of the cytotoxin to a specific binding site or reduce them by preventing this interaction.



I

Bis(arylidene)cyclohexanones - Y=CH_2;
Bis(arylidenepiperidones) - Y=NH

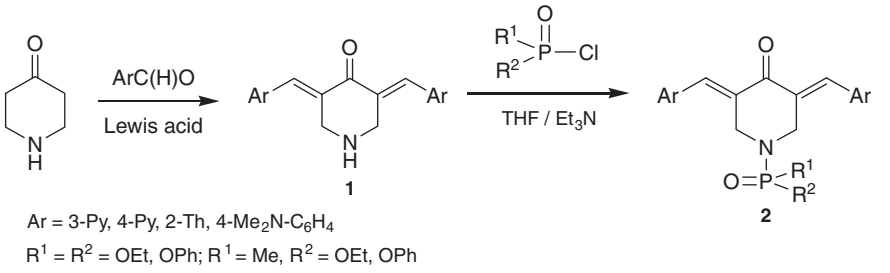
Our investigations in this field are focused on the exploitation of advantageous properties of phosphorus-containing groups, such as inherent bioactivity, ability to impart solubility and bioavailability to the molecule, and improve the capacity of its transportation via a cellular membrane, for modification of the 3,5-bis(arylidene)piperid-4-one structure. In this article we outline the main synthetic approaches to the P-modified derivatives developed by us recently and briefly discuss the positive influence of the phosphorus substituents on the cytotoxic properties of the compounds. Note that the results have partially been published and some are communicated preliminary in this article.

RESULTS AND DISCUSSION

In general, the phosphorus-containing groups may be introduced to the nitrogen atom of the 3,5-bis(arylidene)piperid-4-one molecule using either the direct P-N bonding with formation of phosphorus amides or the phosphorus and heterocyclic nitrogen atoms can be bound with additional linkers of different nature.

Therefore, direct phosphorylation of the preformed NH-3,5-bis(arylidene)piperid-4-ones **1** with appropriate phosphorus acid chlorides in the presence of triethylamine as a

base was the method of choice for the formation of the P-N bond between the phosphorus atom in different surroundings and the nitrogen one of 3,5-bis(arylidene)piperid-4-one scaffold (Scheme 1). After appropriate purification, the desired P-amides **2** were isolated



1 **2**

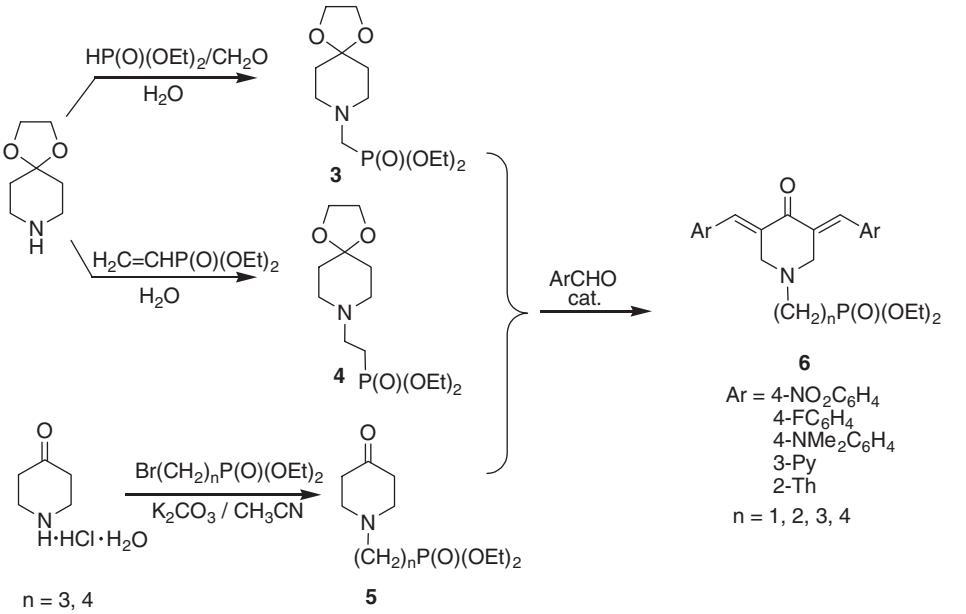
Scheme 1

in yields of about 60% excluding the compounds having 4-pyridine rings.[9,10] It should be noted that the aldol-crotonic condensation of the corresponding aromatic aldehyde, including heteroaromatic ones, with piperid-4-one to afford the starting NH-precursors can be efficiently carried out in the presence of Lewis acids ($LiClO_4$, $MgBr_2$, or boron trifluoride etherate) according to the procedures elaborated by us recently.[11]

In contrast, for the synthesis of N-(ω-phosphorylalkyl)-bis(arylidene)piperid-4-ones **6** the aldol-crotonic condensation followed the synthesis of N-(ω-phosphorylalkyl)-piperid-4-ones **3–5**.[9,12,13] The synthetic approach to compounds **3–5** differed depending on the number of methylene units in alkylene chain between the phosphorus and nitrogen atoms. Thus, the three-component Kabachnik-Fields reaction of diethyl phosphite, commercially available 1,4-dioxa-8-azaspiro[4.5]decane, and formaldehyde was used for the preparation of piperidinyl-substituted α-aminophosphonate **3** in the dioxalane protected form. For the synthesis of β-aminophosphonate **4** the aza-Michael reaction was utilized. It should be emphasized that both syntheses were performed in water as a sole medium without any cosolvent or catalyst, which is especially advantageous from a green chemistry point of view.[14] Finally, the starting phosphorylated piperidones having longer alkylene linker (n = 3 or 4) were readily obtained in good yields via the alkylation of piperid-4-one hydrochloride monohydrate with the corresponding diethyl ω-bromoalkylphosphonate under phase transfer catalysis (PTC) conditions (Scheme 2).[12]

Further condensation of these phosphorylated precursors **3–5** with aromatic aldehydes performed under typical acidic conditions provided the final products **6** in low to moderate yields (25–40%) due to partial dealkylation of ethoxy groups at the phosphorus atom. Application of Lewis acids such as $MgBr_2$ in the presence of Et_3N and $BF_3{\cdot}OEt_2$ and, in some instances, basic conditions (piperidine/EtOH) increased the yields up to ca 50% (Scheme 2). In any case, the condensation was accompanied by simultaneous deprotection of the ketal group in compounds **3** and **4**. Note that the compounds **6** may be considered as ω-aminophosphonates bearing a 3,5-bis(arylidene)piperid-4-one scaffold.

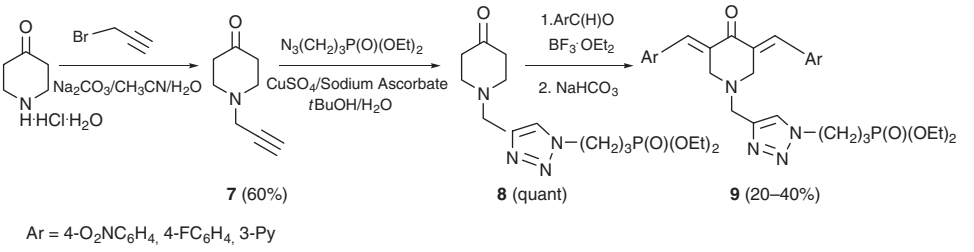
An alternative approach to the ligation of the phosphorus moiety to the 3,5-bis(arylidene)piperid-4-one scaffold may be performed by means of bioorthogonal reactions. Note that in general chemistry in particular, *bioorthogonal reactions* is a generic term for a set of reactions that use the reaction of modular building blocks to construct heteroatom-C bond and combine two biologically active modules with high effectivity and chemoselectivity. In this line, the Cu(I)-catalyzed 1,2,3-triazole formation from azides and



Scheme 2

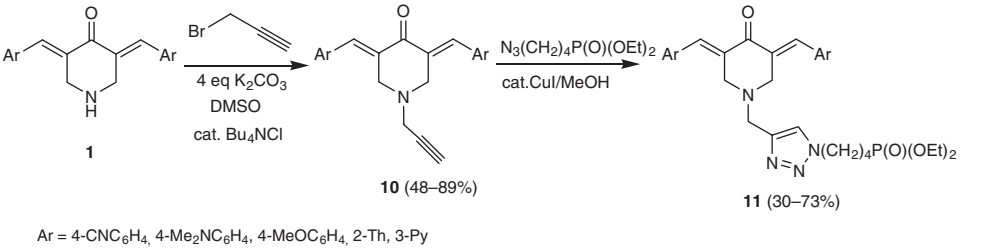
terminal alkynes according to 1,3-dipolar *Huisgen* cycloaddition scheme (often referered to as a click reaction) is a particular powerful ligation reaction working well both for phosphorylated alkynes and phosphorylated azides,[15] whose efficient synthesis in ionic liquids was reported by us recently.[15b] The complexing properties of the phosphoryl group toward copper did not affect the chemoselectivity of the process to afford exclusively the corresponding 4-regioisomers.

Hence, for the design of phosphorus-substituted 3,5-bis(arylidene)piperid-4-ones having a 1,2,3-triazole linker we used two approaches differing in the sequence of reaction steps. In the first approach, the propargyl group was firstly introduced into the molecule of 4-piperidone in the presence of sodium carbonate as a base followed by 1,3-cycloaddition reaction with phosphorylated azide yielding a substituted 4-diethoxyphosphorylalkyl-1,2,3-triazole **8** bearing piperidone ring. Subsequent aldol-crotonic condensation of triazole **8** with an appropriate aldehyde in the presence of boron trifluoride etherate and further neutralization of intermediate tetrafluoroborate salt led to the final compounds **9** (Scheme 3).



Scheme 3

In the second procedure, the propargyl group was introduced into the molecule of the preformed NH-piperidones **1** using the excess of potassium carbonate as a base, dimethyl sulfoxide (DMSO) as a solvent, and tetrabutylammonium chloride as a phase transfer catalyst. The reaction completed in 2 h to give the desired alkyne in 48–89% yield after purification. Further, N-propargyl-3,5-bis(arylidene)piperid-4-ones **10** were used as the starting substrates in the 1,3-dipolar cycloaddition with phosphorylated azides (Scheme 4).

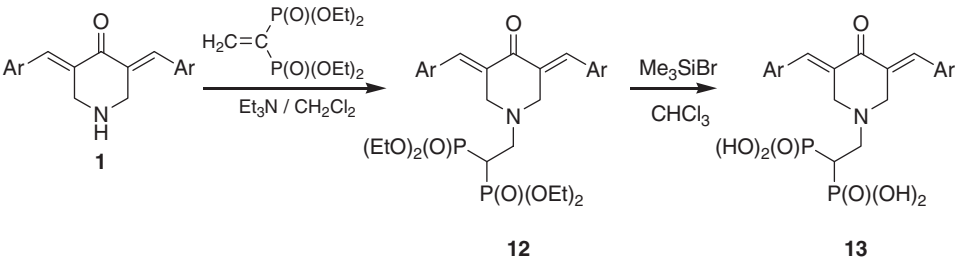


Scheme 4

Note that in the typical procedure for the regioselective Cu(I)-catalyzed alkyne-azide coupling, the catalyst can be directly introduced as a Cu(I) salt or generated in situ by reduction of Cu(II) salts,[16] usually in organoaqueous systems, or by oxidation of Cu(0).[17] For the synthesis of the intermediate compounds **8** from propargyl substituted precursor **7** (soluble in *t*-BuOH/H_2O mixed solvent) the second approach in which Cu(I) salt was generated from Cu(II) precursor in the reaction with sodium ascorbate was more preferable, resulting in 1,2,3-triazole **8** in a quantitative yield. In contrast, for less soluble N-propargyl-3,5-bis(arylidene)piperid-4-ones **10** the first method using CuI as a catalyst and MeOH as a solvent provided better results (up to 73% in the case of Ar = 4-$MeOC_6H_4$; Scheme 4). In any case, the lowest yields of the compounds **9**,**11** were observed in the case of heterocyclic side rings (2-thienyl and 3-pyridinyl).

Furthermore, it seems reasonable to obtain potential twin drugs combining in the molecule the useful properties of 1,5-diaryl-3-oxo-1,4-pentadienyl pharmacophore moiety and the bisphosphonate residue. Indeed, bisphosphonates (BPs), which are analogs of naturally occurring diphosphates, are known as powerful inhibitors of bone resorption and some are currently clinically applied to treat diseases connected with calcium disorders, such as malignant hypercalcemia,[18] Paget's disease, osteoporosis, and tumoral metastasis.[19] BPs are also of interest in the context of cancer and immunotherapy as well as they possess potent effects against parasites responsible for sleeping sickness, Chagas disease, malaria, and leishmaniasis.[20] The third-generation BP drugs, which are up to 10,000-fold more active than those of the first generation (e.g., etidronate), contain an additional moiety in the molecule comprising the nitrogen atom within a cyclic structure, such as in risedronate and zoledronate.[18a]

In order to introduce the bisphosphonate residue in the 3,5-bis(arylidene)piperid-4-one scaffold we used the aza-Michael addition, which is probably the most important method for C-N bond formation, starting from ethylidenbisphosphonate as vinylphosphoryl compound and NH-3,5-bis(arylidene)piperid-4-ones **1** as N-nucleophiles (Scheme 5). This reaction was found to proceed readily in DCM solution in the presence of tertiary amine as a catalyst providing high yields of the desired compounds even on multi-gram scale.[21]



Ar = 4-$NMe_2C_6H_4$, 4-$MeOC_6H_4$, 4-CNC_6H_4, 4-$NO_2C_6H_4$, 3,5-^{t}Bu-4-OHC_6H_2, 3-Py, 2-Th

Scheme 5

It should be noted that all compounds bearing phosphonate or phosphinate groups can be readily converted to the corresponding free phosphonic (phosphinic) acids via the reaction with trimethylbromosilane in chloroform followed by the treatment with aq. MeOH of the intermediate trimethylsilyl esters formed as illustrated in Scheme 5 for the synthesis of the corresponding bisphosphonic acids **13**.

X-ray crystallography[8–10,12] of a few representative phosphorus-modified 3,5-bis(arylidene)piperid-4-ones has revealed that the olefinic double bonds adopt the *E*,*E*-configuration similar to the parent NH-piperid-4-ones and the products of their N-acylation.[22] For illustration, Figure 1 shows the general view of the compound **2** having the direct P-N bonding and thiophene side rings (top) and that for the compound **3** in which the phosphorus atom is attached to the 3,5-bis(arylidene)piperid-4-one scaffold via an ethylene linker (bottom). Studies of N-phosphorylated 3,5-bis(arylidene)piperid-4-ones have shown that introduction of even bulky substituents at the N atom of the piperidone ring does not cause significant rotation of the planes of phenyl or thiophene rings from that of the central heterocycle. The values of dihedral angles show that a conjugated pharmacophore fragment in the molecules of N-alkyl-3,5-bis(arylidene)piperid-4-ones usually is closer to planarity than those in the molecules of their N-phosphorylated analogues. Such deviation from planarity might be caused by a higher volume of the phosphorus substituent at the piperidone nitrogen atom and in some cases by unusual conformation of the phosphorus group in the molecule.

It should be mentioned that under the action of visible light, thermodynamically more stable *E*,*E*-isomers were found to undergo slow photochemical conversion in $CDCl_3$ solution to the corresponding *E*,*Z*-isomers, and we succeeded in isolating *E*,*Z*-*N*-methyl-3,5-bis(thienylidene)piperid-4-one in an individual state.[10]

Biological evaluations of the compounds in vitro were performed on several human tumor cell lines such as Scov3 and Caov3 (ovarian carcinoma), A549 (lung carcinoma), PC3 (prostate carcinoma), KB 3-1 (human oral epidermoid carcinoma cells), and drug-resistant subclone of the latter one, that is, KB 8–5. In general, activity of all of the compounds tested was one order higher compared to that of melphalan used as a positive control. These studies have revealed that the introduction of the phosphorus group directly to the nitrogen atom of the 3,5-bis(arylidene)piperid-4-one molecule resulted in a significant increase of cytotoxic properties compared to the parent NH-analogues and N-alkylated derivatives. Hence, N-ω-phosphorylalkyl substituted compounds **6** in general are slightly less active compared to phosphorus amides **2**. As expected, among the compounds belonging to the particular series,

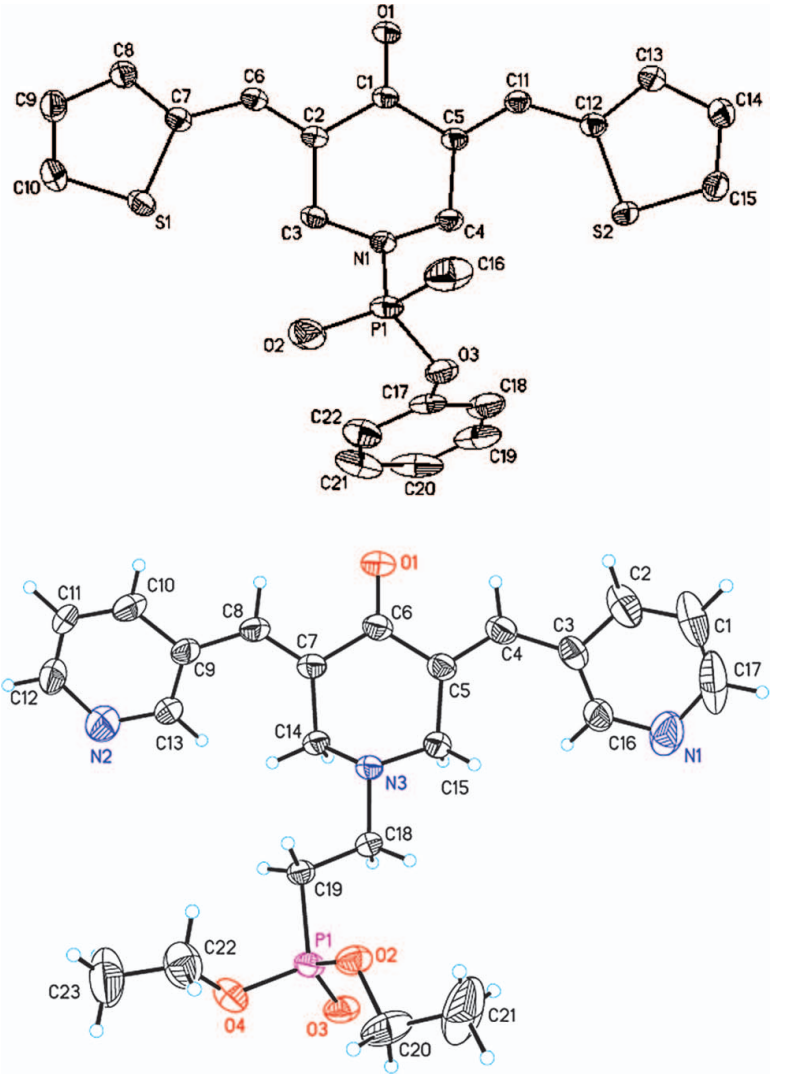


Figure 1 Molecular structure of N-methylphenoxyphosphoryl-3,5-bis(thienylidene)-4-piperid-4-one **2** (top) and N-(diethoxyphosphoryl)ethyl-3,5-bis(pyridinylmethylene)-4-piperidone **6** (bottom) drawn at 40% probability of thermal ellipsoids.

those bearing strong electron-withdrawing pyridine or 4-nitrosubstituted benzene rings exhibited higher antitumor activity, with IC_{50} values in the range of 1–2 μM compared to those containing fewer acceptor thiophene rings or benzene ones with donor 4-dimethylamino groups (IC_{50} up to 80 μM).[10,12,13] Furthermore, among the compounds having 3- and 4-pyridine rings and N-P bonding the investigation has revealed those that possess practically the same high level of activity toward drug-resistant cell line KB 8–5, differing from normal subclone KB 3-1 by the expression of transmembrane-transporting protein Pgp170. This protein, which is responsible for elimination of hydrophobic compounds including the cytostatics from tumor cells, is a plausible reason for the classical multidrug resistances. These

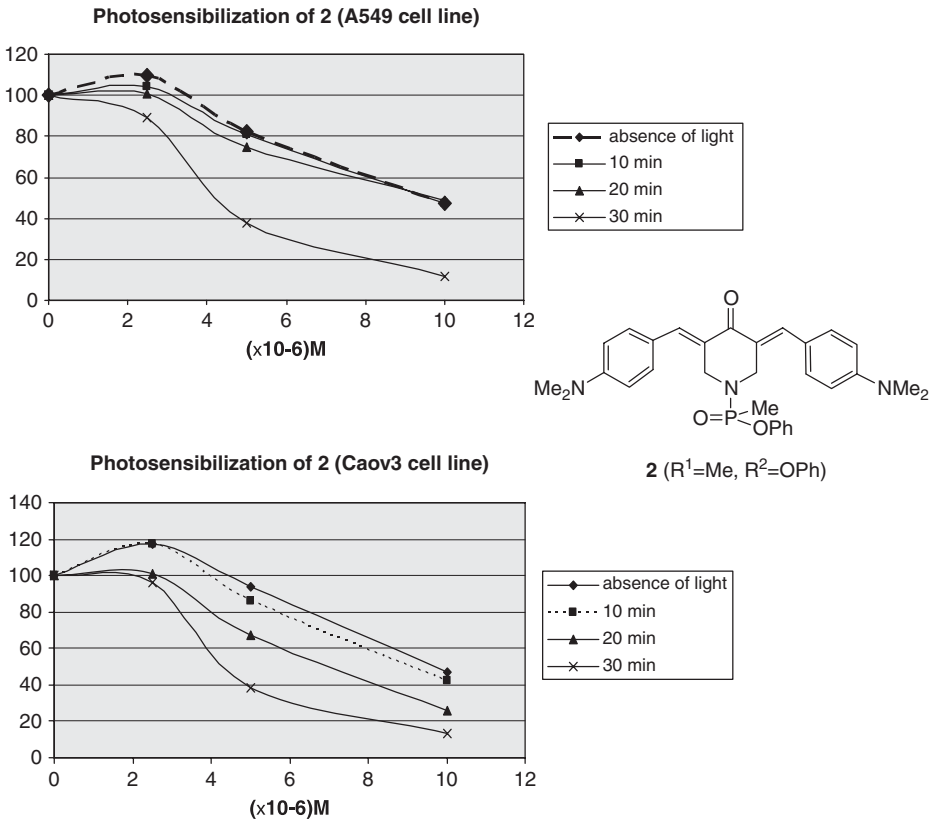


Figure 2 Action of white light on the cytotoxic properties of O-phenyl methyl[(*3E,5E*)-4-oxo-3,5-bis(4-dimethylaminobenzylidene)-1-piperidinyl]phosphinate **2**.

data allow us to suggest that N-phosphorylated-3,5-bis(pyridinylmethylene)-4-piperidones are not the substrates for Pgp170 and hence can be of interest for treatment of resistant tumors. However, this problem requires additional detailed studies.

Regardless of the fact that the individual *E*,*Z*-isomer of N-methyl-3,5-bis(2-thienylmethylene)piperidin-4-one demonstrated decreased cytotoxic properties compared to those of the corresponding *E*,*E*-isomer, the cytotoxicity of N-phosphorylated 3,5-bis(arylidene)piperidin-4-ones with donor substituents in the aromatic rings significantly increased after irradiation of cell cultures treated with the test compound with white light. In other words, these compounds belong to photosensibilized cytostatics. Thus, in the representative assay the percentage of surviving cells (A549, lung carcinoma, and Caov3, ovarian carcinoma) in the presence of methyl(phenoxy)substituted phosphinate **2** decreased significantly under exposure to white light (Figure 2).

CONCLUSIONS

This study has demonstrated suitable synthetic approaches to the introduction of the phosphorus moiety either directly to the nitrogen atom of the 3,5-bis((hetero)arylidene)-piperid-4-one molecule or via an additional linker to afford a few novel series of cytotoxic

compounds belonging to amidophosphates, aminophosphonates, or methylene bisphosphonates. Among the compounds obtained, those bearing 3- and 4-pyridine rings or 4-nitrobenzene ones possess excellent antitumor properties toward both ordinary human carcinoma cell lines and drug-resistant subclones. Thus, we proved the hypothesis of the fruitful combination of the phosphorus residue and 3,5-bis((hetero)arylidene)-piperid-4-one framework yielding promising drug candidates for further investigation.

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