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3,5-Bis(arylidene)piperid-4-ones Containing 1,3,2-Oxazaphosphorinane Moieties: Synthesis and Antitumor Activity

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ABSTRACT: *Two novel series of phosphorus-substituted 3,5-bis(arylidene)piperid-4-ones bearing 1,3,2-oxazaphosphorinane cycle either directly attached to the piperidone core through the P—N bond (diamidophosphates* **4***) or connected with it via thiocarbamoyl linker (thioureas* **5***) were obtained by the phosphorylation of NH precursors with 2-oxo-1,3,2-oxazaphosphorinane chloride or the reaction of the former ones with the corresponding cyclic isothiocyanate. According to the results of cytotoxicity screening against human carcinoma cell lines (A549, CaOv3, KB), thioureas* **5** *were more active than the diamidophosphates* **4** *bearing the same arylidene rings, with compounds with electron-withdrawing side groups displaying* IC_{50} *in the micromolar range of 1.2–7* μM.
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INTRODUCTION

The discovery of antitumor properties of 1,3,2-oxazaphosphorinanes (also referred to as oxazaphosphinanes) by Brock [1] promoted numerous investigations in this area of organophosphorus chemistry, and nowadays, among thousands of drug candidates screened up to date, at least two chemotherapeuticals—cyclophosphamide and ifosfamide (Fig. 1)—found a wide range of applications in clinical practice. These related compounds being not cytotoxic themselves are converted to the active alkylating mustard via the hepatic cytochrome P450 catalyzed 4-hydroxylation in the liver [2]. These compounds can be considered as prodrugs in which 1,3,2-oxazaphosphorinane cycles facilitate transportation of the active cytostatics to cancer cells and allow for a considerable reduction of the general toxicity of plain mustard. Furthermore, 1,3,2-oxazaphosphorinan-2-thiones, especially those bearing *p*-nitrophenoxy and butylthio (XR = 4-O_2N-C_6H_4, BuS) groups (Fig. 1), exhibit high nematocide activity with low mammalian toxicity and have a strong synergistic effect on pyrethroid insecticides [3–5].

Taking into account notable transport properties and metabolic peculiarities of the 1,3,2-oxazaphosphorinane cycle, we focused on the application of this phosphorus moiety for the modification of some pharmacophores to impart them

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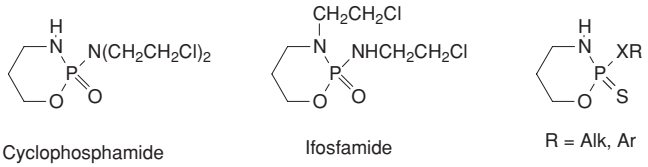


FIGURE 1 Biologically active 1,3,2-oxazaphosphorinanes.

better bioavailability or provide the compounds possessing higher or even other types of bioactivity. 3,5-Bis(arylidene)piperid-4-ones possessing free radical scavenging [6], α-glucosidase inhibitory [7], antimycobacterial [8], and antitumor properties [9] due to the presence of a 1,5-diaryl-3-oxo-1,4-pentadienyl (dienone) pharmacophore, were among the basic skeletons of interest. Antitumor properties of these compounds can be adjusted either by the variation of aromatic substituents or the introduction of different groups at the piperidone nitrogen atom. Indeed, we have recently shown that incorporation of a range of phosphorus-containing moieties, such as phosphonate and methylenebisphonate groups, as well as phosphoric acid residues either directly bound with the heterocyclic nitrogen atom or connected with it via an alkylene linker, into the structure of 3,5-bis(arylidene)piperid-4-ones, resulted in a pronounced increase of their in vitro cytotoxicity [10–13].

In this paper, we report on the synthesis and cytotoxicity of novel 3,5-bis(arylidene)piperid-4-ones modified with 1,3,2-oxazaphosphorinane cycle to impart them better bioavailability or provide higher antitumor properties.

RESULTS AND DISCUSSION

Synthesis

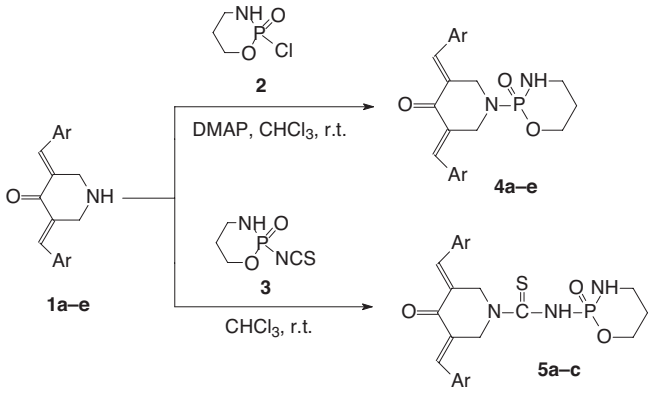
To attach 1,3,2-oxazaphosphorinane cycle to the 3,5-bis(arylidene)piperid-4-one framework, we used two different approaches. The first one was based on the direct phosphorylation of the parent *NH*-3,5-bis(arylidene)piperid-4-ones **1a–e** with cyclic phosphorus acid chloride **2** [14] and provided compounds **4a–e** bearing the direct P—N bond, which may be considered as prodrugs of 3,5-bis(arylidene)piperid-4-ones, releasing the cytotoxic dienone system over the hydrolytic cleavage (Scheme 1). Amides **4a–e** were synthesized using a slight excess (1.1 mol equiv) of acid chloride **2** relative to the corresponding starting *NH*-precursors **1a–e** in $CHCl_3$ in the presence of 4-dimethylaminopyridine (DMAP) as a base at room temperature. Under these optimized conditions, the phosphorylation afforded compounds **4b,c,e** in good yields (60–85%), which decreased to 43% and 38% in the case of 4-dimethylamino and 3-pyridyl derivatives **4a** and **4d**, respectively. Obviously, worse results for the above compounds **4a**,**d** can be explained by the presence of residual water in the starting compounds **1a**,**d**, which could not be removed even by prolonged drying over phosphorus pentoxide.

In the other approach, the desired compounds, the main skeleton of which was connected with the oxazaphosphorinane moiety via a thiocarbamoyl linker, were readily obtained by the reaction of *NH*-precursors **1a–c** with isothiocyanate **3** derived, in turn, from the chloride **2** according to the known procedure [15]. The reaction proceeds smoothly in $CHCl_3$ at room temperature to give the crude thioureas **5a–c** in high yields. The isolated yields of the derivatives **5b,c** were still more than 85% whereas the yield of 3-pyridyl derivative **5a** decreased up to 25% over the chromatographic purification.

The structures of the phosphorylated products **4a–e**, **5a–c** were elucidated on the basis of ^{1}H, ^{31}P, ^{13}C NMR, and IR spectral data along with a single crystal X-ray diffraction analysis performed for diamidophosphate **4e** (Fig. 2). According to the analytical data, some of the compounds obtained are inclined to form either hydrates (**4a,d** and **5a**) or strong solvates with chloroform (**5c**). The ^{31}P NMR spectra of the corresponding products displayed singlet signals at ca. 10 ppm for diamidophosphates **4a–e** and at ca. –2 ppm for thioureas **5a–c**. These values of chemical shifts are typical for such phosphorus atom surrounding. In the ^{1}H NMR spectra of all compounds, the singlet resonances assigned to vinyl hydrogen atoms are observed at ca. 7.7–8.0 ppm, which is usual for this type of compounds. On the whole, the spectral data are consistent with *E,E*-geometry of the dienone moiety and are in good agreement with the literature data for the known analogs. Note that some compounds synthesized possess poor solubility in common organic solvents, thus preventing recording of ^{13}C NMR spectra of good quality.

According to the X-ray investigation of the compound **4e** (as a crystallosolvate with one CH_2Cl_2 molecule), the geometrical parameters of the phosphorus-bound piperidone core are very close (within 0.01 Å) to those in its 3,5-substituted analogs [16, 17]. In particular, the piperidone moiety adopts a chair conformation with the deviation of the nitrogen atom by 0.68(1) Å, the bond P—N is in the axial position and the olefin fragments in its bulky substituents (that are rotated around the C—Ph bonds) have *E* configuration.

The overall geometry of the phosphorus-containing heterocycle in **4e** is also typical for the



SCHEME 1 Synthesis of 3,5-bis(arylidene)piperid-4-ones **4**, **5** modified by 1,3,2-oxazaphosphorinane moieties.

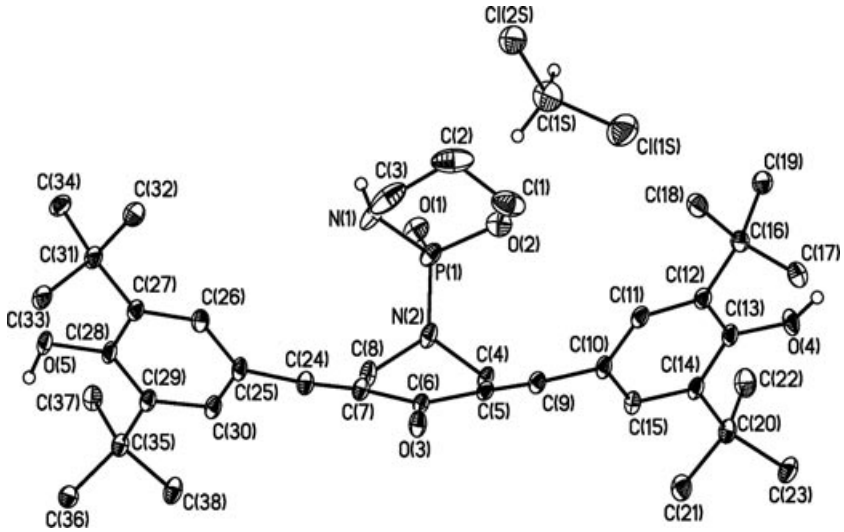


FIGURE 2 General view of the compound **4e** in representation of atoms via thermal ellipsoids at 40% probability level. Hydrogens at carbon atoms are not shown. Selected bond lengths in the oxazaphosphorinane moiety (Å): P(1)–O(1) 1.4743(19), P(1)O(2) 1.588(2), P(1)–N(1) 1.619(2), P(1)–N(2) 1.639(2), O(2)-C(1) 1.458(4), N(1)–C(3) 1.484(4), C(1)–C(2) 1.501(6), C(2)–C(3) 1.510(6).

oxazaphosphorinane compounds with a P-NC_2 moiety (see, e.g., [18–21]), the major difference being the position of the hydrogen atom at N(1)—axial in **4e** and equatorial in others. This caused the expected changes in the bond lengths of the heterocycle, in particular relative to 2-chloro-2-oxo-1,3,2λ^5-oxazaphosphinane **2**, a rather air- and moisture-stable compound, whose structure was also elucidated by X-ray diffraction (Fig. 3).

In both cases, the oxazaphosphinane moiety occupies a chair conformation with the atoms P(1) and C(2) deviated from the N(1)O(2)C(1)C(3) plane by 0.50(1) and –0.66(1) Å in **4e** and by 0.55(1) and –0.67(1) Å in **2**, and the bond lengths within it are practically the same (the variation is ca. 0.01 Å). However, replacement of the chlorine atom by the bulky substituted piperidone causes a slight elongation of P(1)–O(2) bond from 1.5647(11) Å in **2** to 1.588(2) Å in **4e**. This effect can be explained by the above differences in the position of the hydrogen atom at N(1) that allow for the formation of the anomeric interaction lp(N)$\rightarrow\sigma^*$(P—O) in **4e**; the pseudotorsion angle lpN(1)P(1)O(2) is 153.4(1)°. There is also a variation in the C_3H_6 fragment of the oxazaphosphinane moiety, which can be attributed to its strong liberation in a crystal of **4e**.

Taking into account that all the oxazaphosphorinane compounds with a P-NC_2 fragment X-rayed to date (Cambridge Structural Database, release 2011) have the H(N) atom in the equatorial plane

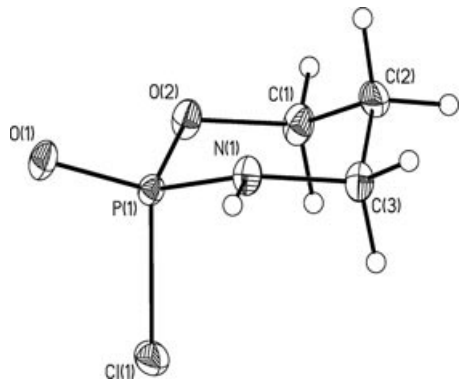


FIGURE 3 General view of the compound **2** in representation of atoms via thermal ellipsoids at 50% probability level. Selected bond lengths in the oxazaphosphorinane moiety (Å): P(1)–O(1) 1.4703(11), P(1)–O(2) 1.5647(11), P(1)–N(1) 1.6147(14), O(2)–C(1) 1.4741(17), N(1)–C(3) 1.4841(19), C(1)–C(2) 1.510(2), C(2)–C(3) 1.519(2).

similarly to **2**, its axial position in **4e** is apparently a consequence of crystal packing as a result of the presence of bulky arylidene substituents or extra proton donors/acceptors.

Thus, the diamidophosphate molecules in the crystal **4e** form centrosymmetric dimers through N(1)—H···O(1) hydrogen bonds (N···O 2.982(4) Å, NHO 172(1)°) in such a way that the second molecule is shifted along the crystallographic axis that is somewhat perpendicular to its largest dimension—the bis(arylidene)-4-piperidone line. At the same time, the group P=O is also involved in the intermolecular H-bond with one of the OH groups (O···O 2.702(3) Å, OHO 153(1)°), resulting in the formation of infinite H-bonded tapes. The second OH group is H-bonded to the atom O(3) (O···O 2.832(3) Å, OHO 129(1)°), assembling the above supramolecular associates into double layers. The formation of the three-dimensional (3D) framework in a crystal is completed by a number of weak interactions C—H···O, C—H···π, π···π, and H···H, including C—H···Cl ones with dichloromethane molecules.

In the crystal **2**, the hydrogen bonds N—H···O (N···O 2.9179(17) Å, NHO 159(1)°) also give rise to centrosymmetric dimers, but this time the mean planes of the resulting H-bonded cycle and the oxazaphosphinane moieties of the neighboring molecules **2** practically coincide. In addition, the presence of the covalently bound chlorine atom makes these dimers hold together through the Cl···O interactions (Cl···O 3.191(1) Å, lp(O)$\rightarrow\sigma$*(P-Cl)); the latter with a number of C—H···Cl and C—H···O contacts complete the formation of the 3D framework of **2**.

TABLE 1 Cytotoxicity of 1,3,2-Oxazaphosphorinane Derivatives **4a**–**e** and **5a**–**c** Against Human Carcinoma Cell Lines Caov3, A549, KB 3-1, and KB 8-5. (IC_{50} (μM))

	Human Carcinoma Cell Lines			
Compound	*CaOv3*	*A549*	*KB 3-1*	*KB 8-5*
4a	>20	>20	30 ± 5	30 ± 4
4b	7 ± 0.4	4.8 ± 0.4	6.0 ± 0.4	18 ± 4
4c	3 ± 0.3	1.5 ± 0.1	1.5 ± 0.2	5.2 ± 0.5
4d	>20	>20	35 ± 4	33 ± 5
4e	>30	>30	>30	>30
5a	4.8 ± 0.3	3.5 ± 0.3	4.5 ± 0.3	7.0 ± 0.5
5b	2.5 ± 0.2	2.7 ± 0.2	1.5 ± 0.1	6.5 ± 0.5
5c	1.2 ± 0.1	1.2 ± 0.1	6.4 ± 0.4	6.2 ± 0.3
Melphalan	50 ± 10	50 ± 10	-	-
Doxorubicin	-	-	1.2 ± 0.1	3.3 ± 0.2

Cytotoxic Properties

The cytotoxic activity of the compounds synthesized was tested in vitro (MTT test; MTT stands for 3-(4,5-dimethyldiazolyl-2)-2,5-diphenyl tetrazolium-bromide) against human cancer cell lines, namely Caov3 (ovarian carcinoma), A549 (lung carcinoma), KB 3-1 (human oral epidermoid carcinoma), and KB 8–5 (drug-resistant subclone of the latter one with Pgp170 hyperexpression). The results are summarized in Table 1, showing the corresponding IC_{50} values (IC_{50} is the concentration of a compound required to inhibit the growth of the cells by 50%). An anticancer agent Melphalan (sarcolysin, alkylation agent) was used as a positive control similar to assays of cytotoxic properties of other 3,5-bis(arylidene)-4-piperidone derivatives described in the literature (see, e.g., [7, 8]). Doxorubicin was used as the second positive control.

The cytotoxicity screening has revealed that compounds obtained are more active than Melphalan used as a positive control for Caov3 and A549 cell lines. Among bisamidophospates **4**, compounds bearing donor dimethylamino groups (**4d**) or a combination of tert-butyl and hydroxy substituents (**4e**) possess much lower cytotoxicity compared with those having electron-withdrawing substituents in the side aryl rings such as fluorine atom (**4b**) and nitro group (**4c**) (IC_{50} in the micromolar range of 1.5–7 μM). Compound **4c** was the most active from this series. A similar correlation of cytotoxic properties of 3,5-bis(arylidene)-4-piperidones, both phosphorylated and nonphosphorylated, with electronic properties of side aryl groups, i.e., an increase in the cytotoxicity with an increase in the electron-withdrawing power of these groups, was previously mentioned in the literature. Unexpectedly, in contrast to a range of the known phosphorylated *E,E*-3,5-bis(3-pyridinylmethylidene)

piperid-4-ones having an electron-withdrawing 3-pyridyl ring and possessing excellent antitumor activity toward the same cell lines, the cytotoxicity of compound **4a** was rather low and comparable with that of **4d** and **4e** bearing donor side groups. Therefore, this compound **4a** represents a rare exception from the above tendency, i.e., an increase in antitumor activity for compounds with electron-withdrawing side groups.

The potency of the diamidophosphates **4** toward KB human oral epidermoid carcinoma cell lines was in general the same as was observed for ovarian and lung carcinoma cells, i.e., **4c** > **4b** >> **4a** ~ **4d** ~ **4e**. Similar to doxorubicin, the cytotoxicity toward the KB3-1 cell line was higher comparing with that for drug-resistant sublone KB8-5.

Thioureas **5** bearing the same arylidene rings were more active than the diamidophosphates **4**, and in this case the derivative **5a** bearing 3-pyridyl rings was only slightly less potent than those having 4-fluoro- and 4-nitro-benzylidene groups. Moreover, thiourea **5c** demonstrated a similar activity toward both clones of KB cell lines. These cell lines differ from each other in the expression of the transmembrane transporting P-glycoprotein (permeability glycoprotein abbreviated as Pgp170) being responsible for the elimination of hydrophobic compounds, including the cytostatics, from tumor cells and assumed to be a reason for multidrug resistance in the treatment of cancers [22]. A similar toxicity toward these cell lines for compound **5c** allowed suggesting that it is not the substrate for Pgp170 and hence can be of interest for the treatment of resistant tumors.

CONCLUSIONS

To summarize the results presented, two convenient procedures for the introduction of the 1,3,2-oxazaphosphorinane ring into a backbone of 3,5-bis((hetero)arylidene)piperid-4-ones have been suggested. The cytotoxicity screening demonstrated that the introduction of such a phosphorus heterocycle resulted in compounds possessing high antitumor properties toward human carcinoma cell lines with IC_{50} values in a micromolecular range for the most potent compounds bearing electron-withdrawing side phenyl rings. The presence of a thiocarbamoyl linker between two heterocycles, i.e., piperidone and 1,3,2-oxazaphosphorinane, led to the pronounced increase in the activity, and thiourea **5c** was found to be the most potent and promising drug candidate from the series. Thus, the introduction of 1,3,2-oxazaphosphorinane moiety into the backbone of biologically active compounds seems to be a useful tool for their modification, providing increased antitumor activity and better bioavailability.

EXPERIMENTAL

NMR spectra were recorded with a Bruker AMX-400 spectrometer (Germany) (^{1}H, 400.13; ^{31}P, 161.98; ^{13}C, 100.61; and ^{19}F 376.49) or Bruker Avance-300 spectrometer (Germany) (^{1}H, 300.13 and ^{31}P, 121.49) using residual proton signals of a deuterated solvent as an internal standard (^{1}H, ^{13}C) and H_3PO_4 (^{31}P) as an external standard. The ^{13}C NMR spectra were registered using the JMODECHO mode; the signals for the C atoms bearing odd and even numbers of protons have opposite polarities. Melting points were determined using an EZ melt apparatus (Stanford research systems, Sunnyvale, CA) and are uncorrected. IR spectra were recorded in KBr pellets on a Magna-IR750 (Nicolet, Madison, WI) Fourier spectrometer, resolution 2 cm^{-1}, 128 scans. The starting 3,5-bis(arylidene)piperid-4-ones **1a–e** [23] and compounds **2** [14] and **3** [15] were prepared according to the known procedures, and their chemical–physical characteristics fit well with the literature data. All reagents and solvents used were obtained from Aldrich (St. Louis, MO) and used without further purification.

N-(2-Oxo-1,3,2λ^5-oxazaphosphinan-2-yl)-3,5-bis(benzyliden)-4-piperidones 4a–e (General Procedure)

A mixture of the corresponding *NH*-3,5-bis(aryliden)piperid-4-one **1a–e** (1 equiv), 2-chloro-2-oxo-1,3,2λ^5-oxazaphosphinane **2** (1.1 equiv), and DMAP (1.2 equiv) in $CHCl_3$ (10 mL) was stirred at room temperature for 7–8 h. The resulting mixture was concentrated in vacuo (or filtered in the case of compounds **4c**), and the product was purified by chromatography on SiO_2 ($CHCl_3$/MeOH 100/1) or recrystallization.

*N-(2-Oxo-1,3,2λ^5-oxazaphosphinan-2-yl)-(3E,5E)-3,5-bis(3-pyridinylmethylidene)-4-piperidinone (**4a**)*

A reaction of 3,5-bis(3-pyridinylmethylidene)-4-piperidinone **1a** (0.28 g, 1.0 mmol) with 2-chloro-2-oxo-1,3,2λ^5-oxazaphosphinane **2** (0.18 g, 1.1 mmol) in the presence of DMAP (0.15 g, 1.2 mmol) provided 0.17 g (43%) of the final product after purification by column chromatography. Yellow solid, mp 151°C (decomp.). IR (KBr, ν, cm^{-1}): 3398, 3209, 2969, 2889, 1668 (C=O), 1611 (C=C), 1582, 1561, 1478, 1412, 1360, 1327, 1267, 1246, 1204, 1195, 1176, 1131, 1096, 1083, 1063, 1045, 1022, 980, 964, 937, 893, 873,

846, 821, 807, 762, 709, 689, 628, 543, 523, 475. ^{31}P (121.49, $CDCl_3$), δ: 10.27. ^{1}H (400.13, $CDCl_3$), δ: 1.38–1.48, 1.62–1.72 (both m, 1H + 1H, $CH_2C\underline{H}_2CH_2$), 2.80–2.91, 2.07–3.18, 3.27–3.33, (three m, 1H + 1H, $NHC\underline{H}_2$), 3.89–3.98, 4.12–4.17 (both m, 1H + 1H, CH_2O), 4.48 (H_A) and 4.56 (H_B) (ABX system, 4H, piperidone NCH_2, $^{2}J_{HH}$ = 15.6 Hz, $^{3}J_{PHA}$ = 5.6, $^{3}J_{PHB}$ = 5.8 Hz), 7.28 (dd, 2H, H_{Py}, $^{3}J_{HH}$ = 4.8 Hz, $^{3}J_{HH}$ = 7.8 Hz), 7.65 (d, 2H, H_{Py}, $^{3}J_{HH}$ = 8.1 Hz), 7.68 (s, 2H, CH=), 8.51 (dd, 2H, H_{Py}, $^{3}J_{HH}$ = 4.8 Hz, $^{4}J_{HH}$ = 1.4 Hz), 8.59 (d, 2H, H_{Py}, $^{4}J_{HH}$ = 1.7 Hz). ^{13}C (100.61, $CDCl_3$), δ: 25.64 (d, $CH_2\underline{C}H_2CH_2$, $^{3}J_{PC}$ = 6.6 Hz), 40.96 (d, $NHCH_2$, $^{2}J_{PC}$ = 2.6 Hz), 45.72 (d, NCH_2, $^{2}J_{PC}$ = 3.3 Hz), 68.03 (d, $POCH_2$, $^{2}J_{PC}$ = 7.2 Hz), 123.33 (C_{Py}), 130.29 (C_{Py}), 132.84 (CH=), 134.31 (C=CH), 136.72 (C_{Py}), 149.68 (C_{Py}), 150.96 (C_{Py}), 185.88 (C=O). Anal. calcd. for $C_{20}H_{20}N_4O_3P\cdot 1/3H_2O$: C 59.85, H 5.19, N 13.96. Found: C 59.84, H 5.55, N 13.91.

*N-(2-Oxo-1,3,2λ^5-oxazaphosphinan-2-yl)-3,5-bis(4-fluorobenzyliden)-4-piperidone (**4b**)*

A reaction of 3,5-bis(4-fluorobenzyliden)-4-piperidone **1b** (0.31 g, 1.0 mmol) with 2-chloro-2-oxo-1,3,2λ^5-oxazaphosphinane **2** (0.17 g, 1.1 mmol) in the presence of DMAP (0.15 g, 1.2 mmol) provided 0.27 g (63%) of the final product after chromatographic purification followed by recrystallization from an acetone–hexane mixture. Yellow solid, mp 166–167°C. ^{31}P (121.49, $CDCl_3$), δ: 10.28. ^{1}H (300.13, $CDCl_3$), δ: 1.46–1.51, 1.72–1.79 (both m, 1H + 1H, $CH_2C\underline{H}_2CH_2$), 2.55 (br s, 1H, NH), 2.86–2.98, 3.12–3.25 (both m, 1H + 1H, CH_2NH), 3.93–4.04, 4.16–4.28 (both m, 1H + 1H, CH_2O), 4.42 (H_A) and 4.49 (ABX system, 4H, piperidone NCH_2, $^{2}J_{HH}$ = 16.2 Hz, $^{3}J_{PHA}$ = 6.9, $^{3}J_{PHB}$ = 6.4 Hz), 7.12 (dd, 2H, CH_{Ar}, $^{3}J_{HH}$ = $^{3}J_{HF}$ = 8.6 Hz), 7.40 (dd, 2H, CH_{Ar}, $^{3}J_{HH}$ = 8.6, $^{3}J_{HF}$ = 5.4 Hz), 7.76 (s, 2H, HC=). ^{13}C (75.47, $CDCl_3$), δ: 25.93 (d, $CH_2\underline{C}H_2CH_2$, $^{3}J_{PC}$ = 5.1 Hz), 41.17 (d, $NHCH_2$, $^{2}J_{PC}$ = 2.3 Hz), 45.87 (NCH_2), 68.17 (d, $POCH_2$, $^{2}J_{PC}$ = 5.7 Hz), 115.97 (d, $C_{Ar}H$, $^{2}J_{CF}$ = 16.4 Hz), 128.00 (C=CH), 130.78 (d, *ipso*-$\underline{C}_{Ar}$—CH=, $^{4}J_{CF}$ = 2.8 Hz), 132.35 (d, $C_{Ar}H$, $^{3}J_{CF}$ = 6.2 Hz), 135.43 (CH=), 163.00 (d, *ipso*-C_{Ar}—F, $^{1}J_{CF}$ = 188.7), 186.7 (C=O). Anal. calcd. for $C_{22}H_{21}F_2N_2O_3P$: C 61.39, H 4.92, N 6.51. Found: C 61.24, H 4.94, N 6.48.

*N-(2-Oxo-1,3,2λ^5-oxazaphosphinan-2-yl)-3,5-bis(4-nitrobenzyliden)-4-piperidone (**4c**)*

A reaction of 3,5-bis(4-nitrobenzyliden)-4-piperidone **1c** (0.37 g, 1.0 mmol) with 2-chloro-2-oxo-1,3,2λ^5-oxazaphosphinane **2** (0.17 g, 1.1 mmol) in the presence of DMAP (0.15 g, 1.2 mmol) provided 0.29 g (60%) of the final product after recrystallization from pyridine with ether. Yellow solid, mp 240–242°C (decomp.). ^{31}P (121.49, DMSO-d_6), δ: 9.74. ^{1}H (300.13, DMSO-d_6), δ: 1.32–1.37, 1.52–1.61 (both m, 1H + 1H, $CH_2C\underline{H}_2CH_2$), 2.67–2.78, 2.90–2.99 (both m, 1H + 1H, $C\underline{H}_2NH$), 3.82–3.93, 3.98–410 (both m, 1H + 1H, CH_2O), 4.44 (d, 4H, piperidone NCH_2, $^{3}J_{HP}$ = 9.5 Hz), 4.79 (dt, 1H, NH, $^{3}J_{HH}$ = 4.3 Hz, $^{2}J_{HP}$ = 6.5 Hz), 7.76 (s, 2H, HC=), 7.80 (d, 2H, CH_{Ar}, $^{3}J_{HH}$ = 8.8 Hz) 8.33 (d, 2H, CH_{Ar}, $^{3}J_{HH}$ = 8.8 Hz). Anal. calcd. for $C_{22}H_{21}N_4O_7P$: C 54.55, H 4.37, N 11.57. Found: C 54.59, H 4.27, N 11.59.

*N-(2-oxo-1,3,2λ^5-oxazaphosphinan-2-yl)-3,5-bis(4-dimethylaminobenzyliden)-4-piperidone (**4d**)*

A reaction of 3,5-bis(4-dimethylaminobenzyliden)-4-piperidone **1d** (0.36 g, 1.0 mmol) with 2-chloro-2-oxo-1,3,2λ^5-oxazaphosphinane **2** (0.17 g, 1.1 mmol) in the presence of DMAP (0.15 g, 1.2 mmol) provided 0.17 g (38%) of the final product after chromatography purification. Red solid, mp 220°C (decomp.). IR (KBr, ν, cm^{-1}): 3427, 3276, 2898, 2816, 1653, 1582, 1524, 1445, 1369, 1325, 1310, 1273, 1245, 1231, 1182, 1171, 1129, 1082, 1066, 1045, 1005, 984, 945, 918, 867, 809, 765, 523. ^{31}P (161.97, $CDCl_3$) δ: 10.46. ^{1}H (400.13, $CDCl_3$), δ: 1.43–1.47, 1.72–1.81 (both m, 1H + 1H, $CH_2C\underline{H}_2CH_2$), 2.65 (d, 1H, NH, $^{2}J_{HP}$ = 4.8 Hz), 2.85–2.93, 3.10–3.19 (both m, 1H + 1H, $C\underline{H}_2NH$), 3.02 (s, 12H, CH_3), 3.96–4.02, 4.13–4.20 (both m, 1H + 1H, CH_2O), 4.45 (H_A) and 4.53 (H_B) (ABX system, 4H, piperidone NCH_2, $^{2}J_{HH}$ = 15.6 Hz, $^{3}J_{PHA}$ = 5.6, $^{3}J_{PHB}$ = 5.8 Hz), 6.69 (d, 2H, CH_{Ar}, $^{3}J_{HH}$ = 8.8 Hz), 7.35 (d, 2H, CH_{Ar}, $^{3}J_{HH}$ = 8.8 Hz), 7.74 (s, 2H, HC=). Anal. calcd. for $C_{26}H_{33}N_4O_3P\cdot 0.5H_2O$: C 63.79, H 7.00, N 11.44. Found: C 63.84, H 6.98, N 10.97.

*N-(2-Oxo-1,3,2λ^5-oxazaphosphinan-2-yl)-(3E,5E)-3,5-bis(3,5-ditert-butyl-4-hydroxybenzylidene)-4-piperidone (**4e**)*

A reaction of 3,5-bis(3,5-di*tert*-butyl-4-hydroxybenzylidene)-4-piperidone **1e** (0.21 g, 0.38 mmol) with 2-chloro-2-oxo-1,3,2λ^5-oxazaphosphinane **2** (0.06 g, 0.40 mmol) in the presence of DMAP (0.05 g, 0.39 mmol) provided 0.21 g (85%) of the final product after purification by column chromatography. Yellow solid, mp 216–251°C (decomp.). IR (KBr, ν, cm^{-1}): 3624, 3549, 3380, 3001, 2958, 2915, 2874, 1660, 1594, 1571, 1562, 1436, 1425, 1390, 1359, 1332, 1260,

1238, 1202, 1194, 1161, 1120, 1094, 1051, 1033, 988, 938, 874, 839, 772. ^{31}P (121.49, $CDCl_3$), δ: 9.89. ^{1}H (300.13, $CDCl_3$), δ: 1.45 (s, 36H, CH_3), 1.52, 1.63–1.80 (both m, 1H + 1H, $CH_2C\underline{H}_2CH_2$), 2.42 (br s, 1H, NH), 2.88–3.04, 3.13–3.27 (both m, 1H + 1H, $C\underline{H}_2NH$), 3.96–4.08, 4.17–4.31 (both m, 1H+1H, CH_2O), 4.48 (H_A) and 4.56 (H_B) (ABX system, 4H, piperidone NCH_2, $^2J_{HH}$ = 15. 6 Hz, $^3J_{PHA}$ = 5.6, $^3J_{PHB}$ = 5.8 Hz), 5.52 (s, 2H, OH), 7.27 (s, 4H, Ar), 7.77 (s, 2H, HC=). ^{13}C (75.47, $CDCl_3$), δ: 25.95 (d, $CH_2\underline{C}H_2CH_2$, $^3J_{PC}$ = 6.6 Hz), 30.06 (Me), 34.24 ($\underline{C}Me_3$), 41.19 ($NHCH_2$), 45.97 (NCH_2), 68.02 (d, $POCH_2$, $^2J_{PC}$ = 6.6 Hz), 126.37 ($\underline{C}_{Ar}$—CH=), 128.08 ($C_{Ar}H$), 130.23 (d, $\underline{C}$=CH, $^3J_{PC}$ = 6.6 Hz), 136.03 ($\underline{C}_{Ar}$—CMe_3), 137.41 (C=$\underline{C}$H), 155.07 ($C_{Ar}OH$), 187.05 (C=O). Anal. calcd. for $C_{38}H_{55}N_2O_5P$: C 70.13, H 8.52, N 4.30. Found: C 69.97, H 8.39, N 4.12.

N-[(2-oxo-1,3,2λ^5-oxazaphosphinan-2-yl)thiocarbamoyl]-3,5-bis(3-pyridinylmethiliden)-4-piperidone (**5a**)

To a solution of 3,5-bis(3-pyridinylmethiliden)-4-piperidone **1a** (0.22 g, 0.8 mmol) in anhydrous $CHCl_3$ (20 mL), 2-isothiocyano-2-oxo-1,3,2λ^5-oxazaphosphinane **3** (0.18 g, 1.0 mmol) in $CHCl_3$ (10 m) was added at room temperature, and the mixture was stirred for 11 h. The precipitated product was filtered off, washed with $CHCl_3$, and dried in vacuum to give 0.39 g of crude compound. Recrystallization of the crude product from *i*-PrOH and washing with $CHCl_3$ and ether afforded 0.09 g (25%) of the desired compound as a solvate with $CHCl_3$ and H_2O. Yellow solid, mp 165–167°C (decomp.). ^{31}P (161.97, DMSO-d_6), δ: —1.90. ^{1}H (400.13, DMSO-d_6), δ: 1.25–1.29, 1.55–1.69 (both m, 1H+1H, $CH_2C\underline{H}_2CH_2$), 2.80–2.91 (m, 1H, $NHC\underline{H}_2$, the second signal of the $NHCH_2$ group is overlapped with that of DMSO-d_6), 3.75–3.92 (m, 1H, OCH_2, the second signal of the OCH_2 group is overlapped with that of DMSO-d_6), 4.42 (s, 1H, NHCS), 5.01 (br s, 1H, HN-P), 5.25(H_A) and 5.33(H_B) (piperidone NCH_2, AB system, 4H, $^2J_{HH}$ = 15.5 Hz), 7.56 (dd, 2H, H_{Py}, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 4.0 Hz), 7.77 (s, 2H, CH=), 8.00 (d, 2H, H_{Py}, $^3J_{HH}$ = 7.8 Hz), 8.63 (d, 2H, H_{Py}, $^3J_{HH}$ = 4.0 Hz), 8.79 (s, 2H, H_{Py}). Anal. calcd. for $C_{21}H_{22}N_5O_3PS{\cdot}CHCl_3{\cdot}0.5H_2O$: C 45.26, H 4.14, N 12.00. Found: C 45.25, H 3.98, N 12.12.

N-[(2-oxo-1,3,2λ^5-oxazaphosphinan-2-yl)thiocarbamoyl]-3,5-bis(4-fluorobenzyliden)-4-piperidone (**5b**)

To a stirred suspension of 3,5-bis(4-fluorobenzyliden)-4-piperidone **1b** (0.28 g, 0.9 mmol) in anhydrous $CHCl_3$ (20 mL), a solution of 2-isothiocyano-2-oxo-1,3,2λ^5-oxazaphosphinane **3** (0.20 g, 1.1 mmol) in $CHCl_3$ (10 mL) was added at room temperature. Dissolution of starting compound **1b** was accompanied by the formation of precipitate of the desired product. After 7 h of stirring, the precipitate formed was filtered off, suspended in $CHCl_3$ (30 mL), stirred for 2 h, filtered off, and dried in vacuum to give compound **5b** (0.36 g, 82%) as a yellow solid, mp 172–173°C. IR (KBr, ν, cm^{-1}): 3422, 3322, 3109, 2969, 2926, 2056, 1674, 1615, 1599, 1575, 1509, 1439, 1413, 1323, 1262, 1239, 1202, 1189, 1160, 1137, 1098, 1056, 1012, 994, 949, 889, 834, 761, 526, 507, 476, 442. ^{31}P (161.97, DMF-d_7), δ:—1.79. ^{19}F (376.49, DMF-d_7), δ:*−110.49*. ^{1}H (400.13, DMF-d_7), δ: 1.61–1.65, 1.94–2.01 (both m, 1H + 1H, $CH_2C\underline{H}_2CH_2$), 2.96–2.99, 3.19–3.26 (both m, 1H + 1H, $C\underline{H}_2NH$), 3.84–3.90, 4.12–4.20 (both m, 1H + 1H, CH_2O), 4.53 (s, 1H, NHCS), 5.07 (s, 1H, HNP), 5.58(H_A) and 5.67 (H_B) (AB system, 4H, piperidone NCH_2, $^2J_{HH}$ = 16.8 Hz), 7.55 (dd, 4H, CH_{Ar}, $^3J_{HH}$ = $^3J_{HF}$ = 8.8 Hz), 7.91 (dd, 4H, CH_{Ar}, $^3J_{HH}$ = 8.8 Hz, $^4J_{HF}$ = 5.7 Hz), 7.99 (s, 2H, HC =). ^{13}C (75.47, DMSO-d_6), δ: 22.57 (d, $CH_2\underline{C}H_2CH_2$, $^3J_{PC}$ = 7.7 Hz), 44.36 (NCH_2), 54.91 ($NHCH_2$), 67.54 (d, $POCH_2$, $^2J_{PC}$ = 7.7 Hz), 116.32 (d, $C_{Ar}H$, $^2J_{CF}$ = 21.4 Hz), 127.97 ($\underline{C}$=CH), 130.59 (d, *ipso*-$\underline{C}_{Ar}$—CH=, $^4J_{CF}$ = 14.2 Hz), 133.36 (d, $C_{Ar}H$, $^3J_{CF}$ = 8.2 Hz), 138.34 (CH=), 163.02 (d, $C_{Ar}F$, $^1J_{CF}$ = 249 Hz), 170.68 (d, C=S, $^2J_{PC}$ = 12.6 Hz), 184.82 (C=O). Anal. calcd. for $C_{23}H_{22}F_2N_3O_3PS$: C 56.44, H 4.53, N 8.58, P 6.33. Found: C 56.37, H 4.48, N 8.47, P 6.08.

N-[(2-Oxo-1,3,2λ^5-oxazaphosphinan-2-yl)thiocarbamoyl]-3,5-bis(4-nitrobenzyliden)-4-piperidone (**5c**)

This compound was obtained in a similar fashion to compound **5a** starting from 3,5-bis(4-nitrobenzyliden)-4-piperidone **1c** (0.33 g, 0.9 mmol) and of 2-isothiocyano-2-oxo-1,3,2λ^5-oxazaphosphinane **3** (0.20 g, 1.1 mmol) in $CHCl_3$ (30 mL). Very fine precipitate was filtered off, washed with $CHCl_3$, and dried in vacuum to give 0.44 g (87%) of a desired product as a solvate with $CHCl_3$. Yellow solid, mp 190–192°C (decomp.). IR (KBr, ν, cm^{-1}): 3379, 3109, 2970, 2855, 2051, 1682, 1618, 1598, 1594, 1518 (NO_2), 1494, 1412, 1345 (NO_2), 1315, 1254, 1203, 1192, 1109, 1048, 989, 939, 886, 854, 806, 754, 507. ^{31}P (161.97, DMSO-d_6), δ: —1.95. ^{1}H (300.13, DMSO-d_6), δ: 1.23–1.40, 1.55–1.75 (both m, 1H + 1H, $CH_2C\underline{H}_2CH_2$), 2.70–2.95 (m, 1H, $NHC\underline{H}_2$, the second signal of the $NHCH_2$ group is overlapped with that of DMSO-d_6),

3.80–3.87 (m, 1H, OCH_2, the second signal of the OCH_2 group is overlapped with that of DMSO-d_6), 4.35 (s, 1H, NHCS), 5.25(H_A) and 5.35(H_B) (piperidone NCH_2, AB system, 4H, $^2J_{HH}$ = 16.0 Hz), 7.82 (d, 4H, CH_{Ar}, $^3J_{HH}$ = 9.0), 7.85 (s, 2H, CH=), 8.34 (d, 4H, CH_{Ar}, $^3J_{HH}$ = 8.6). ^{13}C (75.47, DMSO-d_6), δ: 22.51 (d, $CH_2\underline{C}H_2CH_2$, $^3J_{PC}$ = 7.7 Hz), 44.60 (NCH_2), 54.85 ($NHCH_2$), 67.57 (d, $POCH_2$, $^2J_{PC}$ = 7.7 Hz), 124.07 ($C_{Ar}H$), 131.75 ($C_{Ar}H$), 140.44 (C_{Ar}), 147.81 (O_2N-C_{Ar}), 170.93 (d, C=S, $^2J_{PC}$ = 13.1 Hz), 184.85 (C=O). Anal. calcd. for $C_{23}H_{22}N_5O_7PS{\cdot}0.2CHCl_3$: C 49.11, H 3.94, N 12.34. Found: C 49.24, H 3.87, N 12.41.

X-ray Structure Determination

The crystal of the compound **4e** (as a solvate with one molecule of CH_2Cl_2) suitable for the X-ray diffraction study was grown by slow diffusion of pentane into a solution of the compound in methylene chloride, acid chloride **2** crystallized spontaneously after purification.

Crystals of **4e**·CH_2Cl_2 ($C_{39}H_{57}Cl_2N_2O_5P$, M = 735.74) are monoclinic, space group $P21/c$, at 100 K: a = 14.167(2), b = 17.270(3), c = 17.163(3) Å, β = 110.638(3)°, V = 3929.6(10) Å^3, Z = 4 (Z' = 1), d_{calc} = 1.244 gcm^{-3}, μ(Mo Kα) = 2.50 cm^{-1}, F (000) = 1576. Intensities of 40,956 reflections were measured with a Bruker Smart APEX2 CCD diffractometer [λ(Mo Kα) = 0.71072 Å, ω-scans, $2\theta < 56°$], and 9471 independent reflections [R_{int} = 0.0662] were used in further refinement. Crystals of **2** ($C_3H_7ClNO_2P$, M = 155.52) are orthorhombic, space group *Pbca*, at 100 K: a = 9.5554(19), b = 10.899(2), c = 12.156(2) Å, V = 1265.9(4) Å^3, Z = 8 (Z' = 1), d_{calc} = 1.632 g cm^{-3}, μ(Mo Kα) = 7.66 cm^{-1}, F (000) = 640. Intensities of 9167 reflections were measured with a Bruker Smart APEX2 CCD diffractometer [λ(Mo Kα) = 0.71072 Å, ω-scans, $2\theta < 58°$], and 1682 independent reflections [R_{int} = 0.0380] were used in further refinement. The structures were solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The hydrogen atoms of NH and OH groups were found in difference Fourier synthesis. The positions of H(C) atoms were calculated. All hydrogen atoms were refined in the isotropic approximation in the riding model. For **4e**·CH_2Cl_2, the refinement converged to $wR2$ = 0.1885 and GOF = 1.137 for all independent reflections (R_1 = 0.0652 was calculated against F for 6733 observed reflections with $I > 2\sigma(I)$). For **2**, the refinement converged to $wR2$ = 0.0627 and GOF = 1.000 for all independent reflections (R_1 = 0.0250 was calculated against F for 1352 observed reflections with $I > 2\sigma(I)$). All calculations were performed using SHELXTL PLUS 5.0.

Crystallographic data for **2** and **4e**·CH_2Cl_2 containing the supplementary crystallographic data for this paper, have been deposited with the Cambridge Crystallographic Data Center, CCDC 881463 and 881464, respectively. These data can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

Evaluation of Cytotoxic Properties

Cell lines used for estimation of toxicity of compounds were CaoV3 (human ovarian carcinoma), A549 (human lung carcinoma), KB 3-1 (human oral epidermoid carcinoma cells), and drug-resistant subclone of the latter one, i.e., KB 8-5, with Pgp170 hyperexpression. Cells were grown in RPMI-1640 medium (Sigma-Aldrich, UK) supplemented with 10% fetal bovine serum (FBS; HyClone, USA), 2 mM L-glutamine and gentamicin. Cytotoxicity of the individual compounds was measured for each cell line after 72 h of cultivation by the MTT colorimetric assay. The test is based on the ability of mitochondrial dehydrogenase in viable cells to convert a MTT reagent (ICN Biomedicals, Eschwege, Germany) into a soluble blue formazan dye. Briefly, the different cell lines were seeded into 96-well plates at a concentration of 1×10^4 cells/100 µL/well. The cells were allowed to attach overnight at 37°C in a humidified atmosphere containing 5% CO_2. The tested compounds were initially dissolved in dimethylsulfoxide (DMSO; Sigma-Aldrich) and the working solutions were added to FBS free culture medium. The compounds were added to wells with increasing drug concentrations. After 72 h of incubation, 20 µL of MTT reagent (5 mg/mL) was added and cell cultures were incubated for 3 h at 37°C. After the removal of the culture medium, formazan crystals were dissolved in DMSO to determine the amount of formazan product. The optic density (OD) was determined by the multiwell plate reader (Uniplan, Picon, Russia) at 590 nm. The results were expressed as a percentage decrease of cell viability as compared to untreated controls. Each concentration of the compound tested was examined in triplicate, and the IC_{50} values were determined graphically. The concentrations of compounds used were 5×10^{-5}, 10^{-5}, 10^{-6}, 10^{-7} M. Commercially available Melphalan (Sarcolysin) and Doxorubicin purchased from Arkelan-Glaxo were used as a positive control in the assay.

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