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ORIGINAL PAPER

Chemistry of phosphorus ylides. Part 38: Synthesis and anticancer activity of cyclobutane, oxaphosphetane, oxaphosphinine, azaphosphetidene, and pyridazine derivatives

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Abstract The reactions of nucleophilic active phosphacumulene, phosphallene, and stable phosphonium ylides with quinones, cyclobutenone, α,β-unsaturated compounds, quinone monoanil, and monohydrazone were investigated. Carbocyclic and heterocyclic patterns such as phosphanylidene cyclobutanones, oxaphosphetane, oxaphosphinines, azaphosphetidenes, and pyridazines were obtained. The cytotoxic activity of some new products was evaluated against human cervical and breast carcinoma cell lines. Certain tested compounds showed promising results.

Keywords Phosphanylidene cyclobutanones · Oxaphosphetanes · Oxaphosphinines · Azaphosphetidenes · Pyridazines · Antitumor activity

Introduction

There has been considerable interest in the development of novel compounds with antitumor activity. A variety of antitumor drugs such as quinines [1, 2], indandiones [3, 4], α,β-unsaturated compounds [5, 6], and hydrazones [7–9] are currently in clinical use. Moreover, triaziquone derivatives displayed significant cytotoxic activities against human carcinoma cell lines [10]. In conclusion of our work aimed at the synthesis of carbocyclic and heterocyclic systems containing phosphorus moieties with remarkable biological importance [11–17], we report here on the utility of phosphacumulated and phosphallene ylides as building blocks for the synthesis of phosphanylidene cyclobutylidene, oxabicyclo compounds, spiro-oxetanone, spiro-oxaphosphetanone, oxaphosphinine, azaphosphetidenes, and pyridazines. The cytotoxicity of the synthesized compounds was evaluated against cervical and breast carcinoma cell lines in order to explore their potential as a new class of potent anticancer agents.

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Results and discussion

Treatment of naphthalene-1,2-dione (**1**) with (*N*-phenyliminovinylidene)triphenylphosphorane (**2a**) in tetrahydrofuran (THF) at room temperature afforded the target carbocyclic compounds, namely 1-[2,4-bis(phenylimino)-3-(triphenylphosphanylidene)cyclobutylidene]naphthalen-2(1*H*)-one (**6a**) together with triphenylphosphine oxide. A distinguishing feature in the IR spectrum of **6a** is the presence of only one carbonyl signal at 1,577 cm^{-1}. Moreover, signals at $\delta = 187.78$ (C=O), 164.20 (C=N), and 153.23 (C=P) were recorded in the ^{13}C NMR spectrum. In the ^{31}P NMR spectrum of **6a** a signal at $\delta = 29.74$ ppm was recorded which fits with the presence of a phosphorane on a four-membered ring [18]. The product **6a** is assumed to be formed via the reaction of the phosphacumulene **2a** with naphthalene-1,2-dione (**1**) by a [2+2]-cycloaddition of the C-1 carbonyl group [19, 20] in compound **1** to the ylidic C–P bond of the reagent **2a** to give the oxaphosphetane **4** through the dipolar intermediate **3** [21–23]. The intermediate **4** is decomposed to the unstable ketene **5** [24]

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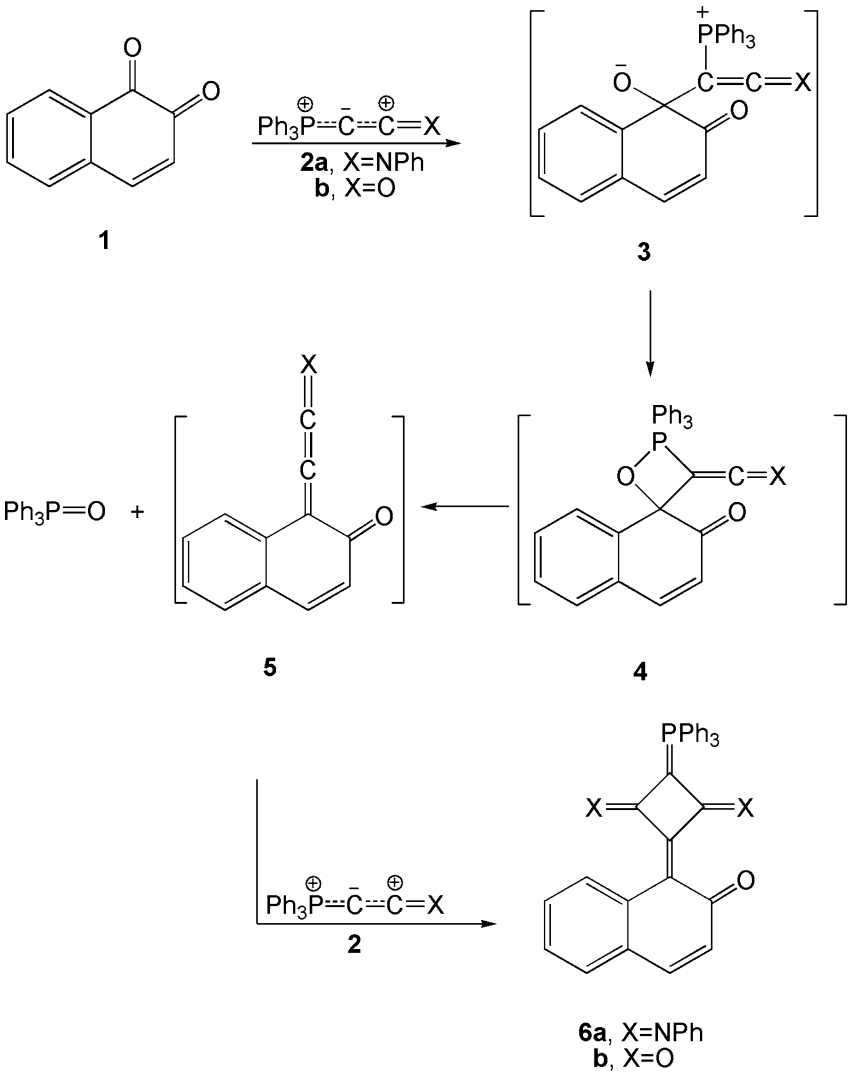
and triphenylphosphine oxide which is a good leaving group. [2+2]-Cyclization of a second molecule of **2a** to the ketene **5** afforded the four-membered ring phosphanylidene cyclobutylidene **6a**. Similarly, when the naphthalenedione was treated with (oxovinylidene)triphenylphosphane (**2b**) the corresponding 2-(2-oxonaphthalen-1(2*H*)-ylidene)-4-(triphenylphosphanylidene)cyclobutane-1,3-dione (**6b**) and triphenylphosphine oxide were obtained (Scheme 1).

A comparative study between the active phosphacumulene **2a** and a stabilized phosphonium ylide, acetylmethylenetriphenylphosphorane (**9**), towards 3,4-diphenylcyclobut-3-ene-1,2-dione (**7**) was also investigated. Thus, when compound **7** was treated with (*N*-phenyliminovinylidene)triphenylphosphorane (**2a**) in boiling toluene, 2,3-diphenyl-4-[2,4-bis(phenylimino)-3-(triphenylphosphanylidene)cyclobutylidene]cyclobut-2-en-1-one (**8**) and triphenylphosphine oxide were isolated. The IR spectrum of the reaction product **8** revealed bands at 1,650 (C=O), 1,593 (C=N), 1,491 (C=P), and 1,441 cm^{-1} (P–Ar). Moreover, the ^{13}C NMR spectrum of **8** displayed distinct resonances at 170.10 (C=O), 166.65 (C=N), and 153.83 (C=P) ppm. A signal at 30.07 ppm was observed in its ^{31}P NMR spectrum. The mass spectrum indicated the presence of an ion peak at $m/z = 710$ [M^+]. On the other hand, when compound **7** was treated with equimolar amounts of acetylmethylenetriphenylphosphorane (**9**) in refluxing toluene, the corresponding 4-(2-oxopropylidene)-2,3-diphenylcyclobut-2-en-1-one (**10**) and triphenylphosphine oxide were obtained. A [2+2]-cycloaddition of the C=O bond of compound **7** to the ylidic C–P bond of **9** is proposed to

Scheme 1

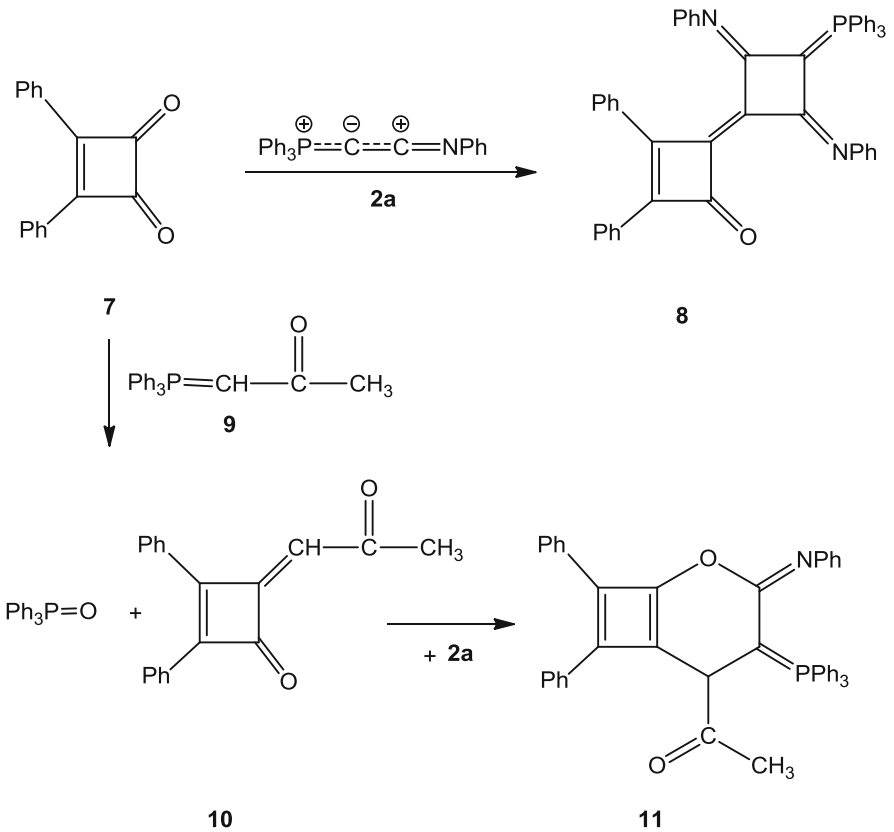


generate the unstable oxaphophetane [22, 23, 25]. In the case of weakly nucleophilic stabilized ylide **9**, the first stage of the reaction is the *threo*-betaine which is more stable than the *erythro*-betaine [26, 27]. By this means subsequent formation of the intermediate four-membered ring [28] and its decomposition into the *trans*-olefin [29] and triphenylphosphine oxide are mainly formed.

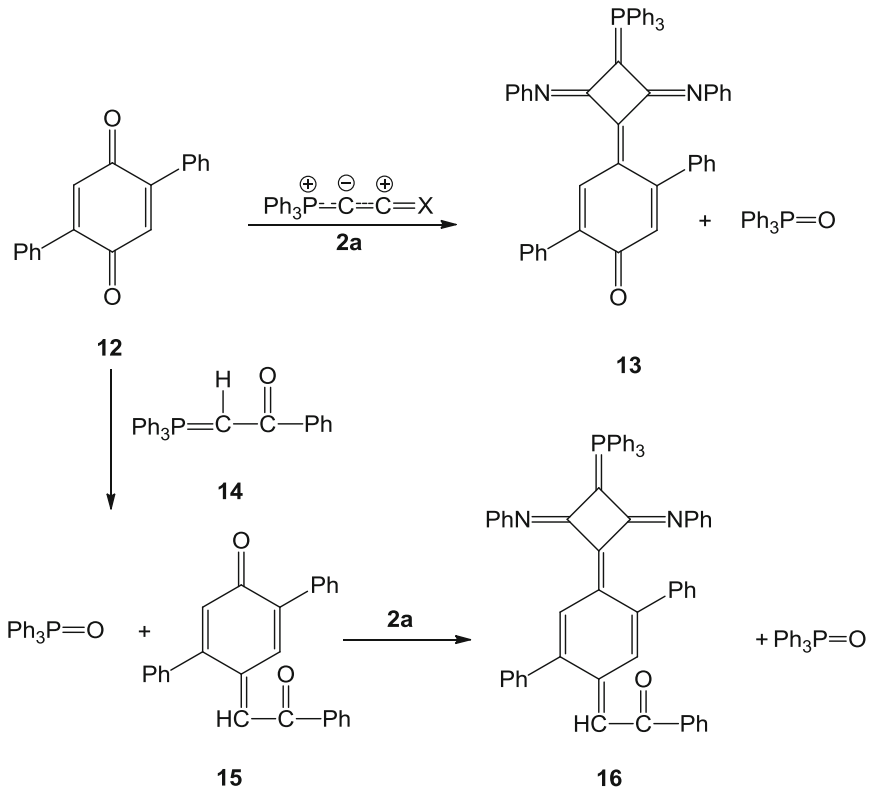
The IR spectrum of **10** showed bands at 1,689 (C=O, acetyl) and 1,637 cm^{-1} (C=O, cyclobutenone). The ^{1}H NMR spectrum of **10** revealed signals at $\delta = 2.70$ (s, 3H, CH_3), 6.00 (s, 1H, CH), and 7.50–8.00 (m, 10H, Ar) ppm. The ^{13}C NMR displayed distinct resonances of the methyl group at $\delta = 29.30$, the CH methine at 153.50, the cyclobutenone C=O at 187.60, and the acetyl C=O at 193.07 ppm. In addition, when the product **10** was treated with the active phosphacumulene **2a** in boiling toluene, 1-[7,8-diphenyl-3-(phenylimino)-4-(triphenylphosphanylidene)-2-oxabicyclo[4.2.0]octa-1(6),7-dien-5-yl]ethanone (**11**) was isolated. Formation of compound **11** is proposed to occur by [2+4]-cycloaddition of the ylide **2a** to compound **10**. The most important features of structure **11** are the presence of signals at 2.70 ppm (s) for the methyl protons and 3.75 ppm (d) for the methine proton ($^{3}J_{HP} = 13.5$ Hz) in its ^{1}H NMR spectrum. The ^{13}C NMR spectrum of **11** displayed distinct resonances of the methyl groups at 24.20, the CH methine at 29.00, the C=P at 166.15, the C=N at 169.80, and the acetyl C=O at 199.00 ppm. Moreover, a signal at 26.26 ppm was observed in its ^{31}P NMR spectrum and the mass spectrum indicated the presence of an ion peak at $m/z = 652$ $[(M+1)^+]$ (Scheme 2).

When 2,5-diphenylcyclohexa-2,5-diene-1,4-dione (**12**) was treated with the phosphacumulene **2a** in THF at room temperature, 4-[2,4-bis(phenylimino)-3-(triphenylphosphanylidene)cyclobutylidene]-2,5-diphenylcyclohexa-2,5-dienone (**13**) and triphenylphosphine oxide were isolated. The ^{13}C NMR spectrum of compound **13** possess three signals at 187.33, 165.35, and 158.60 ppm belonging to C=O, C=N, and C=P, respectively. Moreover, the ^{31}P NMR spectrum revealed a singlet signal at 29.93 ppm and the mass spectrum of **13** showed the presence of an ion peak at $m/z = 734$ $[(M-2)^+]$. On the other hand, compound **12** was boiled in toluene with the stabilized phosphonium ylide benzoylmethylenetriphenylphosphorane (**14**) to give 4-(2-oxo-2-phenylethylidene)-2,5-diphenylcyclohexa-2,5-dienone (**15**) and triphenylphosphine oxide. The IR spectrum of **15** revealed bands at 1,747 and 1,596 cm^{-1} due to

Scheme 2



Scheme 3

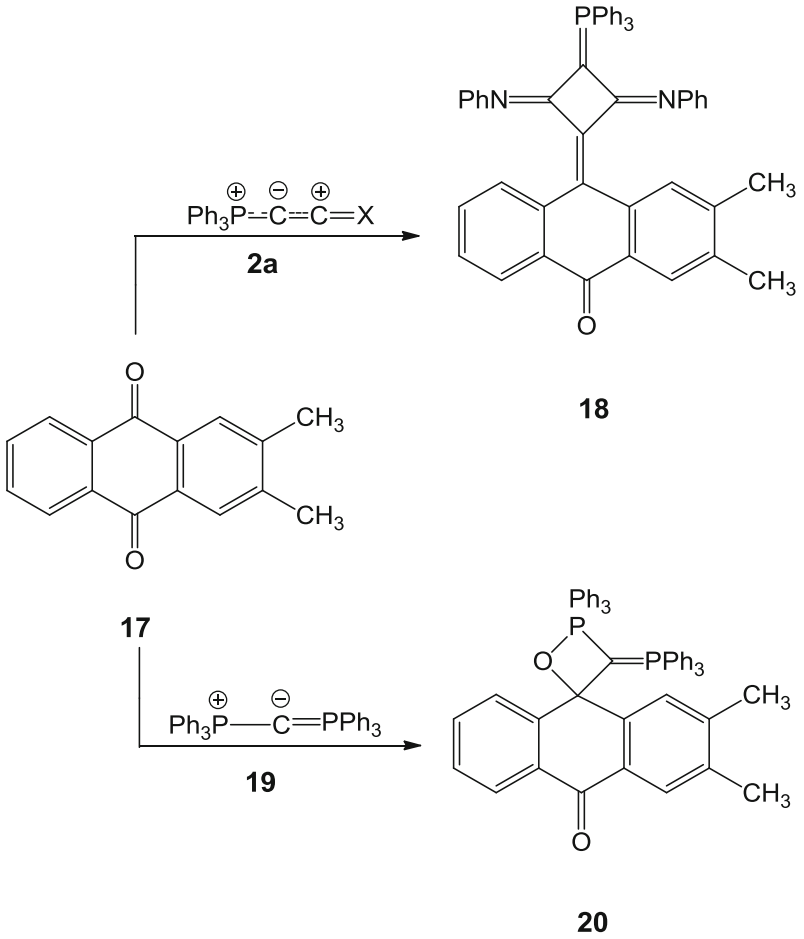


benzoyl and cyclohexanone carbonyl functions. Treatment of compound **15** with the phosphacumulene **2a** gave 2-[4-[2,4-bis(phenylimino)-3-(triphenylphosphanylidene)cyclobutylidene]-2,5-diphenylcyclohexa-2,5-dienylidene]-1-phenylethanone (**16**) and triphenylphosphine oxide. The ^{13}C NMR spectrum of **16** revealed the C=O and C=N signals at 182.73 and 168.90 ppm, respectively, and a signal at 29.78 ppm was found in its ^{31}P NMR spectrum (Scheme 3).

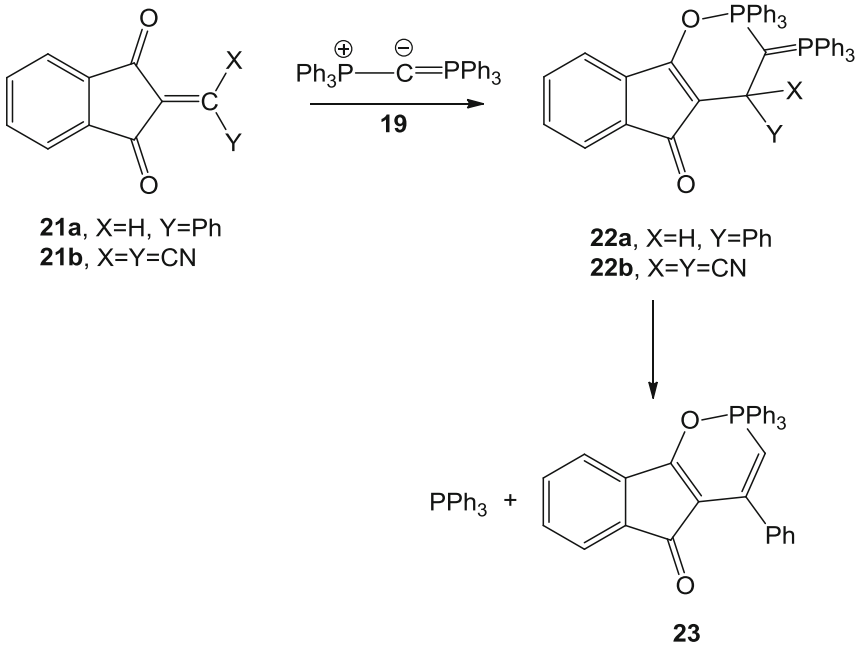
The reaction of 2,3-dimethylanthracene-9,10-dione (**17**) with the phosphacumulene **2a** was performed in toluene at room temperature to give 10-[2,4-bis(phenylimino)-3-(triphenylphosphanylidene)cyclobutylidene]2,3-dimethylanthracen-9(10*H*)-one (**18**) and triphenylphosphine oxide. A signal at 19.21 ppm in its ^{31}P NMR spectrum was found which supports the assigned structure of **18**. In addition, the behavior of the anthracenedione **17** towards the bisphosphorane hexaphenylcarbodiphosphorane (**19**) was studied. When **17** was treated with **19** in toluene at room temperature, 2,3-dimethyl-2′,2′,2′-triphenyl-3′-(triphenylphosphanylidene)-10*H*-spiro[anthracene-9,4′-[1,2]oxaphosphetan]-10-one (**20**) was obtained. The formation of **20** from the reaction of **17** with **19** can be explained by initial nucleophilic attack at the carbanion center in the bisylide **19** on the carbonyl function in **17** to give the phosphobetaine, which is transformed to the four-membered stable oxaphosphetane **20**. The ^{31}P NMR shifts of **20** were 21.23 (O–P) and 15.98 (P=C) ppm which fits with the presence of a phosphorane on a four-membered ring [30, 31] (Scheme 4).

The behavior of 2-benzylidene-1*H*-indene-1,3(2*H*)-dione (**21a**) and 2-(1,3-dioxo-1*H*-inden-2(3*H*)-ylidene)malononitrile (**21b**) towards hexaphenylcarbodiphosphorane (**19**) was studied, too. The reaction was performed in THF at room temperature and proceeded by [4+2]-cycloaddition rather than [2+2]-cycloaddition to give the pyran form. In case of the reaction of **21a** with **19** the corresponding pyran **22a** was initially formed which loses triphenylphosphane by Hoffmann degradation due to the presence of a hydrogen atom in the α-position to give 2,2,2,4-tetraphenylindeno[2,1-*e*][1,2]oxaphosphinin-5(2*H*)-one (**23**) and triphenylphosphane, whereas the stable 5-oxo-2,2,2-triphenyl-3-(triphenylphosphanylidene)-2,3-dihydroindeno[2,1-*e*][1,2]oxaphosphinine-4,4(5*H*)-dicarbonitrile (**22b**) was isolated from the reaction of compound **21b** and the bisphosphorane **19**. The ^{31}P NMR spectrum of the pyran **22b** revealed two singlet signals at 26.10 (O–P) and 21.23 ppm (C=P) which fits with the presence of a phosphorane on a six-membered ring, whereas the pyran **23** revealed a singlet signal at 21.26 ppm (O–P) (Scheme 5).

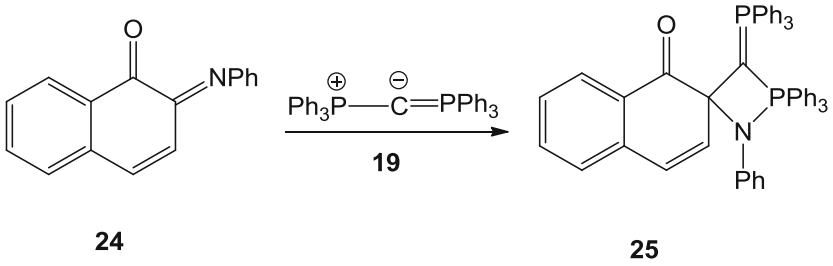
Scheme 4



Scheme 5



Scheme 6



24 **25**

The behavior of hexaphenylcarbodiphosphorane (**19**) towards the monoanil 2-(phenylimino)naphthalen-1(2*H*)-one (**24**) was also studied to determine the site of attack. We found that phosphorane **19** reacts with the anil **24** in boiling THF to give 1,2,2,2-tetraphenyl-3-(triphenylphosphanylidene)-1′*H*-spiro[1,2]azaphosphetidene-4,2′-naphthalen]-1′-one (**25**). The initial step in this reaction is nucleophilic attack by the carbanion center of the phosphorane preferentially at the electron-deficient carbon–nitrogen double bond [32–35], rather than the carbonyl group of the bifunctional monoanil. The IR and ^{31}P NMR were reasons for assigning structure **25**. The IR spectrum of compound **25** showed bands at 1,660 (C=O), 1,592 (C=P), and 1,435 cm^{-1} (P–Ar). In the ^{31}P NMR of **25**, two signals were observed at 21.23 (C=P) and 29.84 ppm (N–P–C) (Scheme 6).

As a point of interest to prepare heterocyclic pyridazines, the behavior of 2-(2-phenylhydrazono)naphthalen-1(2*H*)-one (**26**) towards (*N*-phenyliminovinylidene)triphenylphosphorane (**2a**) was investigated, too. Thus, compound **26** was reacted with the phosphacumulene **2a** in boiling toluene, yielding *N*-(3-phenylbenzo[*f*]cinnolin-2(3*H*)-ylidene)aniline (**28**) and triphenylphosphine oxide. Michael addition of the phenylhydrazone **26** to the phosphacumulene afforded firstly the complicated phosphorane **27a**, which cyclized directly according to an intramolecular Wittig reaction to yield the compound **28**. On the other hand, (oxovinylidene)triphenylphosphorane (**2b**) react less rapidly with the phenylhydrazone **26** to yield the respective resonance-stabilized phosphorane **27b**. The most important features in the spectroscopic data of *N*′-(1-oxonaphthalen-2(1*H*)-ylidene)-*N*-phenyl-2-(triphenylphosphanylidene)acetohydrazide (**27b**) are that the IR spectrum showed two C=O bands at 1,627 cm^{-1} (broad band) and the ^{1}H NMR exhibits absorption at 4.20 ppm (d, $^{2}J_{HP}$ = 19.1 Hz, CH=P). The ^{13}C NMR of **27b** disclosed the presence of the oxonaphthalene C=O at 167.20, N–C=O at 152.00, and CH at 68.64 ppm. A signal was observed at 29.80 ppm in its ^{31}P NMR spectrum, and an ion peak at m/z = 549 [(M−1)$^{+}$] was observed in the MS. Besides, the MS of the cyclic compound **28** showed a peak at m/z = 346 [(M−1)$^{+}$]. We also examined the reaction of 2-(2-phenylhydrazono)-1*H*-indene-1,3(2*H*)-dione (**29**) with the phosphacumulene **2a**. Compound **29** and the reagent **2a** react in a molar ratio of 1:1 in boiling toluene to give 2-phenyl-3-(phenylimino)-2*H*-indeno[2,1-*c*]pyridazin-9(3*H*)-one (**30**) together with triphenylphosphine oxide. The mass spectrum of the pyridazinone **30** showed a peak at m/z = 349 corresponding to its molecular ion. Moreover, the proposed structure **30** was unequivocally confirmed by x-ray crystallography (Fig. 1; Table 1).

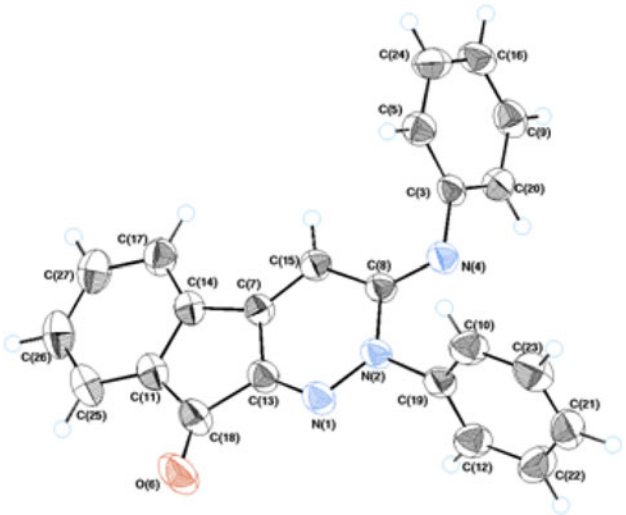


Fig. 1 Molecular structure of pyridazinone **30** with 50 % probability ellipsoids

Therefore, it is safe to state that the reaction course between phosphacumulene ylides and monophenylhydrazone **29** is rather dependent on a number of parameters. These include the nature of the reactant, the type of the solvent, and the reaction temperature (Scheme 7).

Biology

Chemotherapy is a major approach for both localized and metastasized cancers [36]. Therefore, eight of the newly synthesized compounds were screened for their in vitro cytotoxic and growth inhibitory activities against two cell lines tested, namely HELA (cervical carcinoma cell line)

and MCF-7 (breast carcinoma cell line), in comparison with the activity of the known anticancer reference drug doxorubicin. The cytotoxic activities of the tested compounds expressed as IC_{50} (the dose that reduces survival to 50 %) were compiled in Table 2.

From Table 2, it is evident that all of the tested new compounds reveal survival reduction in breast and cervical carcinoma cell lines up to 50 % at different IC_{50} doses. In general, compounds **6a**, **20**, **23**, **25**, and **28** appeared considerably more active when compared with doxorubicin. In case of the HELA carcinoma cell line, the indenone **23** bearing an oxaphosphinine exhibited a significant inhibitory effect at low concentration ($IC_{50} = 2.70$ μg/cm^3) compared with doxorubicin ($IC_{50} = 4.19$ μg/cm^3), followed by **28**, **20**, **6a**, and **25**, recording $IC_{50} = 2.85$, 3.00, 3.45, and 3.90 μg/cm^3, respectively. Besides, compound **27b** showed a remarkable growth inhibition but at a slightly higher concentration ($IC_{50} = 4.20$ μg/cm^3) than the reference drug. On the contrary, the inhibition activity was observed for **8** and **30** at higher concentration ($IC_{50} = 10.50$ and 16.80 μg/cm^3, respectively), which are approximately twofold (for the former) and fourfold (for the latter) less active than doxorubicin.

Table 1 Selected bond length/Å and angles/° for compound **30**

N1–N2	1.355 (12)	N2–N1–C13	116.05 (8)
N1–C13	1.298 (13)	C3–N4–C8	120.48 (8)
N2–C19	1.440 (13)	C13–C7–C14	107.59 (8)
C3–N4	1.412 (12)	C14–C7–C15	133.15 (9)
C3–C5	1.388 (2)	N4–C8–C15	127.93 (8)
C5–C24	1.379 (14)	C18–C11–C25	129.70 (10)
O6–C18	1.215 (13)	N1–C13–C18	125.59 (9)
C7–C13	1.434 (14)	C11–C18–C13	104.35 (9)
C7–C15	1.341 (14)	N2–N1–C13–C7	0.24 (13)
C8–C15	1.452 (13)	N2–N1–C13–C18	177.20 (2)
C10–C19	1.374 (2)	C8–N2–N1–C13	−2.77 (13)
C11–C14	1.410 (14)	C19–N2–C8–N4	0.00 (13)
C22–H22	0.960 (12)	C8–N2–C19–C10	69.500 (2)
		N1–C13–C18–O6	6.1 (2)

Promising results were also obtained against breast carcinoma cell line MCF-7. It is worth noticing that compounds **20**, **23**, **27b**, and **28** have a growth inhibitory pattern on MCF-7 like that on HELA, showing $IC_{50} = 3.15, 2.85, 3.45$, and 3.60 μg/cm^3, respectively, higher than the growth inhibition for doxorubicin, $IC_{50} = 4.35$ μg/cm^3. Moreover, compound **25** showed an inhibitory effect on MCF-7, but in this case at higher concentration ($IC_{50} = 4.65$ μg/cm^3) than the reference ($IC_{50} = 4.35$ μg/cm^3).

The above outlined results indicate that increasing the aromaticity of the compounds may be the key factor for the cytotoxicity activity against HELA and MCF-7 cell lines,

Scheme 7

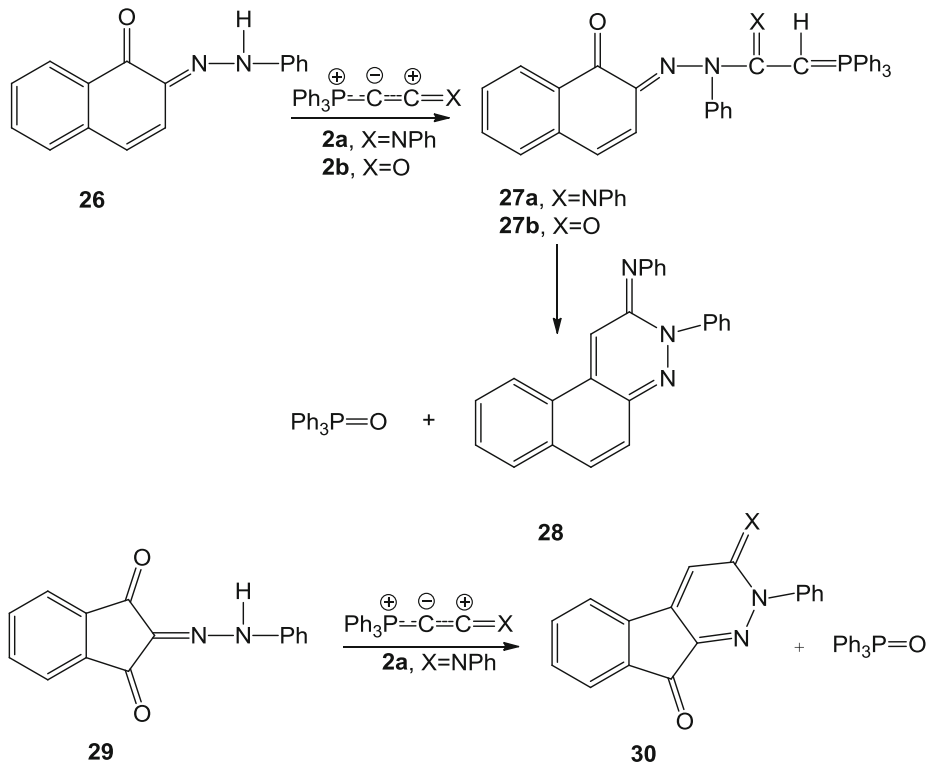


Table 2 Cytotoxic activity of the synthesized compounds against HELA and MCF-7

Compound	IC_{50}/μg cm^{-3}	
	HELA	MCF-7
DXR	4.19	4.35
6a	3.45	7.35
8	10.50	19.50
20	3.00	3.15
23	2.70	2.85
25	3.90	4.65
27b	4.20	3.45
28	2.85	3.60
30	16.80	17.00

IC_{50} value is defined as the concentration at which 50 % survival of cells was observed

Negative control DMSO, no reactivity

particularly when the tested compounds contain one or two triphenylphosphane groups.

Conclusion

The reactions of nucleophilic active phosphacumulene, phosphallene, and stable phosphonium ylides with quinones, cyclobutendione, α,β-unsaturated compounds, quinone monoanil, and monohydrazone represent an interesting approach to the synthesis of new carbocyclic and heterocyclic bioactive compounds. Cycloaddition reactions took place and the reaction products depend on the nature of the reagent used. Moreover, differences in the nucleophilic character and reactivity of the phosphorus reagents were noticed: phosphacumulene > phosphallene > stable phosphonium ylides. Whereas the phosphacumulene reacts smoothly with the reactants, the phosphallene and stable phosphonium ylides react less rapidly [37, 38]. This process can be considered as a simple and efficient route for the formation of phosphanylidenes, cyclobutanones, oxaphosphetanes, oxaphosphinines, azaphosphetidenes, and pyridazines. The preliminary biological screening of certain compounds as anticancer agents suggests that **6a**, **20**, **23**, **25**, and **28** emerge as the most active, showing strong cytotoxicity which is higher than the reference drug, doxorubicin. These findings could provide a relevant basis for the development of the tested compounds as anticancer drugs.

Experimental

Melting points were determined with an electrothermal digital melting point apparatus (Electrothermal Engineering Ltd., Essex, UK). The IR spectra were recorded in KBr disks on Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers (Pye Unicam Ltd. Cambridge, England and Shimadzu, Tokyo, Japan, respectively). ^{1}H, ^{13}C, and ^{31}P NMR spectra were obtained from a Jeol ECA 500 MHz NMR spectrometer (Tokyo, Japan) using deuterated chloroform ($CDCl_3$) as a solvent and TMS as internal reference at 500, 125, and 200 MHz, respectively. Mass spectra (EI-MS) were obtained at 70 eV with a Finnegan MAT SSQ 7000 spectrometer (England). Elemental analysis (C, H, N) results were recorded with an Elementar Vario EL (Germany), phosphorus was measured by spectrophotometric methods, and all of them agreed satisfactory with the calculated values. X-ray crystallography was carried out on a Kappa CCD Enraf–Nonius FR 590 diffractometer at the National Research Center, Dokki, Cairo, Egypt. The reported yields are of pure isolated materials obtained by column chromatography (silica gel 60, Merck). Thin layer chromatography (TLC) was performed on Kieselgel F254 precoated plates (Merck). Solvents were dried/purified according to literature procedures.

1-[2,4-Bis(phenylimino)-3-(triphenylphosphanylidene) cyclobutylidene]naphthalen-2(1H)-one
(**6a**, $C_{44}H_{31}N_2OP$)

A mixture of 158 mg naphthalene-1,2-dione (**1**, 1 mmol) and 754 mg (*N*-phenyliminovinylidene)triphenylphosphorane (**2a**, 2 mmol) [39] in 50 cm^3 dry THF was stirred at room temperature for 8 h. The solvent was evaporated under reduced pressure to give a brown precipitate which was recrystallized by plate TLC using petroleum ether (60–80 °C)/chloroform (1:1, v/v) as an eluent to give 410 mg (65 %) of **6a**. M.p.: 155 °C; IR: $\bar{\nu}$ = 1,577 (C=O), 1,435 (P–Ar) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.05–7.80 (m, 31H, ArH) ppm; ^{13}C NMR ($CDCl_3$): δ = 120.76, 120.54, 122.09, 122.90, 123.87, 128.54, 128.64, 132.22, 132.14, 137.32, 138.66, 142.01, 143.85 (Ar C), 153.23 (C=P), 164.20 (C=N), 187.78 (C=O) ppm; ^{31}P NMR ($CDCl_3$): δ = 29.74 ppm; MS: *m*/*z* (%) = 634.7 (M^+, 10). Triphenylphosphine oxide was isolated, m.p. and mixed m.p.: 151 °C.

2-(2-Oxonaphthalen-1(2H)-ylidene)-4-(triphenylphosphanylidene)cyclobutane*-1,3-dione*
(**6b**, $C_{32}H_{21}O_3P$)

A mixture of 158 mg naphthalene-1,2-dione (**1**, 1 mmol) and 604 mg (oxovinylidene)triphenylphosphorane (**2b**, 2 mmol) [40] in 50 cm^3 dry THF was stirred at room temperature for 12 h. The crude brown precipitate obtained was filtered off and recrystallized from methylene chloride and ether to afford 300 mg (62 %) of **6b**. M.p.: 160 °C; IR: $\bar{\nu}$ = 1,623 (2C=O, a broad band), 1,434 (P–Ar) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.00–7.90 (m, 21H, ArH) ppm; ^{13}C

NMR ($CDCl_3$): δ = 124.09, 128.55, 128.66, 132.10, 132.18, 132.90, 133.29, 140.21, 143.65, 143.88, 144.49, 146.65 (Ar C), 155.78 (C=P), 187.00 (C=O, naphthalenone), 199.45 (C=O, cyclobutanone) ppm; ^{31}P NMR ($CDCl_3$): δ = 29.95 ppm; MS: *m/z* (%) = 484.4 ([M−1]$^+$, 10). Triphenylphosphine oxide was isolated, m.p. and mixed m.p.: 151 °C.

2,3-Diphenyl-4-[2,4-bis(phenylimino)-3-(triphenylphosphanylidene)cyclobutylidene]cyclobut-2-en-1-one (**8**, $C_{50}H_{35}N_2OP$)

A mixture of 234 mg 3,4-diphenylcyclobut-3-ene-1,2-dione (**7**, 1 mmol) [41] and 754 mg (*N*-phenyliminovinylidene)triphenylphosphorane (**2a**, 2 mmol) were refluxed in 30 cm^3 dry toluene for 8 h. The solvent was evaporated under reduced pressure to give a brown precipitate, which was recrystallized from ethanol to afford 490 mg (69 %) of **8**. M.p.: 235 °C; IR: $\bar{\nu}$ = 1,650 (C=O), 1,593 (C=N), 1,491 (C=P), 1,441 (P–Ar) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.47–7.72 (m, 35H, ArH) ppm; ^{13}C NMR ($CDCl_3$): δ = 114.76, 116.56, 116.99, 118.07, 120.49, 121.63, 122.33, 124.12, 125.20, 125.54, 131.96, 136.27, 144.01 (Ar C), 153.82 (C=P), 166.65 (C=N), 170.10 (C=O) ppm; ^{31}P NMR ($CDCl_3$): δ = 30.07 ppm; MS: *m/z* (%) = 710.8 (M$^+$, 7). Triphenylphosphine oxide was isolated, m.p. and mixed m.p.: 151 °C.

4-(2-Oxopropylidene)-2,3-diphenylcyclobut-2-en-1-one (**10**, $C_{44}H_{14}O_2$)

A solution of 318 mg acetylmethylenetriphenylphosphorane (**9**, 1 mmol) [42] in 30 cm^3 of dry toluene was added dropwise to a stirred solution of 234 mg 3,4-diphenylcyclobut-3-ene-1,2-dione (**7**, 1 mmol). The reaction mixture refluxed for 20 h. After toluene was distilled off under reduced pressure, the residue was treated with dry ether, filtered off, and recrystallized from benzene/petroleum ether (40–60 °C) to give brown crystals, 188 mg (65 %) of **10**. M.p.: 162 °C; IR: $\bar{\nu}$ = 1,689 (C=O, acetyl), 1,637 (C=O, cyclobutenone) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.70 (s, 3H, CH_3), 6.00 (s, 1H, CH), 7.50–8.00 (m, 10H, ArH and cyclobutylidene H) ppm; ^{13}C NMR ($CDCl_3$): δ = 29.30 (CH_3), 122.99, 124.11, 124.86, 127.54, 128.04, 136.28, 137.29 (Ar C), 153.50 (*C*H–C=O) 187.60 (C=O, cyclobutenone), 193.07 (C=O, acetyl) ppm; MS: *m/z* (%) = 274.3 (M$^+$, 7). Triphenylphosphine oxide was isolated, m.p. and mixed m.p.: 151 °C.

1-[7,8-Diphenyl-3-(phenylimino)-4-(triphenylphosphanylidene)-2-oxabicyclo[4.2.0]octa-1(6),7-dien-5-yl]-ethanone (**11**, $C_{45}H_{31}NO_2P$)

A mixture of 274 mg 4-(2-oxopropylidene)-2,3-diphenylcyclobut-2-en-1-one (**10**, 1 mmol) [43] and 377 mg (*N*-phenyliminovinylidene)triphenylphosphorane (**2a**, 1 mmol) in 50 cm^3 dry toluene was refluxed for 12 h. The solvent was evaporated under reduced pressure to afford a brown precipitate which upon recrystallization from ether gave 370 mg (56 %) of **11**. M.p.: 120 °C; IR: $\bar{\nu}$ = 1,583 (C=O, a broad band), 1,436 (P–Ar) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.70 (s, 3H, CH_3), 3.75 (d, 1H, $^3J_{PH}$ = 13.5 Hz, CH=P), 7.30–7.90 (m, 30H, ArH) ppm; ^{13}C NMR ($CDCl_3$): δ = 24.20 (CH_3), 29.00 (CH), 114.37, 122.09, 123.12, 124.86, 125.54, 130.94, 131.77, 134.58, 136.27, 143.21, 145.02 (Ar C), 166.15 (C=P), 169.80 (C=N), 199.00 (C=O) ppm; ^{31}P NMR ($CDCl_3$): δ = 26.26 ppm; MS: *m/z* (%) = 652.7 ([M+1]$^+$, 4).

4-[2,4-Bis(phenylimino)-3-(triphenylphosphanylidene)cyclobutylidene]-2,5-diphenylcyclohexa-2,5-dienone (**13**, $C_{52}H_{37}N_2OP$)

A mixture of 260 mg 2,5-diphenylcyclohexa-2,5-diene-1,4-dione (**12**, 1 mmol) [44, 45] and 754 mg (*N*-phenyliminovinylidene)triphenylphosphorane (**2a**, 2 mmol) in 50 cm^3 dry THF was stirred at room temperature for 10 h. The brown precipitate obtained was filtered off and recrystallized from ether to afford 510 mg (69 %) of **13**. M.p.: 215 °C; IR: $\bar{\nu}$ = 1,593 (C=O and C=N, a broad band), 1,434 (P–Ar) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.13–7.71 (m, 37H, ArH) ppm; ^{13}C NMR ($CDCl_3$): δ = 118.87, 119.23, 122.09, 126.34, 128.04, 128.94, 129.25, 129.34, 130.65, 131.22, 132.08, 138.64, 145.21, 146.45 (Ar C), 158.60 (C=P), 165.35 (C=N), 187.33 (C=O) ppm; ^{31}P NMR ($CDCl_3$): δ = 29.93 ppm; MS: *m/z* (%) = 734.8 ([M−2]$^+$, 3). Triphenylphosphine oxide was isolated, m.p. and mixed m.p.: 151 °C.

2-[4-[2,4-Bis(phenylimino)-3-(triphenylphosphanylidene)-cyclobutylidene]-2,5-diphenylcyclohexa-2,5-dienylidene]-1-phenylethanone (**16**, $C_{60}H_{43}N_2OP$)

A mixture of 362 mg 4-(2-oxo-2-phenylethylidene)-2,5-diphenylcyclohexa-2,5-dienone (**15**, 1 mmol) [43] and 754 mg (*N*-phenyliminovinylidene)triphenylphosphorane (**2a**, 2 mmol) in 50 cm^3 dry toluene was refluxed for 8 h. The solvent was evaporated under reduced pressure to afford a pale yellow precipitate which was recrystallized from ethanol to give 430 mg (51 %) of **16**. M.p.: 180 °C; IR: $\bar{\nu}$ = 1,648 (C=O and C=N, a broad band), 1,401 (P–Ar) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 6.90 (s, 1H, CH), 7.30–7.80 (m, 43H, ArH) ppm; ^{13}C NMR ($CDCl_3$): δ = 117.19, 122.03, 123.10, 126.16, 128.27, 128.51, 129.44, 129.50, 129.59, 132.82, 133.26, 133.26, 133.34, 141.65, 143.33 (Ar C), 147.5 (C=P), 168.90 (C=N), 182.73 (C=O) ppm; ^{31}P NMR ($CDCl_3$): δ = 29.78 ppm; MS: *m/z* (%) = 836.8 ([M−2]$^+$, 3). Triphenylphosphine oxide was isolated, m.p. and mixed m.p.: 151 °C.

10-[2,4-Bis(phenylimino)-3-(triphenylphosphanylidene)-cyclobutylidene]-2,3-dimethylanthracen-9(10H)-one (**18**, $C_{50}H_{37}N_2OP$)

A mixture of 236 mg 2,3-dimethylanthracene-9,10-dione (**17**, 1 mmol) [46] and 754 mg (*N*-phenyliminovinylid-

ene)triphenylphosphorane (**2a**, 2 mmol) in 50 cm^3 dry toluene was stirred at room temperature for 15 h. The solvent was evaporated under reduced pressure to give a green precipitate which was recrystallized from benzene to afford 460 mg (65 %) of **18**. M.p.: 160 °C; IR: $\bar{\nu}$ = 1,597 (C=O), 1,434 (P–Ar) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.16 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 7.25–8.06 (m, 26H, ArH) ppm; ^{13}C NMR ($CDCl_3$): δ = 20.05 (CH_3), 23.00 (CH_3), 120.11, 122.19, 126.95, 127.46, 128.37, 128.56, 128.66, 129.54, 132.05, 132.14, 132.22, 134.46, 139.54, 140.67 (Ar C), 151.87 (C=P), 162.20 (C=N), 182.00 (C=O) ppm; ^{31}P NMR ($CDCl_3$): δ = 19.21 ppm; MS: *m/z* (%) = 710.8 ($[M-2]^+$, 3). Triphenylphosphine oxide was isolated, m.p. and mixed m.p.: 151 °C.

2,3-Dimethyl-2′,2′,2′-triphenyl-3′-(triphenylphosphanylidene)-10H-spiro[anthracene-9,4′-[1,2]oxaphosphetan]-10-one (**20**, $C_{53}H_{42}O_2P_2$)

A mixture of 236 mg 2,3-dimethylanthracene-9,10-dione (**17**, 1 mmol) and 536 mg hexaphenylcarbodiphosphorane (**19**, 1 mmol) [47] in 40 cm^3 dry toluene was stirred at room temperature for 1 h. The precipitate obtained was filtered off and recrystallized from ether to afford 430 mg (55 %) of **20**. M.p.: 145 °C; IR: $\bar{\nu}$ = 1,625 (C=O), 1,435 (P–Ar) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.32 (s, 3H, CH_3), 2.41 (s, 3H, CH_3) 7.16–7.57 (m, 36H, ArH) ppm; ^{13}C NMR ($CDCl_3$): δ = 18.80 (CH_3), 19.01 (CH_3), 71.40 (O–*C*–C=P), 117.23, 119.89, 125.12, 126.26, 128.74, 129.59, 132.81, 133.47, 133.30, 135.99, 137.08, 138.67, 143.11 (Ar C), 152.63 (C=P), 182.40 (C=O) ppm; ^{31}P NMR ($CDCl_3$): δ = 15.98 (C=P), 21.23 (O–P–C) ppm; MS: *m/z* (%) = 770.8 ($[M-2]^+$).

5-Oxo-2,2,2-triphenyl-3-(triphenylphosphanylidene)-2,3-dihydroindeno-[2,1-e][1,2]oxaphosphinine-4,4(5H)-dicarbonitrile (**22b**, $C_{49}H_{34}N_2O_2P_2$)

A mixture of 208 mg 2-(1,3-dioxo-1*H*-inden-2(3*H*)-ylidene)malononitrile (**21b**, 1 mmol) [48] and 536 mg hexaphenylcarbodiphosphorane (**19**, 1 mmol) in 50 cm^3 dry THF was stirred at room temperature for 8 h. The solvent was evaporated under reduced pressure to give a brown precipitate which was chromatographed on silica gel using chloroform/ethyl acetate (6:4, v/v) as an eluent to afford 450 mg (60 %) of **22b**. M.p.: >350 °C; IR: $\bar{\nu}$ = 2,193 (C≡N), 1,666 (C=O), 1,621 (C=P), 1,435 (P–Ar) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.44–7.73 (m, 34H, ArH) ppm; ^{13}C NMR ($CDCl_3$): δ = 119.20 (C≡N), 122.55, 128.90, 128.98, 129.07, 129.25, 132.15, 132.22, 132.30, 132.84, 134.18, 134.80, 140.67, 143.265, 144.43 (Ar C), 156.21 (C=P), 182.97 (C–O), 196.08 (C=O) ppm; ^{31}P NMR ($CDCl_3$): δ = 21.23 (C=P), 26.10 (O–P–C) ppm; MS: *m/z* (%) = 742.7 ($[M-2]^+$).

2,2,2,4-Tetraphenylindeno[2,1-e][1,2]oxaphosphinin-5(2H)-one (**23**, $C_{35}H_{25}O_2P$)

A mixture of 234 mg 2-benzylidene-1*H*-indene-1,3(2*H*)-dione (**21a**, 1 mmol) [49] and 536 mg hexaphenylcarbodiphosphorane (**19**, 1 mmol) in 50 cm^3 dry THF was stirred at room temperature for 8 h. The solvent was evaporated under reduced pressure and the remaining residue was chromatographed on silica gel using chloroform/ethyl acetate (8:2, v/v) as an eluent to afford 280 mg (55 %) of **23**. M.p.: 152 °C; IR: $\bar{\nu}$ = 1,640 (C=O), 1,434 (P–Ar) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 4.73 (d, 1H, $^2J_{HP}$ = 17 Hz, CH=P), 7.42–7.60 (m, 24H, ArH) ppm; ^{13}C NMR ($CDCl_3$): δ = 105.56 (CH–P), 122.37, 123.89, 123.19, 125.33, 126.04, 129.52, 132.69, 132.73, 132.78, 133.39 (Ar C), 177.10 (C=O) ppm; ^{31}P NMR ($CDCl_3$): δ = 21.26 ppm; MS: *m/z* (%) = 506.5 ($[M-2]^+$). Triphenylphosphane was isolated, m.p. and mixed m.p.: 78 °C.

1,2,2,2-Tetraphenyl-3-(triphenylphosphanylidene)-1′H-spiro[1,2]azaphosphetidine-4,2′-naphthalen]-1′-one (**25**, $C_{53}H_{41}NOP_2$)

A mixture of 233 mg 2-(phenylimino)naphthalen-1(2*H*)-one (**24**, 1 mmol) [50] and 536 mg hexaphenylcarbodiphosphorane (**19**, 1 mmol) in 50 cm^3 dry THF was refluxed for 8 h. The solvent was evaporated under reduced pressure to give a brown precipitate which was crystallized from ether to afford 550 mg (71 %) of **25**. M.p.: 202 °C; IR: $\bar{\nu}$ = 1,660 (C=O), 1,592 (C=P), 1,435 (P–Ar) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.22–7.41 (m, 41H, ArH) ppm; ^{13}C NMR ($CDCl_3$): δ = 119.07, 119.22, 121.12, 122.29, 124.33, 125.67, 126.53, 128.42, 128.51, 129.43, 131.92, 133.28, 137.08, 138.43, 140.44 (Ar C), 148.55 (C=P), 181.29 (C=O) ppm; ^{31}P NMR ($CDCl_3$): δ = 21.23 (C=P), 29.84 (N–P–C) ppm; MS: *m/z* (%) = 767.8 ($[M-2]^+$).

N′-(1-Oxonaphthalen-2(1H)-ylidene)-N-phenyl-2-(triphenylphosphanylidene)acetohydrazide (**27b**, $C_{36}H_{27}N_2O_2P$)

A mixture of 248 mg 2-(2-phenylhydrazono)naphthalen-1(2*H*)-one (**26**, 1 mmol) [51] and 302 mg (oxovinylidene)triphenylphosphorane (**2b**, 1 mmol) in 50 cm^3 dry toluene was refluxed for 15 h. The solvent was evaporated under reduced pressure to give a yellow precipitate which was chromatographed on silica gel using chloroform/acetone (6:4, v/v) as an eluent to afford 366 mg (66 %) of **27b**. M.p.: 172 °C; IR: $\bar{\nu}$ = 1,627 (2C=O, a broad band), 1,591 (C=P), 1,435 (P–Ar) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 4.20 (d, 1H, $^2J_{HP}$ = 19.1 Hz, CH=P), 7.23–7.69 (m, 26H, ArH) ppm; ^{13}C NMR ($CDCl_3$): δ = 118.22, 120.09, 122.33, 123.26, 124.64, 128.53, 128.63, 128.88, 130.99, 134.39, 139.58, 142.07 (Ar C), 152.02 (C=P), 157.80 (C=O, acetamide), 167.20 (C=O, naphthalenone) ppm; ^{31}P NMR ($CDCl_3$): δ = 29.80 ppm; MS: *m/z* (%) = 549 ($[M-1]^+$, 6).

N-(3-Phenylbenzo[f]cinnolin-2(3H)-ylidene)aniline (**28**, $C_{24}H_{17}N_3$)

A mixture of 248 mg 2-(2-phenylhydrazono)naphthalen-1(2*H*)-one (**26**, 1 mmol) and 377 mg (*N*-phenyliminovinylidene)triphenylphosphorane (**2a**, 1 mmol) in 50 cm^3 dry toluene was refluxed for 8 h. The solvent was evaporated under reduced pressure to give an orange precipitate which was chromatographed on silica gel using acetone/chloroform (8:2, v/v) as an eluent to afford 180 mg (52 %) of **28**. M.p.: 108 °C; IR: $\bar{\nu} = 1{,}590$ (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.22$–7.54 (m, 17H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 116.88$, 120.09, 121.33, 123.42, 128.22, 128.42, 128.51, 129.16, 131.92, 131.97, 132.06, 133.24, 137.21, 138.98 (Ar C), 155.00 (C=N) ppm; MS: *m*/*z* (%) = 346 ($[M-1]^+$, 12). Triphenylphosphine oxide was isolated, m.p. and mixed m.p.: 151 °C.

2-Phenyl-3-(phenylimino)-2H-indeno[2,1-c]pyridazin-9(3H)-one (**30**, $C_{23}H_{15}N_3O$)

A mixture of 250 mg 2-(2-phenylhydrazono)-1*H*-indene-1,3(2*H*)-dione (**29**, 1 mmol) [52] and 377 mg (*N*-phenyliminovinylidene)triphenylphosphorane (**2a**, 1 mmol) in 50 cm^3 dry toluene was refluxed for 7 h. The solvent was evaporated under reduced pressure to give an orange precipitate, which was chromatographed on silica gel using petroleum ether (60–80 °C)/chloroform (7:3, v/v) as an eluent to afford **30**, then recrystallized from a mixture of dichloromethane and ether (1:3) to afford, after standing overnight and cooling, orange crystals; 230 mg (66 %) of **30**. M.p.: 255 °C; IR: $\bar{\nu} = 1{,}705$ (C=O), 1,640 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 6.90$–7.78 (m, 15H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 111.08$ (*C*–C=NPh), 114.56, 121.75, 121.32, 122.26, 122.87, 124.94, 126.84, 128.16, 135.90, 138.39, 1,389.34, 140.67, 143.81, 143.98, 145.02 (Ar C), 162.20 (C=N), 185.08 (C=O) ppm; MS: *m*/*z* (%) = 349 (M^+, 33). Triphenylphosphine oxide was isolated, m.p. and mixed m.p.: 151 °C.

A single crystal of compound **30** was grown by slow crystallization in a mixture of CH_2Cl_2 and ether (1:3). The crystal structure was solved and refined using maxus (nonius, Deflt and MacScience, Japan) [53]. Mo-Kα radiation ($\lambda = 71{,}073$ Å) and a graphite monochromator were used for data collection. The chemical formula and ring labeling system are shown in Table 3. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC-860453. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Table 3 Crystal structure and data refinement parameters for compound **30**

Empirical formula	$C_{23}H_{15}N_3O$
Formula weight	349.393
Crystal system/space group	Monoclinic
a/Å	23.9632(5)
b/Å	9.2543(2)
c/Å	17.0030(4)
α/°	90.00
β/°	115.5013(9)
γ/°	90.00
V/Å^3	3,403.28(13)
Z	8
D_x/Mg cm^{-3}	1.364
μ/mm^{-1}	0.09
Color/shape	Dark brown/prismatic
Temp./K	298
θ range for collection	2.910–27.51
Reflection collected	2,528
Independent reflections	4,248
Data/restraints/	0
parameters	244
R(gt)	0.038
Final *R* indices [$I > 3(I)$]	R_{int} 0.024

Cytotoxicity screening

The present study aimed to illustrate the effect of some newly synthesized compounds on the human cervical carcinoma cell line (HELA) and human breast carcinoma cell line (MCF-7) in comparison with doxorubicin (DXR), in a trial to get more effective and less toxic agents. Experiments were set up using the two human carcinoma cell lines to identify the potential toxicity of eight selected newly synthesized compounds (**6a**, **8**, **20**, **23**, **25**, **27b**, **28**, and **30**) along with DXR as a standard reference compound in the sulforhodamine B (SRB) assay reported by Skehan et al. [54]. Cells were plated in 96-multiwell plates (104 cells/well) for 24 h before treatment with compounds to allow attachment of cells to the wells. Different concentrations of the compound under test (0, 1, 2.5, 5, and 10 μg/well) were added to the cell monolayer. Each concentration was evaluated three times (each dose was incubated with the cells in three different wells). Monolayer cells were incubated with the compounds for 48 h at 37 °C and in an atmosphere of 5 % CO_2. After 48 h, the cells were fixed, washed, and stained with SRB. Excess stain was washed with acetic acid and the attached stain was recovered with a tris EDTA buffer. The color intensity was measured using an ELISA reader. The relation between the surviving fraction and the concentration (μg cm^{-3}) was plotted to obtain the survival

curve of each tumor cell line after treatment with the specified compounds.

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