Reaction of 2-hydroxy-N`-[(4-oxo-4*H*-chromen-3-yl)methylidene]benzohydrazide with some phosphorus reagents: Synthesis and evaluation of anticancer activities of some novel α-hydrazinophosphonic acid, 1,4,5,2-oxadiazaphosphinines and 1,3,2-benzoxazaphosphinines bearing a chromone ring.

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Abstract

Some novel 1,4,5,2-oxadiazaphosphinines, 1,3,2-benzoxazaphosphinines and α-hydrazinophosphonic acid bearing a chromone ring have been obtained from reaction of 2-hydroxy-N`-[(4-oxo-4*H*-chromen-3-yl)methylidene]benzohydrazide (**2**) with some phosphorus reagents such as phosphonic acid and its diesters, phosphorus sulfides and phosphorus halides in dry dioxane. The compounds were evaluated for their anticancer activities and on the expression of VEGF inhibition. Among the synthesized compounds, compounds **3** and **7** exhibited high effect against breast cancer cells MCF-7 in comparison with the standard drug and on the expression of VEGF inhibition.

Keywords: Chromone, Hydrazone, 1,4,5,2-Oxadiazaphosphinines and 1,3,2-Benzoxazaphosphinines, Anticancer, VEGF.

Introduction

Chromone compounds are oxygen-containing heterocyclic compounds with a benzo-annulated γ-pyrone ring. They are a group of naturally and synthetic compounds which have received attention in the literature, mainly due to their biological properties [1,2]. These biological activities are antioxidant, antimicrobial, anticonvulsant and antihypertensive [3-6]. Furthermore, the functionalized phosphorus containing heterocyclic compounds have attracted considerable attention because of widely pharmaceutical activities such as analgesic, hydrolytic enzyme inhibitors, anti-inflammatory and anticancer [7-10].

On the other hand, angiogenesis, which is the formation of new capillary blood vessels from preexisting ones, is a crucial process that promotes tumor growth, survival, and metastasis [11]. Since it was hypothesized that the inhibition of angiogenesis could be an effective strategy for cancer therapy [12] several regulators of angiogenesis, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), basic fibroblast growth factor (BFGF), and angiopoietin, have been identified [13-16]. VEGF signaling pathway that acts through the VEGF receptor 2 (VEGFR-2) has been shown to play a key role in the regulation of tumor angiogenesis, in which the binding of VEGF to VEGFR-2 leads to receptor dimerization, which is followed by the autophosphorylation of tyrosine residues in the intracellular kinase domain, resulting in potent mitogenic and chemotactic effects on endothelial cells [17]. The expression of VEGF is upregulated by tumor-related changes, such as hypoxia, protooncogene activation, and the aberration of tumor-suppressor genes [18,19]. The overexpression of VEGF correlates with poor

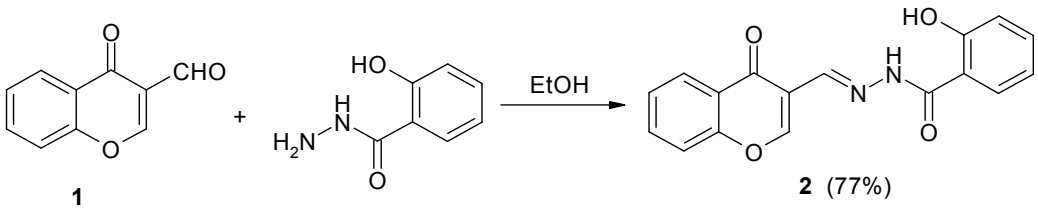
prognosis and the clinical stage of patients with solid tumors [20,21]. Therefore, VEGF has been thought to be an attractive target for the treatment of cancer.

In the last years, our work was focused on the development of new synthetic methodology around bioactive phosphorus compounds [22-25]. In the present work, we disclosed a methodology to synthesize six-membered phosphorus heterocycles with expected biological activities. The method depends on cyclization of 2-hydroxy-N`-[(4-oxo-4*H*-chromen-3-yl)methylidene]benzohydrazide (**2**) with different kind of phosphorus reagents such as phosphorus di-esters, phosphorus sulfides and phosphorus halides. The synthesized compounds were examined for their anticancer properties against human breast MCF-7, liver HepG2, colon HCT116 and prostate PC3 cancer cell lines that may act through angiogenesis inhibition.

Results and discussion

Chemistry

Treatment of 3-formylchromone (**1**) with salicylic acid hydrazide in absolute ethanol for 30 minutes gave 2-hydroxy-N`-[(4-oxo-4*H*-chromen-3-yl)methylidene] benzohydrazide (**2**) in good yield (Scheme 1) [26].



Scheme 1

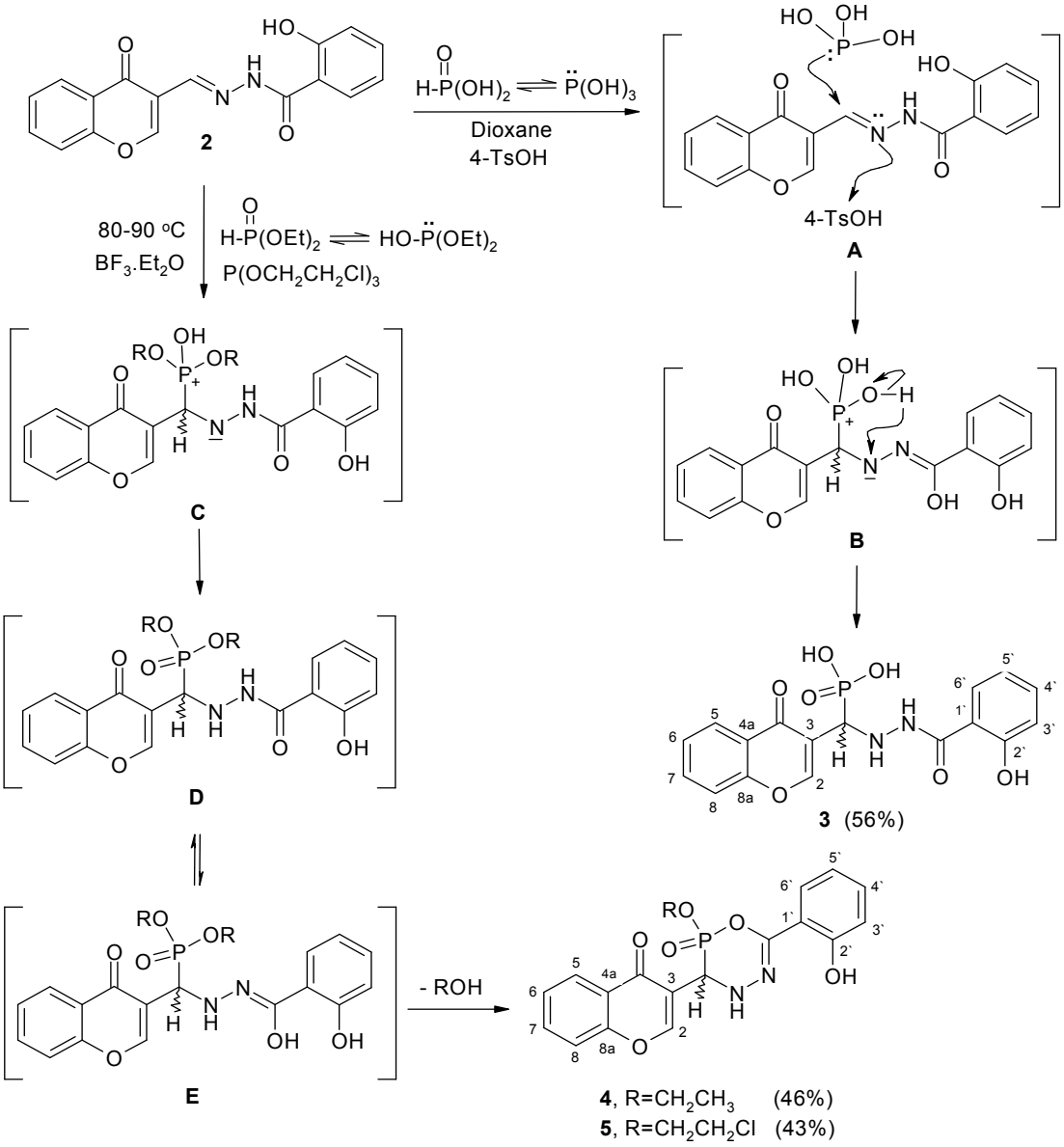
Compound **2** could be used as a synthone to construct phosphorus heterocyclic systems containing the chromone nucleus. This prompted us to investigate the reactivity of hydrazone **2** towards some phosphorus reagents with the aim of preparing new six-

membered phosphorus heterocycles bearing a chromone ring, which might have chemotherapeutic and biological value.

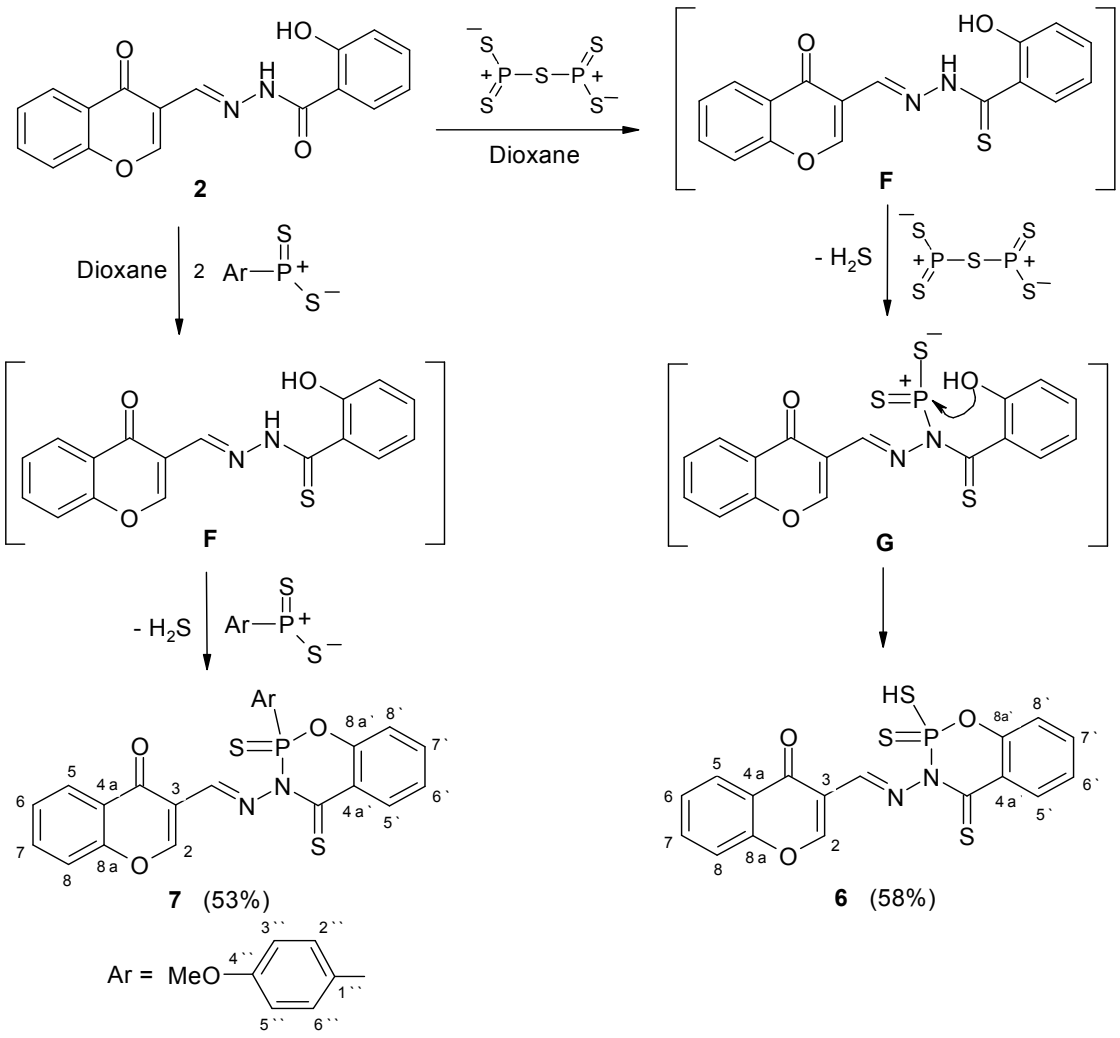
Reaction of hydrazone **2** with phosphonic acid in dry dioxane containing 4-toluenesulfonic acid as a catalyst under *Pudovik* reaction conditions gave the corresponding α-hydrazinophosphonic acid **3** in moderate yield (Scheme 2) [27]. When hydrazone **2** was allowed to react with diethyl phosphite and tris(2-chloroethyl) phosphite in the presence of trifluoroboron etherate as a catalyst at 80−90 °C under *Pudovik* reaction conditions, affording the corresponding 1,4,5,2-oxadiazaphosphininyl chromones **4** and **5**, respectively (Scheme 2). The formation of compounds **4** and **5** could be explained *via* phospha *Micheal*-addition of phosphites on the azomethine bond to form the corresponding dialkyl α-hydrazinophosphonates **D**, which can be existed in forms **E**. The latter nonisolable intermediates underwent cyclization *via* nucleophilic attack of OH_{enol} at the phosphonate groups to remove alcohol molecule affording the desired product **4** and **5** (Scheme 2). The ^{1}H- and C^{13}-NMR spectra of product **4** supported its existence in two isomers due to duplication of P−CH and NH groups.

The hydrazone **2** as *bi*-functional substrate is ready applicable to cyclized with phosphorus pentasulfide (P_2S_5 or P_4S_{10}) and 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide, known as Lawesson's reagent (LR) to give phosphorus heterocycles having sulfur atoms. Thus, 3-{[(2-sulfanyl-2-sulfido-4-thioxo-1,3,2-benzoxazaphosphinin-3(4*H*)yl)imino] methyl}-4*H*-chromen-4-one (**6**) and 3-{[2-(4-methoxyphenyl)-2-sulfido-4-thioxo-1,3,2-benzoxazaphosphinin-3(4*H*)yl)imino]methyl}-4*H*-chromen-4-one (**7**) were obtained in moderate yields from reaction of hydrazone **2** with phosphorus pentasulfide and Lawesson's reagent, respectively, in dry dioxane for

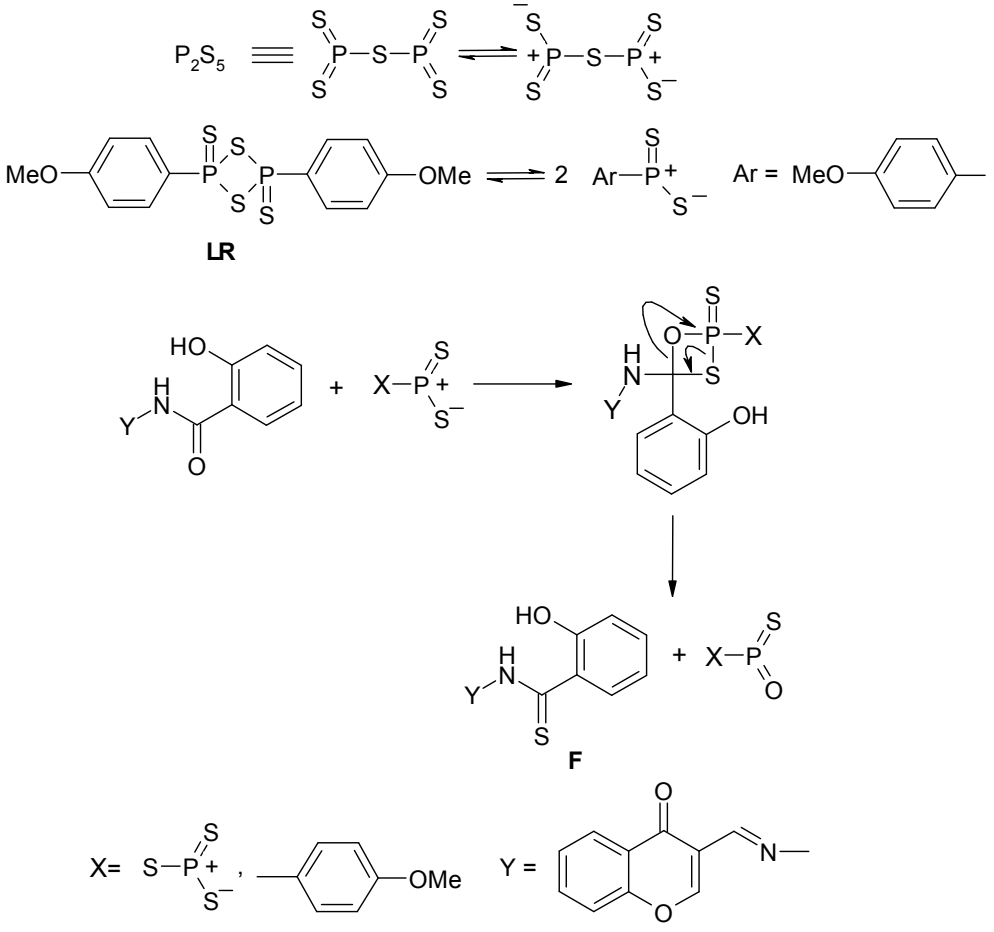
8−10 hours (Scheme 3). The possible explanation for the formation of products **6** and **7** was illustrated in Scheme 3. The hydrazone **2** reacted with P_2S_5 and LR to give the intermediates **F** which formed *via* thionation of $C{=}O_{amide}$ group (for details, see Scheme 4). The latter intermediate underwent cyclization *via* its reaction with another molecule of phosphorus reagent to afford the desired product.



Scheme 2



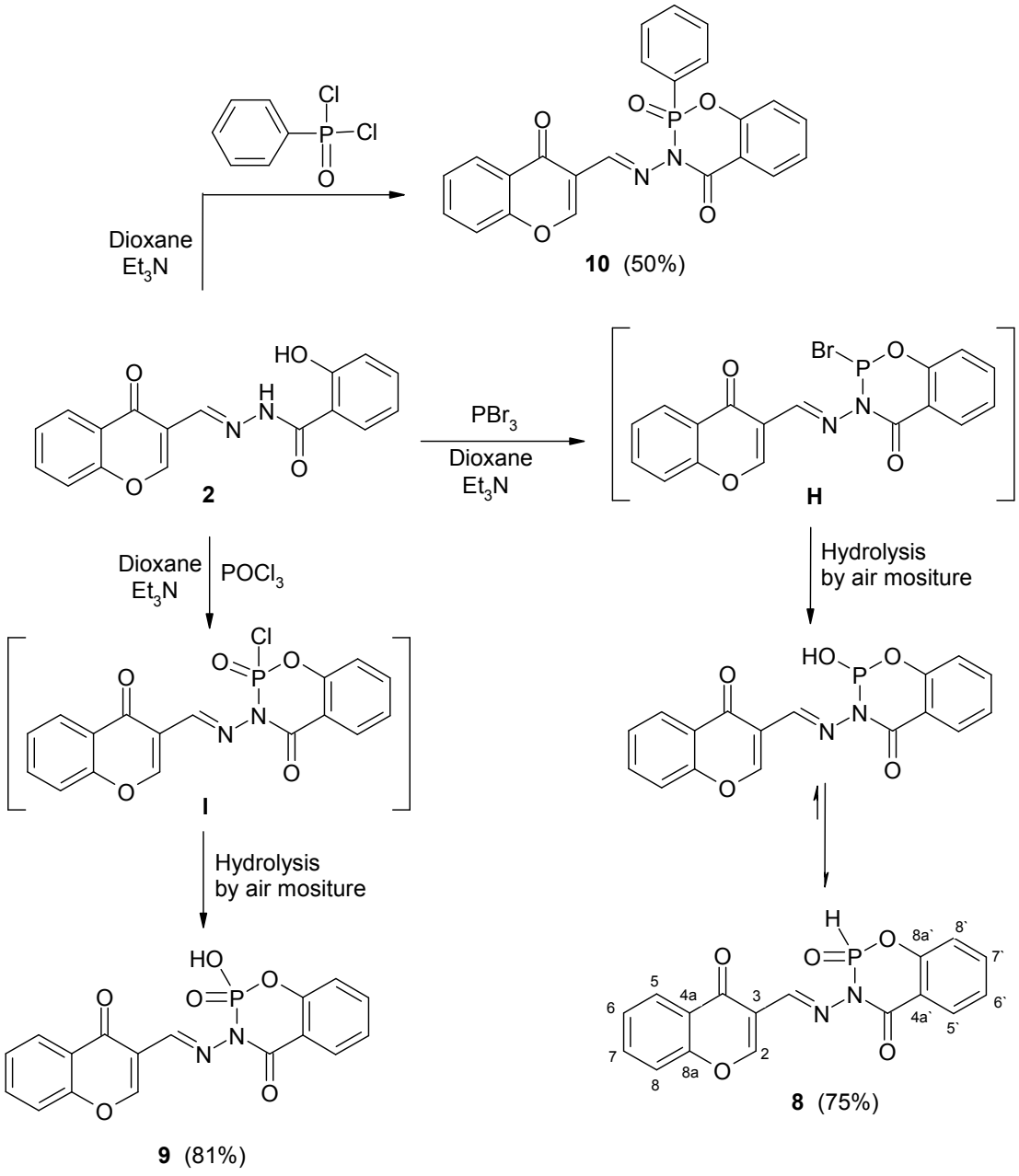
Scheme 3



Scheme 4

Keeping in view the importance of six-membered organophosphorus heterocyclic compounds, we herein report the synthesis of novel 1,3,2-benzoxazaphosphinines *via* the ring-closure reactions of hydrazone **2** with some phosphorus halides. Thus, reaction of hydrazone **2** with phosphorus tribromide, phosphorus oxychloride and phenyl phosphonic dichloride in dry dioxane containing two equivalent amounts of triethylamine yielded the corresponding 1,3,2-benzoxazaphosphininyl chromones **8**, **9** and **10**, respectively, in good yields (Scheme 5). The suggested mechanism for formation of the product **8** and **9** occurred *via* a double nucleophilic attack of NH and OH groups at phosphorus atoms to remove two molecules of triethylammonium halide affording the nonisolable

intermediates **H** and **I**, which underwent hydrolysis by air moisture and washing with water. The structure elucidation of compounds **8**–**10** was performed by IR, NMR spectroscopy and mass spectrometry.



Scheme 5

Biological evaluation

Anticancer activity of the synthesized compounds

The synthesized compounds were evaluated for their anticancer activities against MCF-7 (human breast cancer), HepG2 (human liver cancer), HCT116 (human colon cancer) and PC3 (human prostate cancer) cell lines by SRB assay [28]. The anticancer activities of the synthesized compounds were expressed by median growth inhibitory concentration (IC_{50}) as shown in Table 1. Unfortunately, the results revealed that the investigated compounds did not exert any activity against liver HepG2, colon HCT116 and prostate PC3 cells. However, they recorded variable activities against breast MCF-7 cells (Table 1). It was clear that presence of phosphorus heterocycles enhanced the anticancer activities in comparison with compound **2**. However, compounds **2**, **6**, **8** and **10** showed weak anticancer activities. Compounds **4** (IC_{50}=11.7±1.50 µg/ml) and **5** (IC_{50}=9.37±1.30 µg/ml) that have 1,4,5,2-oxadiazaphosphinine rings with alkoxy groups, were moderate potent anticancer agents near to the standard drug (IC_{50}=8.50±0.90 µg/ml). Also, compound **9** (IC_{50}=12.00±1.46 µg/ml) was the most active one between the 1,3,2-oxazaphosphinine derivatives **8**, **9** and **10** due to the presence of acidic OH group. The linking of the α-hydrazinophosphonic acid with the chromone moiety in compound **3** (IC_{50}=8.11±1.12 µg/ml) played an important role to exhibit the most effect against the MCF-7 cells. Moreover, compound **7** (IC_{50}=8.60±0.88 µg/ml) was similar to the reference drug Tamoxifen (IC_{50}=8.50±0.90 µg/ml) that may due to the presence of $MeOC_6H_4$ moiety attached to the 1,3,2-oxazaphosphininethione moiety.

Table 1. The anticancer effect of the synthesized compounds against breast cancer cells and on the expression of VEGF inhibition.

Compound	IC_{50} (µg/ml)	VEGF (µg/ml)
2	47.70±5.80	2015.00±260.00 (4%)
3	8.11±1.12	230.00±26.50 (89%)
4	11.70±1.50	996.00±112.00 (53%)
5	9.37±1.30	922.00±103.00 (56%)
6	38.90±5.00	1998.00±230.00 (5%)
7	8.60±0.88	322.10±40.30 (85%)
8	25.70±3.00	1710.00±180.00 (19%)
9	12.00±1.46	1010.00±12.00 (52%)
10	21.90±4.16	1810.80±190.70 (13%)
Tamoxifen	8.50±0.90	110.27±14.00 (95%)

Data were expressed as Mean ± Standard error (S.E.) of three independent experiments. Values between brackets indicated percentage changes as compared with control cancer cells.

Inhibitory effect of the synthesized compounds on VEGF

The inhibitory effect of synthesized compounds on the expression of VEGF as a marker for angiogenesis was determined [29,30] as triplicate determinations and the data were presented in Table 1. The results showed that most of the tested compounds showed potent inhibition against expression of VEGF in human breast cancer cell line MCF-7 as compared to the cancer cells. Compounds **3** and **7** were found to be potent inhibitor against expression of VEGF with percentage of inhibition values of 89 and 85% as compared with the positive drug, Tamoxifen (95%). These results were parallel with that

of their anticancer activity, which suggested that the potent anticancer activities of the synthesized compounds were likely to their VEGF inhibitory activities. Otherwise, compounds **4**, **5** and **9** revealed moderate activities against VEGF with percentage of inhibition values were 53, 56 and 52%, respectively. The rest of compounds showed weak activity.

Experimental

The melting point was determined in an open capillary tube on a digital Stuart SMP-3 apparatus. Infrared spectra were measured on FT-IR (Nicolet IS10) spectrophotometer using KBr disks and Perkin-Elmer 293 spectrophotometer using KBr disks. ^{1}H- and ^{13}C-NMR spectra were measured on Gemini-300BB spectrometer (300 and 75 MHz), using DMSO-d_6 as a solvent and TMS (δ) as an internal standard. Also, several samples were measured on a Bruker 600 MHz spectrometer operating at 600 and 150 MHz for ^{1}H- and ^{13}C-NMR spectra, respectively. Mass spectra were recorded on a Gas Chromatographic GCMSqp 1000 ex Shimadzu instrument at 70 ev. Elemental microanalyses were performed Perkin-Elmer 2400II at the Chemical War department, Ministry of Defense. The purity of the synthesized compounds was checked by thin layer chromatography (TLC) and elemental microanalyses.

Synthesis of 2-hydroxy-N`-[(4-oxo-4H-chromen-3-yl)methylidene]benzohydrazide (2)

A mixture of 3-formylchromone (**1**) (1.74 g, 10 mmol) and salicylic acid hydrazide (1.52 g, 10 mmol) in ethanol (30 ml) was heated under reflux for 30 minutes. The formed solid was filtered off and recrystallized from diluted DMF to give the desired product as canary yellow crystalline solid in 77% yield; mp 238−240 °C (Lit. [26] mp 224−226 ^{o}C).

Synthesis of [{2-[(2-hydroxyphenyl)carbonyl]hydrazinyl}(4-oxo-4H-chromen-3-yl) methyl]phosphonic acid (3)

Phosphonic acid (0.82 g, 10 mmol) was added to a solution of compound **2** (1.54 g, 5 mmol) in dry dioxane (60 ml) in presence of a catalytic amount of 4-toluenesulfonic acid (0.1 g). The mixture was heated under reflux for 15 h. The reaction mixture was concentrated into its half volume. After adding some water (10 ml), the formed solid was filtered off and crystallized from dilute ethanol to give yellow crystalline solid in 56% yield; mp 190−194 (dec.) °C.

Synthesis of 3-[2-ethoxy-6-(2-hydroxyphenyl)-2-oxido-3,4-dihydro-2H-1,4,5,2-oxadiazaphosphinin-3-yl]-4H-chromen-4-one (**4**)

A mixture of diethyl phosphite (2 ml, 15 mmol) and compound **2** (1.54 g, 5 mmol) in presence of trifluoroboron etherate (0.1 ml) as a catalyst, was fused on water bath for 5 h. The formed semi-solid was dissolved in hot little amount of ethanol and left to cool. After adding some water (5 ml), the formed solid was filtered off and recrystallized from dilute ethanol to give pale yellow crystalline solid in 46% yield; mp 200−202 °C.

Synthesis of 3-[2-(2-chloroethoxy)-6-(2-hydroxyphenyl)-2-oxido-3,4-dihydro-2H-1,4,5,2-oxadiazaphosphinin-3-yl]-4H-chromen-4-one (**5**)

A mixture of tris(2-chloroethyl)phosphite (2 ml, 15 mmol) and compound **2** (1.54 g, 5 mmol) in presence of trifluoroboron etherate (0.1 ml) as a catalyst, was fused on water bath for 5 h (add 0.2 ml of distilled water after 2 h). The reaction mixture was treated with ethyl acetate to give solid which was filtered off and crystallized from dilute ethanol to yield beige solid in 43% yield; mp 183−185°C.

Synthesis of 3-{[(2-sulfanyl-2-sulfido-4-thioxo-1,3,2-benzoxazaphosphinin-3(4H)-yl) imino]methyl}-4H-chromen-4-one (6)

A mixture of phosphorus pentasulfide (1.11 g, 5 mmol) and compound **2** (1.54 g, 5 mmol) in dry dioxane (50 ml), was heated under reflux for 8 h. The reaction mixture was concentrated into its half volume and left to cool. The formed solid was filtered off and recrystallized from dioxane to give orange crystalline solid in 58% yield; mp 276−278 °C.

Synthesis of 3-[{[2-(4-methoxyphenyl)-2-sulfido-4-thioxo-1,3,2-benzoxazaphosphinin -3(4H)-yl]imino}methyl]-4H-chromen-4-one (7)

Lawesson's reagent (1.6 g, 4 mmol) was added to a solution of compound **2** (1.23 g, 4 mmol) in dry dioxane (50 ml). The mixture was heated under reflux for 10 h. The reaction mixture was concentrated to its half volume and left to cool. After adding some water (10 ml), the obtained solid was filtered off and recrystallized from ethanol to give brick red crystalline solid in 53% yield; mp 105−108 °C.

Synthesis of 3-{[(2-oxido-4-oxo-2,3-dihydro-4H-1,3,2-benzoxazaphosphinin-3-yl) imino]methyl}-4H-chromen-4-one (8)

A solution of phosphorus tribromide (0.5 ml, 5 mmol) in dry dioxane (5 ml), was added dropwise to a solution of compound **2** (1.54 g, 5 mmol) in dry dioxane (60 ml) in presence of a catalytic amount of triethylamine (0.7 ml, 10 mmol) at 5−10 ^{o}C for 30 minutes. The mixture was heated under reflux for 10 h. The formed solid was filtered off, washed with distilled water and crystallized from dilute ethanol to give beige solid in 75% yield; mp 230−234 °C.

Synthesis of 3-{[(2-hydroxy-2-oxido-4-oxo-4H-1,3,2-benzoxazaphosphinin-3-yl) imino]methyl}-4H-chromen-4-one (9)

A solution of phosphorus oxychloride (0.5 ml, 5 mmol) in dry dioxane (5 ml), was added dropwise to a solution of compound **2** (1.54 g, 5 mmol) in dry dioxane (60 ml) in presence of catalytic amount of triethylamine (0.7 ml, 10 mmol) at 5−10 ^{o}C for 30 minutes. The mixture was heated under reflux for 10 h. The formed solid was filtered off, washed with distilled water and crystallized from dilute ethanol to give beige solid in 81% yield; mp 208−211 °C.

Synthesis of 3-{[(2-oxido-2-phenyl-4-oxo-4H-1,3,2-benzoxazaphosphinin-3-yl)imino] methyl}-4H-chromen-4-one (10)

A solution of phenyl phosphonic dichloride (0.7 ml, 5 mmol) in dry dioxane (5 ml), was added dropwise to a solution of compound **2** (1.54 g, 5 mmol) in dry dioxane (50 ml) in presence of a catalytic amount of triethylamine (0.7 ml, 10 mmol) at 5−10 ^{o}C for 30 minutes. The mixture was heated under reflux for 4 h. The formed solid was filtered off, washed with distilled water and crystallized from dilute ethanol to give pale yellow crystalline solid in 50% yield; mp 253−255 °C.

Cell lines and culturing

Human cancer cell lines (breast MCF-7, liver HepG2, colon HCT116 and prostate PC3) were obtained from the ATCC (Rockville, MD, USA) were used. The cancer cells were maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% heat inactivated fetal calf serum (GIBCO), penicillin (100 U/ml) and streptomycin (100 µg/ml) at 37 ^{o}C in humidified atmosphere containing 5% CO_2. Cells at a concentration of 0.50 x 10^6 were grown in a 25 cm^2 flask in 5 ml of complete culture

medium. The anticancer activity of the tested compounds was measured *in vitro* using the Sulfo-Rhodamine-B stain (SRB) assay according to Skehan *et al* [28]. Briefly, cells were inoculated in 96-well microtiter plate (10^4 cells/ well) for 24 hours before treatment with the tested compounds to allow attachment of cell to the wall of the plate. The synthesized compounds were dissolved in DMSO at 1 mg/ml immediately before use and diluted to the appropriate volume just before addition to the cell culture. Different concentration of the synthesized compounds and Tamoxifen were added to the cells. Three wells were prepared for each individual dose. Cells were incubated with the compounds for 48 hours at 37 ^{o}C and in atmosphere of 5% CO_2. After 48 hours, cells were fixed, washed, and stained for 30 minutes with 0.4% (w/v) SRB dissolved in 1% acetic acid. Unbound dye was removed by four washes with 1% acetic acid, and attached stain was recovered with Tris-EDTA buffer. Color intensity was measured in an ELISA reader. The relation between surviving fraction and drug concentration is plotted to get the survival curve for each cell line after the specified time. The concentration required for 50% inhibition of cell viability (IC_{50}) was calculated and the results are given in Table 1. The results were compared to the effect of the reference drug, Tamoxifen.

VEGF inhibitory assay

The cells in culture medium were treated with 20 µl of IC_{50} values of the synthesized compounds or the standard reference drug, Tamoxifen dissolved in DMSO, then incubated for 24 hours at 37 ºC, in a humidified 5% CO_2 atmosphere. The cells were harvested and homogenates were prepared in saline using a tight pestle homogenizer until complete cell disruption [29]. The kit uses a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of human VEGF in samples [30]. Add

VEGF to monoclonal antibody enzyme well which is pre-coated with human VEGF monoclonal antibody, incubation; then, add VEGF antibodies labeled with biotin, and combined with Streptavidin-HRP to form immune complex; then carry out incubation and washing again to remove the uncombined enzyme. Then add Chromogen solution A, B, the color of the liquid changes into the blue, and at the effect of acid, the color finally becomes yellow. The chroma of color and the concentration of the human VEGF of sample were positively correlated and the optical density was determined at 450 nm. The level of human VEGF in samples was calculated (μg/ml) as duplicate determinations from the standard curve. Percent inhibition was calculated by the comparison of the tested compounds treated to control cancer cells.

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