One-pot synthesis, antimicrobial activities, and drug-likeness analysis of some novel 1,2-benzoxaphosphinines, phospholobenzofuran, and chromonyl/coumarinyl/indenonyl phosphonate

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ABSTRACT

Some novel phosphorus compounds of types 1,2-benzoxaphosphinines, phospholo-[3,4-b][1]benzofuran, and chromonyl/coumarinyl/indenonyl phosphonates were achieved. The methodology depended on reaction of 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-dione (1) with diethyl phosphite in the absence and presence of electrophilic reagent. Reaction of substrate 1 with diethyl phosphite in the presence of a base afforded 3-benzoyl-4-hydroxy-2-oxido-2H-1,2-benzoxaphosphinine (2), while its reaction with diethyl phosphite in the presence of ammonia, formaldehyde and chloroacetyl chloride under basic conditions gave the corresponding 4-ethoxy-4-oxido-2-phenyl-3,4-dihydro[1,2]benzoxaphosphinino[3,4-b] pyrrole (6) and 1-benzoyl-2-ethoxy-3-hydroxy-2H-phospholo[3,4-b][1]benzofuran (7), respectively. In addition, treatment of compound 1 with diethyl phosphite in the presence of DMFDMA, ethyl chloroacetate and oxalyl chloride under the same conditions led to the formation of chromonyl/coumarinyl/indenonyl phosphonates 3, 8, and 10, respectively, in moderate yields. The reaction mechanisms for the formation of these products were presented and explained. The molecular structures of products were deduced by spectral and analytical tools. The antimicrobial activity for the novel products were evaluated. The antimicrobial results were supported by SwissADME server based in silico computations. Both products 6 and 10 showed excellent antimicrobial properties.

GRAPHICAL ABSTRACT

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Introduction

In modern organic synthesis, multi-component reactions (MCRs) have become a very powerful synthetic design approach, combining synthetic efficiency with conceptual performance.\[^{1-4}\] This is owing to their capacity to incorporate together three or more components in one-pot, resulting in great selectivity and high atom economy.\[^{5}\] Moreover, MCRs are emerging as environmentally friendly synthetic techniques for assembling very complex molecules with wide range of structural diversity for diverse applications.\[^{6}\] It is known that MCRs performed traditional processes in a variety of aspects, including synthetic efficiency, reduction of isolation, purification processes, ease of operation, reducing costs, energy, and waste production.\[^{7,8}\] On the other hand, phosphorus containing compounds have acquired a significant interest due to their broad synthetic utility and pharmaceutical importance including anti-HIV,\[^{9}\] anticancer,\[^{10,11}\] antineoplastic,\[^{12}\] anti-inflammatory,\[^{13}\] and antimicrobial.\[^{14}\] Among those phosphorus compounds, diethyl phosphonate derivatives are a significant category that have been extensively studied due to their presence in a variety of biological agents.\[^{15-17}\] They exhibited significant anticancer,\[^{18}\] antibacterial,\[^{19}\] and antiviral activities.\[^{20}\] In pursuit of one-pot methodologies, we earlier reported efficient protocols for the synthesis of some bioactive phosphorus compounds, such as pyrazolo[4',3',5,6]pyrano[3,2-d][1,2]azaphosphole (I), functionalized pyrrolo[3',2':5,6]pyrano[2,3-c]pyrazolyl phosphonates (II),\[^{21}\] pyrano[2',3':4,5]pyrimido[1,6-b][1,2,4,5\(^{5}\)]triazaphosphepine (III),\[^{22}\] and pyrano[2',3':4,5]pyrimido[1,6-b][1,2,4,5\(^{5}\)]triazaphosphinines (IV).\[^{23}\] (Fig. 1).

Keeping the view of importance of biological significance of phosphorus compounds and as a continuation in design of bioactive phosphorus compounds using a simple and efficient methodology,\[^{24-27}\] herein, we describe a one-pot process for the synthesis of functionalized novel phosphorus compounds especially that bearing diethyl phosphonate. The methodology depended on three-component protocol involves a reaction between 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-dione, diethyl phosphite

![Figure 1. Structure of some bioactive phosphorus compounds.](image-url)
Results and discussion

The synthetic methodology for the synthesis of labeled compounds is consisting of two steps. First, diethyl phosphite reacted with some active electrophilic reagents. Then, the resulting adducts were treated in situ with equimolar amounts of 1-(2-hydroxyphenyl)-3-phenyl-propane-1,3-dione (1)\textsuperscript{[28]} in dry dioxane containing sodium hydride as a catalyst.

Thus, reaction of the substrate 1 with diethyl phosphite in an equimolar quantity in dry dioxane containing a catalytic amount of sodium hydride for 10 h at 90–100 °C isolated 3-benzoyl-4-hydroxy-2-oxido-2\textsubscript{H}-1,2-benzoxaphosphinine (2) (Scheme 1). In this reaction, formation of the 1,2-benzoxaphosphinine system was constructed by a nucleophilic attack by oxygen atom of hydroxyl group in compound 1, on the phosphorus atom of diethyl phosphite forming the non-isolable intermediate A. The latter intermediate underwent cyclization by the attack of active methylene anion on the electrophilic phosphorus atom to give the intermediate B which was rearranged into the isolated product 2 after 1,3-hydrogen shift (Scheme 1). The IR spectrum of compound 2 showed characteristic absorption bands at 3420 and 1639 cm\textsuperscript{-1} relevant to OH and C=O groups, respectively. Its \textsuperscript{1}H-NMR showed a distinct doublet at δ 6.74 (J\textsubscript{PH} = 685 Hz) for P–H proton, whereas the OH proton signal was observed at δ 12.03 ppm. Furthermore, the \textsuperscript{13}C-NMR spectrum of this compound revealed the specific signals for carbon atoms C–3, C–4 and C=O at δ 98.8 (d, J\textsubscript{PC} = 98 Hz), 162.7 and 163.1 ppm, respectively.

Scheme 1. Reaction of the substrate 1 with diethyl phosphite.
Mixing of diethyl phosphite with dimethylformamide dimethylacetal (DMFDMA) in the presence of sodium hydride in dioxane for 4 h, followed by adding of the substrate 1 led to the formation of diethyl [3-benzoyl-4-oxo-4\(H\)-chromen-2-yl]phosphonate (3) (Scheme 2). It is reasonable to assume that the first step of the reaction might involve the reaction of diethyl phosphite with DMFDMA under basic conditions to give the active intermediate C. The latter intermediate caused cyclization of compound 1 to form the adduct D, which underwent spontaneously auto-oxidation in air to give the isolated product 3 (Scheme 2). The IR spectrum of product 3 confirmed the presence of two ketonic groups at 1647 and 1618 cm\(^{-1}\).[29,30] In its \(^1\)H-NMR spectrum, the signals of aromatic protons corresponded to nine protons that were displayed at \(\delta\) 7.50–8.11 ppm, whereas the two ethoxy protons were observed at \(\delta\) 1.06, 1.37 (t, 6H) and 3.79, 4.16 (q, 4H) ppm. The \(^{31}\)P-NMR spectrum of this product recorded a singlet at \(\delta\) 9.92 ppm for phosphonate moiety.[31] Moreover, its \(^{13}\)C-NMR spectrum displayed the characteristic signals that confirmed the suggested structure. Especially, the carbon atom C–2 appeared as a doublet signal at \(\delta\) 158.1 (\(J_{PC} = 87\) Hz) ppm. The mass spectrum showed the molecular ion peak at \(m/z\) 386 corresponding to the calculated molecular mass.

Similarly, treatment of substrate 1 with diethyl (aminomethyl)phosphonate 4 [formed in situ between diethyl phosphite, formaldehyde and ammonia][32] in dry dioxane under the basic condition, was performed (Scheme 3). The interesting novel 4-ethoxy-4-oxido-2-phenyl-3,4-dihydro[1,2]benzoxaphosphinino[3,4-\(b\)]pyrrole (6) was isolated in moderate yield. Depending on its spectral data (see Experimental section), the plausible mechanism for the synthesis of product 6 was presented in Scheme 3. Initially, there is a condensation reaction between adduct 4 and compound 1 to give the non-isolable

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**Scheme 2.** Reaction of the substrate 1 with the formed intermediate of diethyl phosphite and DMFDMA.
intermediate $E$, which underwent another condensation process forming the non-isolable intermediate $F$ (route $b$ and not $a$). Then, this intermediate $F$ underwent an intramolecular ring closure via removal of ethanol molecule, followed by 1,3-hydrogen shift to afford the final product $6$.  

The previous successful synthesis of novel phosphorus compounds encouraged us to develop the scope of reaction of starting material $1$ with diethyl phosphite in the presence of a variety of active $\alpha$-haloester and acid chlorides. Thus, the reaction of diethyl phosphite with chloroacetyl chloride in dry dioxane under basic reaction condition for 3 h, followed by adding of compound $1$ afforded 1-benzoyl-2-ethoxy-3-hydroxy-2-$H$-phospholo[3,4-\textit{b}] [1]benzofuran (7) in moderate yield (Scheme 4). The IR spectrum for product 7 revealed the existence of OH and C=O groups at 3427 and 1637 cm$^{-1}$, respectively, whereas its mass spectrum recorded the molecular ion peak at $m/z$ 354 which validated its structure. The $^{31}$P-NMR spectrum exhibited a singlet at $\delta$ 6.23 ppm. Further, its $^1$H-NMR spectrum offered further evidence for the proposed structure, whereas the specific OH proton appeared at $\delta$ 12.70 ppm and the ethoxy protons appeared at $\delta$ 1.14 (CH$_3$) and 4.18 (CH$_2$O) ppm. The $^{13}$C-NMR spectrum of this product highlighted two specific doublets for C–1 and C–3 atoms of the phosphole ring at $\delta$ 114.1 ($J_{PC} = 119$ Hz) and 150.5 ($J_{PC} = 103$ Hz), respectively. The formation of
product 7 was supposed to proceed via an initial formation of the adduct H, which condensed with the OH group of compound 1 to give the non-isolable O-acyl derivative I. This intermediate underwent cyclization processes via elimination of molecules of water and ethanol to form the structure K that was rearranged through 1,5-hydrogen shift into the product 7 (Scheme 4).

In the same way, when the latter reaction was repeated using ethyl chloroacetate under the same reaction conditions, the diethyl [2-oxo-4-(2-oxo-2-phenylethyl)-2H-chromen-3-yl] phosphonate (8) was obtained in moderate yield as depicted in Scheme 5. However, all attempts to cyclize compound 8 into the angular triheterocyclic system 9 under different basic conditions were unsuccessful (Scheme 5). The IR spectrum of the product 8 revealed the presence of two C=O bands at 1696 and 1654 cm$^{-1}$. Its mass spectrum showed the molecular ion at $m/z$ 400 (M$^+$, 2%) corresponding to a molecular formula C$_{21}$H$_{21}$O$_6$P, while its $^1$H-NMR showed a singlet at $\delta$ 3.60 ppm attributed to CH$_2$CO, besides the other expected signals for aromatic and diethoxy protons. In addition, its $^{13}$C-NMR spectrum showed the distinctive carbon atoms of C=O$_{\text{Lactone}},$ C=O$_{\text{Ketonic}},$ and CH$_2$ at $\delta$ 177.5, 166.9, and 41.7 ppm, respectively.

Finally, diethyl phosphite was treated with oxalyl chloride in dry dioxane in the presence of NaH to produce the non-isolable adduct O. Upon treatment of the latter adduct with compound 1, the non-isolable O-acyl intermediate P was formed. The intermediate P was cyclized via elimination of water molecule affording the seven-membered heterocycle Q that underwent decarboxylation to give the isolated indenonyl phosphonate 10 (Scheme 6).[33] The IR spectrum of isolated product 10 exhibited two characteristic ketonic C=O groups at 1696 and 1652 cm$^{-1}$. Its mass spectrum and elemental analysis
data suggested the molecular formula C_{20}H_{19}O_{5}P. The $^1$H-NMR spectrum displayed nine aromatic protons at $\delta$ 7.48–8.14 ppm and ten aliphatic protons for the diethoxy phosphonate moiety which supported the expected structure. Moreover, its $^{13}$C-NMR spectrum confirmed this proposal by recording the aromatic carbon atoms in range $\delta$ 125.1–148.1 ppm while the specific two C=O groups appeared at $\delta$ 167.7 and 188.8 ppm. The phosphonate moiety was confirmed by appearance of a singlet at $\delta$ 11.02 ppm in its $^{31}$P-NMR spectrum.\[34\]

**Antimicrobial activities**

The antibacterial properties for the synthesized compounds were tested against three organisms: *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Escherichia coli*. They were also tested for antifungal properties against three organisms: *Aspergillus niger*, *Aspergillus clavatus*, and *Candida albicans*\[35,36\]. Table 1 displays the minimum inhibitory concentration (MIC) for the tested compounds (see Supplementary Material). Ciprofloxacin and Ketoconazole were employed as standard antibacterial and antifungal drugs, respectively. The prepared compounds exhibited variable antimicrobial properties against the tested pathogens. In compared to the standard drugs, the products 3 and 8

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**Scheme 5.** Reaction of the substrate 1 with the formed intermediate of diethyl phosphite and ethyl chloroacetate.
did not exhibit any adequate inhibitory actions against all bacterial and fungal organisms. Furthermore, compounds 2 and 7 demonstrated acceptable effects over all organisms. Interestingly, the 1,2-benzoaphosphininopyrrole 6 and diethyl indenonyl phosphonate 10 derivatives recorded excellent antibacterial and antifungal effects equal to the standard drugs. We can conclude that the presence of skeletons of type 1,2-benzoaphosphininopyrrole and diethyl indenonyl phosphonate in the molecular frame can exhibit excellent antimicrobial properties. Therefore, it is necessary to design a series of the 1,2-benzoaphosphininopyrrole and diethyl indenonyl phosphonate compounds which may be important for other pharmaceutical applications and biological significance.

**Drug-likeness and in silico ADME studies**

SwissADME is a free web tool used to predict and compute properties, such as physicochemical descriptors, lipophilicity, water solubility, pharmacokinetic, drug-likeness and medicinal chemistry of small molecular systems. These mentioned properties are obtained with the help of ADME (absorption, distribution, metabolism and excretion) based in silico computations. ADME plays important roles in drug design studies. For computational prediction of chemical ADME properties, in silico models are usually
The most developed model that used to analyze drug-likeness property of compounds in SwissADME free web site is Lipinski’s rule of five. Lipinski’s rule of five is a developed model to predict its biological activity or pharmacological effects depending on physical and chemical properties of any compound. The candidate products must have five fundamental important special feature as follows: (1) MlogP $\leq 5$, (2) Molecular weight (MW) $\leq 500$ g/mol, (3) Number of H-bond acceptor (HBA) $\leq 10$ and number of H-bond donors (HBD) $\leq 5$, (4) Number of rotatable bonds (nRot) $\leq 10$, and

Figure 2. The bioavailability radar for the synthesized compounds.
Topological Polar Surface Area (TPSA) < 140 Å². From Table 2 (see Supplementary Material), we can state that our synthesized compounds are accordance with the criteria defined Lipinski rules and no violation was found. Additionally, in this part the bioavailability radars and predicted Boiled-Egg plot of these products were shown in Figures 2 and 3, respectively (see Supplementary Material). From Figure 2, it was observed that no product is out of the bioavailability radar in the most properties. The Brain Or Intestinal Estimated permeation method (BOILED-EGG) is suggested as an accurate and impressive technique for drug discovery and development in literature.[39] In Figure 3, compound 6 was found in the BBB area while compounds 2, 7, and 10 were found to be closer to the BBB than both 3 and 8. As a result, our molecules have been found to have good to excellent physicochemical profile. Finally, acceptable pharmacokinetics SwissADME parameters, such as GI absorption, BBB, P-glycoprotein substrate, sitokrom P450 (CYP) inhibitors (CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4) and Log Kp (skin permeation) were obtained and presented as in Table 3 (see Supplementary Material).

**Experimental**

On a digital Stuart SMP-3 apparatus, the melting point was determined in an open capillary tube. FT-IR (Nicolet IS10) spectrophotometer with KBr disks and Perkin-Elmer 293 spectrophotometer with KBr disks were used to measure infrared spectra. DMSO-$d_6$ as a solvent and TMS ($\delta$) as an internal standard were used to measure $^1$H- and $^{13}$C-NMR spectra on a Gemini-300BB spectrometer (400 and 100 MHz). On a Bruker spectrophotometer (162 MHz), $^{31}$P-NMR spectra were measured with DMSO-$d_6$ as a solvent, TMS as an internal standard, and 85% $H_3PO_4$ as an external reference. In
a single quadrupole mass analyzer, mass spectra were recorded on the direct probe controller inlet part (Thermo-Scientific GCMS). At the Ministry of Defense’s Chemical War Department, element microanalysis was performed using a Perkin-Elmer 2400II. Thin layer chromatography (TLC) and elemental microanalysis were used to ensure the purity of the products.

**Synthesis of 3-benzoyl-4-hydroxy-2-oxido-2H-1,2-benzoxaphosphinine (2)**

A mixture of diethyl phosphite (0.7 g, 5 mmol) and equimolar amount of compound 1 (1.2 g, 5 mmol) in dry dioxane (30 mL) containing sodium hydride (0.24 g, 10 mmol), was heated under reflux for 10 h. The mixture was concentrated into its half volume. After cooling, the solution was poured onto cold water. The formed solid was filtered off and crystallized from the diluted ethanol to give beige solid in yield 72%, mp 181–183°C. IR (KBr), (ν_{max}, cm^{-1}): 3420 (br, OH), 3068 (C–H_{arom}), 2742 (br, P–H), 1639 (C=O), 1593, 1561 (C=C), 1240 (P=O), 1052 (P–O–C). ¹H-NMR (400 MHz, DMSO-d₆): 6.45 (d, 2H, J = 8.4 Hz, Ar–H), 6.74 (d, 1H, J_{PH} = 685, P–H), 7.18 (t, 1H, J = 7.2 Hz, Ar–H), 7.24 (d, 2H, J = 7.2 Hz, Ar–H), 7.38 (t, 1H, J = 7.2 Hz, Ar–H), 7.51 (t, 1H, J = 7.6 Hz, Ar–H), 7.55–7.59 (m, 1H, Ar–H), 7.91 (dd, 1H, J = 8.0 and 1.6 Hz, Ar–H), 12.03 (brs, 1H, OH). ¹³C-NMR (100 MHz, DMSO-d₆): 98.8 (d, J_{PC} = 98 Hz, C–3), 115.6 (C–4a), 116.5 (C–8), 121.8 (C–6), 123.6 (C–5), 128.8 (C–7), 129.8 (C–3’,5’phenyl), 130.3 (C–2’,6’phenyl), 131.3 (C–4’phenyl), 138.4 (C–1’phenyl), 153.4 (C–8a), 162.7 (C–4), 163.1 (C=O). MS (EI, m/z): 286 (M⁺, 16%). Anal. Calcd. for C₁₅H₁₁O₄P (286.23): C, 62.94; H, 3.87%. Found: C, 62.71; H, 3.69%.

**Conclusion**

We suggested a novel method to synthesize 2-oxido-2H-1,2-benzoxaphosphinines, phospholo[3,4-b][1]benzofuran and three examples of diethyl phosphonates bearing chromone, coumarin and indenone moieties. The method suggested reaction of diethyl phosphite with different examples of electrophilic reagents, followed by addition of 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-dione in one-pot reaction. The method was effective to construct novel phosphorus compounds that were in good purity and easily to work up. The products that having 1,2-benzoaphosphino[3,4-b]pyrrole and diethyl indenonyl phosphonate frames exhibited excellent antimicrobial activities. The drug-likeness results can state that our new molecules have been found to have good to excellent physicochemical profile. Finally, these results are thought to contribute to potential antimicrobial agent development studies.

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