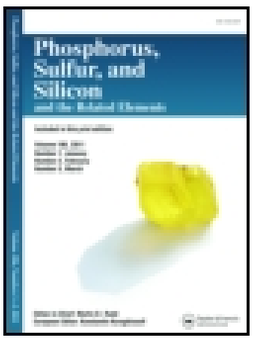

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Synthesis and antioxidant properties of some novel 1,3,4,2-oxadiazaphosphepino[6,7-c]quinolinones and pyrazolo[3,4:4',3']quinolino[5,1-c][1,4,2]oxazaphosphinine

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Synthesis and antioxidant properties of some novel 1,3,4,2-oxadiazaphosphepino[6,7-*c*]quinolinones and pyrazolo[3,4:4`,3`]quinolino[5,1-*c*][1,4,2]oxazaphosphinine

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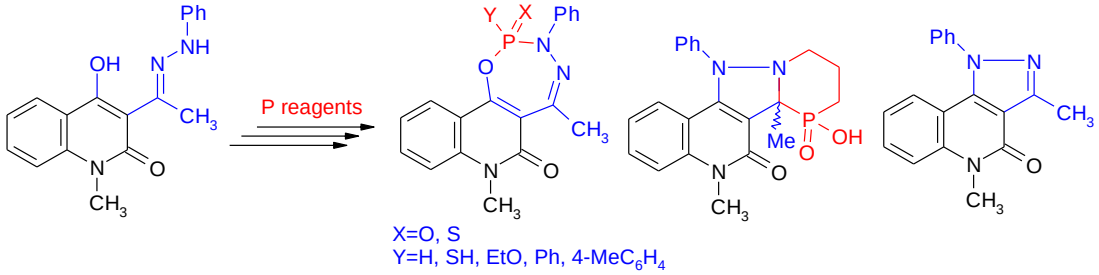
ABSTRACT

A series of novel 1,3,4,2-oxadiazaphosphepino[6,7-*c*]quinolinones **3**–**5**, **9** and **11** have been synthesized from treatment of 4-hydroxy-1-methyl-3-[1-(2-phenyl-hydrazinylidene)ethyl]quinolin-2(1*H*)-one (**2**) with some phosphorus sulfides, diethyl phosphite and phenyl phosphonic dichloride, respectively, in dry dioxane. Also, reaction of hydrazone **2** with tris(2-chloroethyl)phosphite under the same reaction conditions gave pyrazolo[3,4:4`,3`]quinolino[5,1-*c*][1,4,2]oxazaphosphinine **10**. However, when hydrazone **2** was treated with phosphonic acid, phosphorus tribromide or phosphorus oxychloride, 3,5-dimethyl-1-phenyl-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one (**7**) was isolated in all cases. The compounds were evaluated for their antioxidant activities. Among the synthesized compounds, 1,3,4,2-oxadiazaphosphepino[6,7-*c*]quinolinone-2-sulfide **5** and its analogue 2-oxide **11** exhibited higher antioxidant activities than the standard antioxidant.



Keywords

Quinolinone; hydrazone; oxadiazaphosphepine; oxazaphosphinine; antioxidant

ACCEPTED MANUSCRIPT

INTRODUCTION

2-Quinolinone compounds are class of bioactive heterocyclic systems, which received much attention due to their important pharmacological activities[1,2] such as antioxidant, anti-inflammatory, antimalarial, antimicrobial and anticancer properties.[3-7] Phosphorus compounds have also received increasing attention in the last years due to their wide range of applications in medicinal and organic chemistry.[8,9] In particular, phosphorus heterocycles have broad biological activities such as anticancer, antimicrobial, analgesic and anti-inflammatory activity.[10-13] Due to synthetic and biological values of 2-quinolinones and phosphorus heterocycles, we expected that the combination of phosphorus heterocycles with 2-quinolinone moiety in one molecular frame may lead to enhanced biological properties. However, to the best of our knowledge, synthesis of phosphorus heterocycles derived from 4-hydroxy-2-quinolinone has not been reported in the literature. Our recent work has involved the synthesis of bioactive phosphorus compounds bearing heterocycles.[14-16] The target of the present research is the synthesis of novel phosphorus heterocycles containing 2-quinolinone system, and investigates their potential antioxidant properties.

RESULT AND DISCUSSION

Chemistry

4-Hydroxy-1-methyl-3-[1-(2-phenylhydrazinylidene)ethyl]quinolin-2-(1*H*)-one (**2**) was obtained by reaction of 3-acetyl-4-hydroxyquinolin-2(1*H*)-one (**1**) with phenylhydrazine in dimethylformamide in excellent yield (Scheme 1).[17,18]

The hydrazone **2** was used as starting material to construct some novel phosphorus heterocycles linked to 2-quinolinone ring *via* its treatment with some phosphorus reagents. Thus,

treatment of hydrazone **2** with phosphorus pentasulfide, *O*,*O*-diethyldithiophosphoric acid and Lawesson's reagent (LR) in dry dioxane under reflux furnished the corresponding 1,3,4,2-oxadiazaphosphepino[6,7-*c*]quinolinones **3**–**5**, respectively (Scheme 2). The structures of compounds **3**–**5** were supported on the basis of their elemental analyses and spectral data. Their IR spectra showed absorption bands in regions 1656–1664 and 756–812 cm^{-1} ascribed to C=O and P=S functionalities. In addition, the absence of bands for OH and NH groups confirmed the cyclization process with participation of the phosphorus atom. Also, their ^{1}H NMR spectra supported the suggested structures. The SH proton in compound **3** and the methoxy protons in compound **5** were observed at δ 3.45 and 3.78 ppm, respectively, while the ethoxy protons of compound **4** appeared at δ 1.21–1.29 ppm (CH_3) and 4.00–4.20 ppm (CH_2). In their ^{13}C NMR spectra, the most important signals in the range δ 12.7–12.8, 28.6 and 158.2–158.3 ppm, were assigned to CH_3, NCH_3 and C=O, respectively. Furthermore, the NMR signals for the carbon atoms of the ethoxy and methoxy groups in compounds **4** and **5** were observed at δ 16.6, 59.5 and 55.2 ppm, respectively. The ^{31}P NMR spectrum of compound **5** showed a singlet at δ 61.1 ppm. The mass spectra displayed the corresponding molecular ion peaks at *m/z* 401, 413 and 475, respectively.

As an extension of this study, the behavior of hydrazone **2** towards phosphonic acid, diethylphosphite and tris(2-chloroethyl)phosphite, was also investigated. Thus, reaction of hydrazone **2** with phosphonic acid in dry dioxane containing 4-toluenesulfonic acid as a catalyst under *Pudovik* reaction conditions, did not give the expected α-hydrazinophosphonic acid **6** (Scheme 3). Instead 3,5-dimethyl-1-phenyl-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one (**7**) was formed (Scheme 3).[19] The formation of compound **7** instead of **6** may be due to the

preference of hydrazone **2** to cyclize than to react with the phosphorus reagent. The presence of strong acidic medium using phosphonic acid and 4-toluenesulfonic acid may facilitate the cyclization process.[18]

Similarly, when the hydrazone **2** was treated with diethyl phosphite at 80–90 ^{o}C in the presence of BF_3 etherate under *Pudovik* reaction conditions[20] unexpectedly the oxadiazophosphepino[6,7-*c*]quinolinone **9A**,**B** and not the α-hyrazinophosphonate **8** was formed (Scheme 3). The suggested mechanism for the formation of compound **9** is a cyclization of hydrazone **2** *via* the nucleophilic attack of NH and OH groups at phosphorus atom and elimination of two molecules of ethanol. The IR spectrum of compound **9** revealed the absence of NH group and the appearance of absorption bands at 3289, 1287 and 1657 cm^{-1} assigned to P–OH, P=O and C=O groups, respectively. The mass spectrum of compound **9** displayed its molecular ion peak M^+ in agreement with its molecular formula. The ^{1}H NMR spectrum revealed the P–H proton as a doublet resonating at δ 6.70 ppm with a P,H coupling constant of 630 Hz, as well as the other expected signals. Its ^{31}P NMR spectrum showed two signals at δ 7.6 ppm (form **9A**) and 16.1 ppm (form **9B**). The IR, ^{1}H and ^{31}P NMR spectra confirmed the presence of compound **9** in two tautomeric forms because of *phosphite-phosphonate* tautomerism.[21]

The novel cyclic phosphonic ester **10** was obtained *via* reaction of hydrazone **2** with tris(2-chloroethyl)phosphite under the same reaction conditions (Scheme 4). A plausible mechanism for formation of product **10** may start with a *Michael* addition of the phosphite to the azomethine bond to give the non isolatable intermediate **D**, which undergoes cyclization *via* nucleophilic attack of NHPh at position 4 of the quinoline ring to eliminate a water molecule affording the pyrazolyl intermediate **E**. The latter non isolatable intermediate undergoes another cyclization

via elimination of hydrogen chloride, followed by acid-catalyzed hydrolysis to afford the final product (Scheme 4).[22] Its IR spectrum showed the specific absorption bands at 3395 (P–OH), 1660 (C=O) and 1289 cm^{-1} (P=O). Also its ^{1}H NMR spectrum displayed three specific signals at δ 2.75, 4.21 and 5.50 ppm ascribed to NCH_2, OCH_2 and P–OH protons, respectively, as well as multiplets at δ 6.98–7.79 ppm assigned to nine aromatic protons. Furthermore, its ^{13}C NMR spectrum showed signals at δ 15.9, 36.4 and 158.1 ppm, which were assigned to NCH_2, OCH_2 and C=O, respectively. Its ^{31}P NMR spectrum showed a singlet at δ 13.1 ppm. The mass spectrometry was an excellent tool to prove the proposed structure and showed its molecular ion peak at *m/z* 397.

The reactivity of hydrazone **2** towards some phosphorus halides was also investigated. Thus, heterocyclization of hydrazone **2** with phenyl phosphonic dichloride in dry dioxane containing two equivalents of triethylamine yielded the corresponding oxadiazaphosphepinoquinolinone **11** in good yield (Scheme 5). The IR spectrum of **11** showed the presence of bands at 1658 (C=O) and 1270 (P=O) cm^{-1}, and the absence of the bands for NH and OH groups of hydrazone **2**. Its ^{1}H and ^{13}C NMR spectra confirmed the presence of five additional aromatic protons and six additional carbon atoms due to presence of the Ph-P=O moiety, whereas its ^{31}P NMR spectrum displayed a singlet at δ 34.2 ppm. The mass spectrum showed its molecular ion peak M^{+} at *m/z* 429.

Finally, when hydrazone **2** was allowed to react with equimolar amounts of phosphorus tribromide or phosphorus oxychloride in dry dioxane containing two equivalents of triethylamine the previously described compound **7** (Scheme 3) was formed. The suggested mechanism for the formation of compound **7** in this case, may involve a halogenation process *via* the phosphorus

halide at position 4 of the quinolinone ring, followed by cyclization *via* dehydrohalogenation with the help of triethylamine affording the final product **7** in high yield (Scheme 5).[18]

Antioxidant activity

The antioxidant properties of the synthesized compounds were evaluated by two in *vitro* methods in order to compare the results and to establish some structure-antioxidant activity relationships. The evaluation study was carried out at various concentrations at 50, 75 and 100 μg/mL. DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging activity evaluation is a standard assay in antioxidant activity studies and offers a rapid technique for screening the radical scavenging activity of specific compounds or extracts.[23,24] A freshly prepared DPPH solution exhibits a deep purple colour with an absorption maximum at 517 nm. This purple colour generally disappears when an antioxidant is present in the medium. Thus, antioxidant molecule can quench DPPH free radical (*i.e.,* by providing hydrogen atoms or electrons) and convert it to a colorless product (*i.e.*, 2,2-diphenyl-1-picrylhydrazine), resulting in a decrease of absorbance. Hence, more rapidly the absorbance decrease, the more potent the antioxidant activity of the compound. Percentage activity of ethanolic solutions of the synthesized compounds was examined and compared (Table S 1 Supplemental Materials).. The antioxidant activity of β-carotenoid is based on its radical adducts with free radicals from linoleic acid. The linoleic acid free radical attacks the highly unsaturated β-carotene model. The presence of antioxidants can decrease the extent of β-carotene bleaching by neutralizing the linoleate-free radical and other free radicals formed in the system.[25] Accordingly, the absorbance decreases rapidly in the samples without an antioxidant, whereas in the presence of an antioxidant, they retain the colour for a longer time. The percentage (%) antioxidant activity of newly synthesized

compounds under study is shown in Table S 2 (Supplemental Materials). The 50 % inhibitory concentration IC_{50} towards DPPH activity of newly synthesized compounds was also calculated (Table S 3). We can conclude from the results that the synthesized compounds showed promising radical scavenging abilities according to the two methods used and compared with ascorbic acid as standard antioxidant. The results revealed that most of the compounds exhibited good radical scavenging abilities at lower concentrations. However, the gradual increase in the activity in all cases was observed with increase in the concentrations of the test compounds. It was perceived that compounds **2**, **7** and **10** exhibited moderate activities, whereas **3**, **4** and **9** displayed good antioxidant properties. It is clear that the presence of phosphorus heterocycles especially with the oxadiazaphosphepine ring enhanced the antioxidant properties in comparison with the other compounds **2** and **7**. Among the tested compounds, the oxadiazaphosphepinoquinolinones **5** and **11** were the most potential antioxidant agents. This may be due to effective conjugation as well as presence of methoxy group as electron donating group.

EXPERIMENTAL

Melting points were determined in an open capillary tube with a digital Stuart SMP-3 apparatus. Infrared spectra were measured with a FT-IR (Nicolet IS10) spectrophotometer and a Perkin-Elmer 293 spectrophotometer using KBr disks. ^{1}H and ^{13}C NMR spectra were measured with a Gemini-300 BB spectrometer at 300 MHz and 75 MHz, respectively, using DMSO-d_6 as solvent and TMS as an internal standard. ^{31}P NMR spectra were obtained with a Bruker spectrometer at 242 MHz and at room temperature using DMSO-d_6 as a solvent and 85 % H_3PO_4 as external reference. Mass spectra were recorded with a Gas Chromatographic GCMSqp 1000 ex Shimadzu instrument at 70 eV. Elemental microanalyses were performed with a Perkin-Elmer

2400II instrument at the Chemical War Department, Ministry of Defense. The purity of the synthesized compounds was checked by thin layer chromatography (TLC) and elemental microanalyses. The starting material 4-hydroxy-1-methyl-3[1-(2-phenyl-hyrazinylidene)ethyl]quinolin-2(1*H*)-one (**2**) was prepared as described in the literature.[17]

Synthesis of 5,7-dimethyl-3-phenyl-2-sulfanyl-2-sulfido-3,7-dihydro[1,3,4,2]oxa-diazaphosphepino[6,7-*c*]quinolin-6(2*H*)-one (3)

A mixture of phosphorus pentasulfide (1.11 g, 5 mmol) and compound **2** (1.53 g, 5 mmol) in dry dioxane (50 mL), was heated under reflux for 10 h. The reaction mixture was concentrated to half of its volume and left to cool down to ambient temperature. The solid formed was filtered off and recrystallized from ethanol to give an orange crystalline solid in 43 % yield; mp 180−182 °C. IR (KBr), (ν_{max}, cm^{-1}): 3056 (C–H_{arom}), 2930 (C–H_{aliph}), 1656 (C=O), 1615 (C=N), 1597 (C=C), 1095 (P–O–C), 756 (P=S). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.56 (s, 3H, CH_3), 3.45 (br, 1H, P–SH exchangeable with D_2O), 3.58 (s, 3H, NCH_3), 6.99–7.08 (m, 2H, Ar–H), 7.51–7.67 (m, 5H, Ar–H), 7.90 (d, *J* = 7.0 Hz, 1H, H–11). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.7 (CH_3), 28.6 (NCH_3), 110.3 (C–5a), 111.1 (C–8), 116.2 (C–11a), 120.5 (C–10), 121.4 (C–4`$_{phenyl}$), 122.1 (C–11), 127.1 (C–2`,6`$_{phenyl}$), 129.8 (C–3`,5`$_{phenyl}$), 130.1 (C–9), 139.1 (C–7a), 140.0 (C–1`$_{phenyl}$), 147.6 (C–5), 150.0 (C–11b), 158.2 (C=O). MS (*m/z*): 401 (M^+). Anal. Calcd. for $C_{18}H_{16}N_3O_2PS_2$ (401.44): C, 53.85; H, 4.02; N, 10.47; S, 15.97. Found: C, 53.49; H, 3.82; N, 10.08 S, 15.62 %.

Synthesis of 5,7-dimethyl-2-ethoxy-3-phenyl-2-sulfido-3,7-dihydro[1,3,4,2]oxa-diazaphosphepino[6,7-*c*]quinolin-6(2*H*)-one (4)

A solution of phosphorus pentasulfide (1.11 g, 5 mmol) in absolute ethanol (30 mL) was heated under reflux for 1 h. A solution of compound **2** (1.53 g, 5 mmol) in dry dioxane (30 mL) was added to this ethanolic solution. The mixture was heated under reflux for 8 h. The reaction mixture was concentrated to half of its volume and left to cool down to ambient temperature. The solid formed after adding of some water (10 mL), was filtered off and recrystallized from dilute DMF to give a beige crystalline solid in 80 % yield; mp 163−164 °C. IR (KBr), (ν_{max}, cm^{-1}): 3056 (C–H_{arom}), 2935, 2885 (C–H_{aliph}) 1659 (C=O), 1617 (C=N), 1574 (C=C), 1091 (P–O–C), 812 (P=S). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.21–1.29 (m, 3H, CH_3), 2.56 (s, 3H, CH_3), 3.57 (s, 3H, NCH_3), 4.00–4.20 (m, 2H, OCH_2), 6.87–7.67 (m, 8H, Ar–H), 8.04 (d, *J* = 6.9 Hz, 1H, H–11). ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.7 (CH_3), 16.6 (CH_3), 28.6 (NCH_3), 59.5 (OCH_2), 111.1 (C–5a), 112.6 (C–8), 116.1 (C–11a), 121.4 (C–4`$_{phenlyl}$), 122.1 (C–10), 124.3 (C–11), 127.1 (C–2`,6`$_{phenyl}$), 129.8 (C–3`,5`$_{phenyl}$), 132.0 (C–9), 139.2 (C–7a), 140.0 (C–1`$_{phenyl}$), 145.0 (C–5), 147.6 (C–11b), 158.2 (C=O). MS (*m/z*): 413 (M^+). Anal. Calcd. for $C_{20}H_{20}N_3O_3PS$ (413): C, 58.10; H, 4.88; N, 10.16; S, 7.76. Found: C, 57.69; H, 4.55; N, 9.88; S, 7.39 %.

Synthesis of 5,7-dimethyl-2-(4-methoxyphenyl)-3-phenyl-2-sulfido-3,7-dihydro-[1,3,4,2]oxadiazaphosphepino[6,7-*c*]quinolin-6(2*H*)-one(5)

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 mixture was concentrated to half of its volume and left to cool down to ambient temperature. The solid obtained was filtered off and recrystallized from dilute ethanol to give an orange solid in 53 %

yield; mp 205−207 °C. IR (KBr), (ν_{max}, cm^{-1}): 3055 (C–H_{arom}), 2981, 2923 (C–H_{aliph}), 1664 (C=O), 1618 (C=N), 1598 (C=C), 1095, 1079 (O–C), 773 (P=S). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.58 (s, 3H, CH_3), 3.61 (s, 3H, NCH_3), 3.78 (s, 3H, OCH_3), 6.97–7.07 (m, 5H, Ar–H),7.53–7.67 (m, 8H, Ar–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.8 (CH_3), 28.6 (NCH_3), 55.2 (OCH_3), 110.4 (C–5a), 111.2 (C–8), 113.4 (C–3``,5``$_{aryl}$), 116.2 (C–11a), 120.7 (C–10), 121.5 (C–4`$_{phenyl}$), 122.2 (C–11), 124.1, 126.6 (C–2``,6``$_{aryl}$), 127.1 (C–2`,6`$_{phenyl}$), 129.8 (C–3`,5`$_{phenyl}$), 130.2 (C–9), 132.3 (d, J_{PC} = 9.5 Hz, C–1``$_{aryl}$), 139.7 (C–7a), 140.1 (C–1`$_{phenyl}$), 147.7 (C–5), 150.0 (C–11b), 158.3 (C=O), 161.2 (C–4``$_{aryl}$). ^{31}P NMR (240 MHz, DMSO-d_6): δ = 61.1 ppm. MS (*m/z*): 475 (M^+). Anal. Calcd. for $C_{25}H_{22}N_3O_3PS$ (475.49): C, 63.15; H, 4.66; N, 8.84; S, 6.74. Found: C, 62.83; H, 4.23; N, 8.49;S, 6.37 %.

Synthesis of 3,5-dimethyl-1-phenyl-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one (7)

Method A: Phosphonic acid (0.82 g, 10 mmol) was added to a solution of compound **2** (1.53 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 12 h. The reaction mixture was concentrated to half of its volume. After adding of some water (30 mL), the solid formed was filtered off and crystallized from dilute ethanol to give a yellow crystalline solid in 57 % yield; mp 190−192 °C (Lit.[18] mp 190−193 °C).

Method B: A solution of phosphorus tribromide (0.5 mL, 5 mmol) in dry dioxane (5 mL), was added dropwise to a solution of compound **2** (1.53 g, 5 mmol) in dry dioxane (60 mL) in presence of a catalytic amount of triethylamine (0.7 mL, 10 mmol) at 5−10 °C during 30 min. The mixture was heated under reflux for 10 h. After adding of some water (30 mL) the solid

formed was filtered off and crystallized from dilute ethanol to give a yellow solid in 60 % yield; mp 189−192 °C.

Method C: A solution of phosphorus oxychloride (0.5 mL, 5 mmol) in dry dioxane (5 mL), was added dropwise to a solution of compound **2** (1.53 g, 5 mmol) in dry dioxane (60 mL) in presence of a catalytic amount of triethylamine (0.7 mL, 10 mmol) at 5−10 °C during 30 min. The mixture was heated under reflux for 10 h. The reaction mixture was concentrated to half of its volume and left to cool down to ambient temperature. After adding of some water (30 mL) the solid formed was filtered off and crystallized from dilute ethanol to give a yellow solid in 75 % yield; mp 192−194 °C. IR (KBr), (ν_{max}, cm^{-1}): 3051 (C–H_{arom}), 2980, 2918 (C–H_{aliph}), 1658 (C=O), 1616 (C=N), 1595 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.56 (s, 3H, CH_3), 3.59 (s, 3H, NCH_3), 7.01–7.09 (m, 2H, Ar–H), 7.53–7.67 (m, 7H, Ar–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.7 (CH_3), 28.6 (NCH_3), 110.3 (C–3a), 111.2 (C–6), 116.2 (C–9a), 120.7 (C–8), 121.4 (C–4`$_{phenyl}$), 122.1 (C–9), 127.1 (C–2`,6`$_{phenyl}$), 129.8 (C–3`,5`$_{phenyl}$), 130.1 (C–7), 140.0 (C–9b), 139.6 (C–5a), 139.2 (C–1`$_{phenyl}$), 147.6 (C–3), 158.2 (C=O). Anal. Calcd. for $C_{18}H_{15}N_3O$ (289.33): C, 74.72; H, 5.23; N, 14.52. Found: C, 74.48; H, 4.96; N, 14.17 %.

Synthesis of 5,7-dimethyl-2-oxido-3-phenyl-3,7-dihydro[1,3,4,2]oxadiaza-phosphepino[6,7-*c*]quinolin-6(2*H*)-one (9A) and 5,7-dimethyl-2-hydroxy-3-phenyl-3,7-dihydro[1,3,4,2]oxadiazaphosphepino[6,7-*c*]quinolin-6(2H)-one (9B)

A mixture of diethyl phosphite (1.4 mL, 10 mmol) and compound **2** (1.53 g, 5 mmol) in presence of BF_3 etherate (0.1 mL) as a catalyst was allowed to react on a water bath for 6 h. The reaction mixture was treated with cold water to give a solid, which was filtered off and recrystallized from dilute ethanol to yield a beige solid in 59 % yield; mp 201−203 °C. IR (KBr),

(ν_{max}, cm^{-1}): δ = 3289 (br, OH), 3054 (C–H_{arom}), 2922 (C–H_{aliph}), 1657 (C=O), 1617 (C=N), 1596 (C=C), 1287 (P=O), 1096 (P–O–C). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.57 (s, 3H, CH_3), 3.61 (s, 3H, NCH_3), 4.22 (br, 1H, P–OH exchangeable with D_2O), 6.70 (d, 1H, *J* = 630 Hz, P–H), 7.02–7.10 (m, 2H, Ar–H), 7.53–7.67 (m, 6H, Ar–H), 7.90 (d, *J* = 7.0 Hz, 1H, H–11). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.7 (CH_3), 28.6 (NCH_3), 110.5 (C–5a), 111.2 (C–8), 116.2 (C–11a), 120.5 (C–10), 121.5 (C–4`$_{phenyl}$), 122.1 (C–11), 127.1 (C–2`,6`$_{phenyl}$), 129.8 (C–3`,5`$_{phenyl}$), 130.1 (C–9), 139.2 (C–7a), 139.8 (C–1`$_{phenyl}$), 147.6 (C–5), 152.0 (C–11b), 158.2 (C=O).^{31}P NMR (240 MHz, DMSO-d_6): δ = 7.6 and 16.1 ppm. MS (*m/z*): 353 (M^+). Anal. Calcd. for $C_{18}H_{16}N_3O_3P$ (353.31): C, 61.19; H, 4.56; N, 11.89. Found: C, 60.79; H, 4.18; N, 11.61 %.

Synthesis of 11,12b-dimethyl-1-hydroxy-1-oxido-6-phenyl-3,4,11,12b-tetrahydro-pyrazolo[3,4:4`,3`]quinolino[5,1-*c*][1,4,2]oxazaphosphinin-12(6*H*)-one (10)

A mixture of tris(2-chloroethyl)phosphite (2.7 mL, 10 mmol) and compound **2** (1.53 g, 5 mmol) in presence of BF_3 etherate (0.1 mL) as a catalyst, were allowed to react on a water bath for 8 h (0.2 mL of distilled water added after 2 h). The reaction mixture was treated with cold water to give the solid which was filtered off and recrystallized from dilute ethanol to yield a beige solid in 77 % yield; mp 223−225 °C (dec.). IR (KBr), (ν_{max}, cm^{-1}): 3395 (OH), 3053 (C–H_{arom}), 2952 (C–H_{aliph}), 1660 (C=O), 1599 (C=C), 1289 (P=O), 1099 (P–O–C). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.45 (s, 3H, CH_3), 2.75 (s, 2H, CH_2N), 3.55 (s, 3H, NCH_3), 4.21 (s, 2H, OCH_2), 5.50 (br, 1H, P–OH exchangeable with D_2O), 6.98–7.15 (m, 3H, Ar–H), 7.49–7.67 (m, 5H, Ar–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.7 (CH_3), 15.9 (NCH_2), 28.5 (NCH_3), 36.4 (OCH_2), 110.3 (C–12a), 112.1 (d, *J* = 142.3 Hz, C–12b), 116.1 (C–10), 117.9 (C–6b), 121.4 (C–8), 122.2 (C–4`$_{phenyl}$), 123.5 (C–7), 127.1 (C–2`,6`$_{phenyl}$), 129.9 (C–3`,5`$_{phenyl}$), 130.4 (C–9), 139.3

(C–10a), 139.8 (C–1`$_{phenyl}$), 140.1 (C–6a), 158.1 (C=O). ^{31}P NMR (240 MHz, DMSO-d_6): δ = 13.1 ppm. MS (*m/z*): 397 (M^+). Anal. Calcd. for $C_{20}H_{20}N_3O_4P$ (397.36): C, 60.45; H, 5.07; N, 10.57. Found: C, 60.11; H, 4.73; N, 10.19 %.

Synthesis of 5,7-dimethyl-2,3-diphenyl-2-oxido-3,7-dihydro[1,3,4,2]oxadiaza-phosphepino[6,7-*c*]quinolin-6(2*H*)-one (11)

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** (1.53 g, 5 mmol) in dry dioxane (50 mL) in presence of a catalytic amount of triethylamine (0.7 mL, 10 mmol) at 5−10 °C during 30 min. The mixture was heated under reflux for 4 h and then filtered off to remove the triethyl ammonium chloride. The filtrate was concentrated to half of its volume and left standing at ambient temperature. The solid formed was filtered off, washed with cold water and recrystallized from dilute ethanol to give the product as beige solid in 78 % yield; mp 200−203 °C.IR (KBr), (ν_{max}, cm^{-1}): 3097, 3050 (C–H_{arom}), 2980, 2918 (C–H_{aliph}), 1658 (C=O), 1616 (C=N), 1595 (C=C), 1095 (P–O–C), 1270 (P=O). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.56 (s, 3H, CH_3), 3.58 (s, 3H, NCH_3), 7.00–7.08 (m, 2H, Ar–H), 7.51–7.65 (m, 4H, Ar–H), 7.89–7.92 (m, 4H, Ar–H), 8.08–8.12 (m, 4H, Ar–H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 12.7 (CH_3), 28.6 (NCH_3), 110.4 (C–5a), 111.1 (C–8), 114.5 (C–2``,6``$_{phenyl}$), 115.8 (C–4"$_{phenyl}$), 116.1 (C–11a), 120.6 (C–3``,5``$_{phenyl}$), 120.7 (C–10), 121.4 (C–4`$_{phenyl}$), 122.1 (C–11), 127.1 (C–2`,6`$_{phenyl}$), 129.8 (C–3`,5`$_{phenyl}$), 130.0 (C–9), 133.9 (d, $J_{PC}$ = 10 Hz, C–1"$_{phenyl}$), 139.6 (C–7a), 140.0 (C–1`$_{phenyl}$), 147.6 (C–5), 149.5 (C–11b), 158.2 (C=O). ^{31}P NMR (240 MHz, DMSO-d_6): δ = 34.2 ppm. MS (*m/z*): 429 (M^+). Anal. Calcd. for $C_{24}H_{20}N_3O_3P$ (429.40): C, 67.13; H, 4.69; N, 9.79. Found: C, 66.84; H, 4.31; N, 9.43 %.

Antioxidant activity

DPPH radical scavenging activity

The DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging effect was determined according to the reported method.[23,24] One milliliter solution of various concentrations of the test compounds (50, 75, and 100 μg/mL) in ethanol were added to 4 mL of 0.004 % (w/v) ethanol solution of DPPH. The tubes were then incubated in the dark room at RT for 30 min. A DPPH blank was prepared without compound, and ethanol was used for the baseline correction. Changes (decrease) in the absorbance at 517 nm were measured using a UV-Vis spectrophotometer. The radical scavenging activities were expressed as the inhibition percentage and were calculated using the formula: % radical scavenging activity = $(AB–AA)/AB \times 100$ where *AB* = absorption of blank and *AA* = absorption of the tested compound. The radical scavenging activity of ascorbic acid was also measured and compared with that of the different synthesized compound. The compound concentration providing 50 % inhibition (IC_{50}) was calculated.

Antioxidant activity by β-carotene-linoleic acid assay

Each compound at the final concentrations of 50, 75, and 100 μg/mL was incorporated into β-carotene-linoleic acid model system independently and the activity was monitored spectrophotometrically at 470 nm.[25] The substrate suspension was prepared by addition of β-carotene (4 mg dissolved in 5 mL of chloroform) to a covered round bottomed flask containing Tween-40 (600 mg) followed by the addition of linoleic acid (60 mL). The chloroform was removed completely under vacuum using rotary evaporator at 40 °C. The resulting solution was diluted with triple distilled water (30 mL) and the emulsion was mixed well and diluted with

oxygenated water (120 mL). The aliquot (4 mL) was transferred to different stopper test tubes containing compounds in distilled ethanol. Control was prepared with distilled ethanol (1 mL) and emulsion (4 mL). Ascorbic acid solution as internal standard of the same concentration was also analyzed for comparison. Zero adjustment was done using distilled water. As soon as the emulsion was added to each test tube, the zero time (t = 0) absorbance was measured at 470 nm using spectrophotometer and subsequently absorbance was measured for every 30 min up to 3 h (t = 180) time interval. The tubes were placed in a water bath at 50 °C between the readings. Percentage antioxidant activities of each compound were evaluated in triplicates in terms of photooxidation of β-carotene using the following formula:

$$\% \text{ antioxidant activity} = 100 \times \{1- (A_o - A_t / A_{oo} - A_{to})\}$$

where: A_o = Initial absorbance of the sample. (t = 0 min)

A_t = Absorbance of the sample after time 't'. (t = 180 min)

A_{oo} = Initial absorbance of the control. (t = 0 min)

A_{to} = Absorbance of control after time 't'. (t =180 min)

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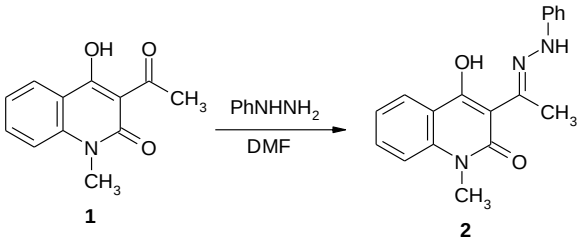
REFERENCES

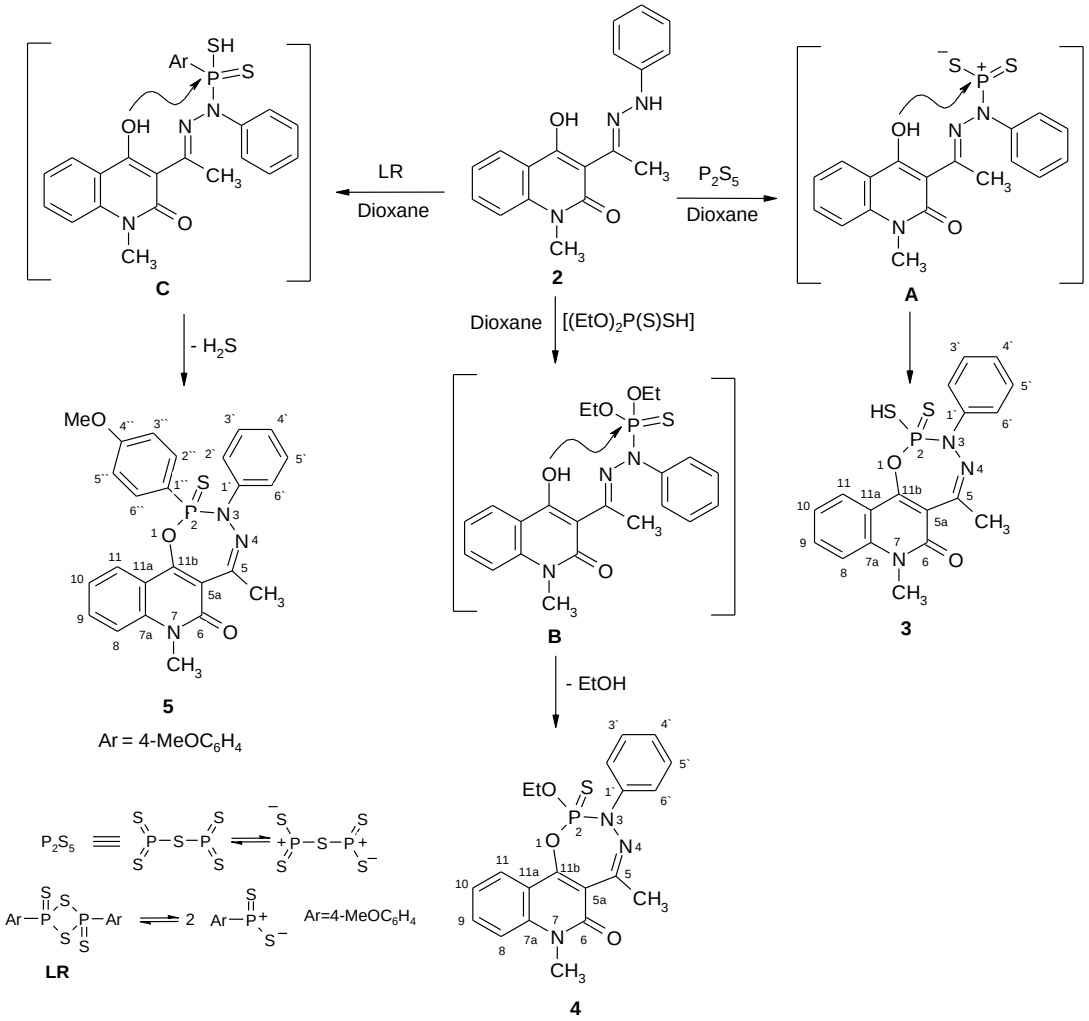
1. Abhishek, K.; Jennifer, F.; Pankaj, K. *Eur. J. Med. Chem*. **2011**, 46, 5283–5292.
2. Suthar, S. K.; Jaiswal, V.; Lohan, S.; Bansal, S.; Chaudhary, A.; Tiwari, A.; Alex, A. T.; Joseph, A. *Eur. J. Med. Chem*. **2013**, 63, 589–602.
3. Zhang, Y.; Fang, Y. L.; liang, H.; Wang, H. S.; Hu, K.; Liu, X. X.; Yi, X. H.; Peng, Y. *Bioorg. Med. Chem. Lett*. **2013**, 23, 107–111.
4. Cuo, M.; Zheng, C. J.; Song, M. X.; Wu, Y.; Sun, L. P.; Li, Y. J.; Liu, Y.; Piao, H. R. *Bioorg. Med. Chem. Lett*. **2013**, 23, 4358–4361.
5. Shi, J.; Xiao, Z.; Ihnat, M. A.; Kamatb, C.; Pamdita, B.; Hua, Z. G.; Li, P. K. *Bioorg. Med. Chem. Lett.* **2003**, 13, 1187–1189.
6. Sarvaswari, S.; Vijayakumar, V.; Siva, R.; Priya, R. *Appl. Biochem. Biotechnol*. **2015**, 175, 43–64.
7. Joseph, B.; Darro, F.; Behard, A.; Lesur, B.; Collignon, F.; Decaestecker, C.; Frydman, A.; Guillaumet, G.; Kiss, R. *J. Med. Chem*. **2002**, 45, 2543–2555.
8. Bollmark, M.; Johansson, T.; Kullberg, M.; Kraszewski, A. *Nucleusides, Nucleotides, Nucleic acids* **2003**, 22, 617–621.
9. Oliveira, F. M.; Barbosa, L. C.; Ismail, F. M. *RSC Adv*. **2014**, 4, 18998–19012.
10. Foroogh, B.; Farhad, P.; Fatemeh, D.; Yousefi, R.; Mohammad, B. S.; Bagher, M.; Ali, K. N. *RSC Adv*. **2016**, 6, 5915–5924.
11. Akbas, H.; Okumus, A.; Kili, Z.; Hokelek, T.; Suzen, Y.; Koc, L. Y.; Acik, L.; Celik, B. *Eur. J. Med. Chem*. **2013**, 70, 294–307.

12. Abdou, W. M.; Barghash, R. F.; Bekheit, M. S. *J. Arch. Pharm. Chem. Life Sci*. **2012**, 345, 884–895.
13. Abdou, W. M.; Kamel, A. A.; Shaddy, A. A. *Eur. J. Med. Chem*. **2010**, 45, 5217–5224.
14. Ali, T. E.; Abdelaziz, S. A.; El.-Edfawy, S. M.; Mohamed, E. A.; Abdel-Kariem, S. M. *Heterocycles* **2013**, 87, 2513–2532.
15. Ali, T. E.; Abdel-Aziz, S. A.; El-Edfawy, S. M.; Mohamed, E. A.; Abdel-Kariem, S. M. *Synth*. *Commun*. **2014**, 44, 3610–3629.
16. Abdel-Rahman, R. M.; Ali, T. E.; Abdel-Kariem, S. M. *Arkivoc* **2016**, i, 183–211.
17. Kappe, Th.; Aigner, R.; Jobstl, M.; Hohengassner, P.; Stadlbauer, W. *Heterocycl*. *Commun*. **1995**, 1, 341–352.
18. Stadlbauer, W.; Hojas, G. *J. Heterocycl*. *Chem*. **2004**, 41, 681–690.
19. Melani, F.; Checchi, L.; Palazzino, G.; Filacchioni, G.; Martini, C.; Penacchi, E.; Lucacchini, A. *J. Med*. *Chem*. **1986**, 29, 291–295.
20. Ali, T. E.; El-Edfawy, S. M. *Res*. *Chem*. *Intermed*. **2016**, 42, 1329–1347.
21. Mamaev, V. M.; Prisyajnuk, A. V.; Logutenko, L. S.; Babin, Y. V. *Mendeleev Commun*. **2001**, 11, 221–222.
22. Ali, T. E. *Phosphorus*, *Sulfur, Silicon Relat. Elem*. **2010**, 185, 88–96.
23. Kato, K.; Terao, S.; Shimamoto, N.; Hirata, M. *J. Med. Chem*. **1988**, 31, 793–798.
24. Siddhuraju, P.; Becker, K. *Food Chem*. **2007**, 101, 10–19.
25. Xing, R.; Yu, H.; Liu, S.; Zhang, W. B.; Zhang, Q.; Li, Z.; Li, P. *Bioorg*. *Med*. *Chem*. **2005**, 13, 1387–1392.

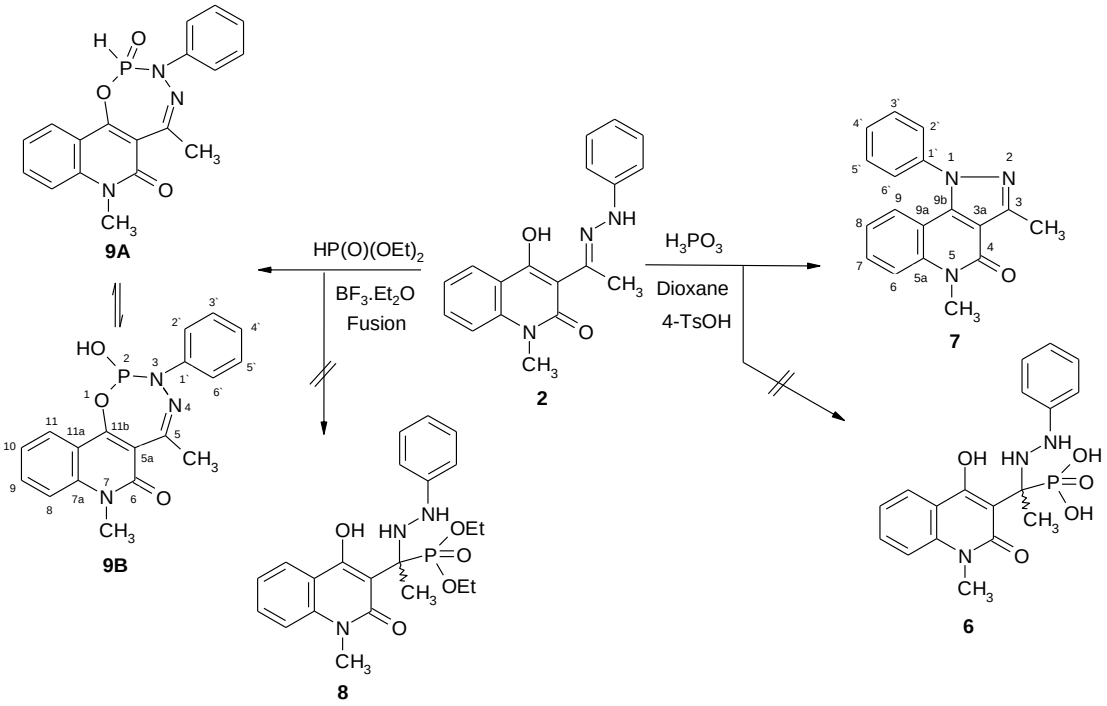


1 **2**

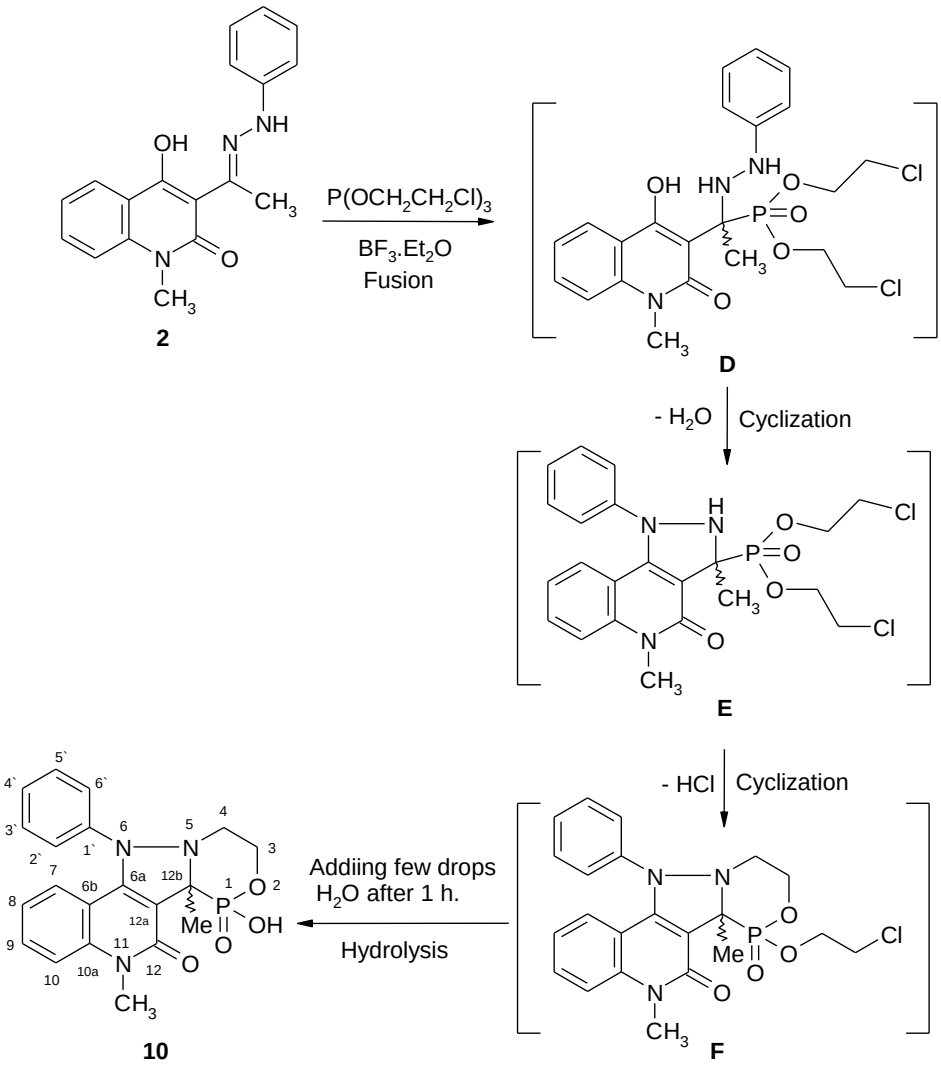
Scheme 1 Synthesis of hydrazone **2**



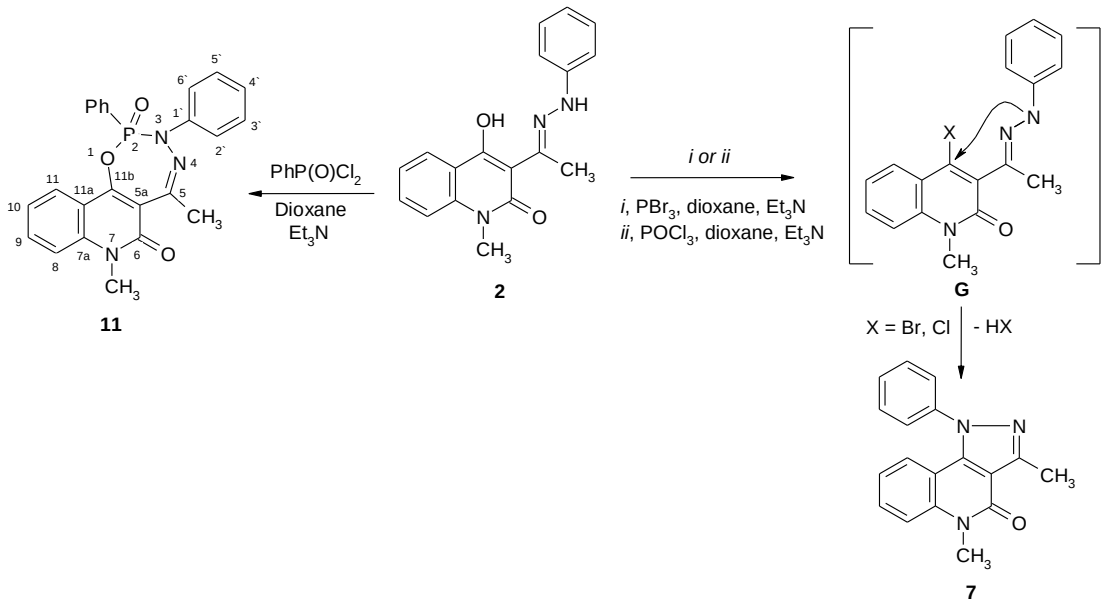
Scheme 2 Reaction of hydrazone **2** with sulfur containing phosphorus reagents



Scheme 3 Reaction of hydrazone **2** with phosphonic acid and diethyl phosphite



Scheme 4 Reaction of hydrazone 2 with tris(2-chloroethyl)phosphite



Scheme 5 Reaction of hydrazone **2** with $PhP(O)Cl_2$, PBr_3 and $POCl_3$