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SYNTHETIC METHODS FOR PHOSPHORUS COMPOUNDS CONTAINING CHROMONE AND THIOCHROMONE RINGS

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Abstract – The chromone and thiochromone rings are prominent heterocyclic substructures present in numerous natural and pharmacologically active compounds. To date, many chromone analogues containing phosphorus compounds are interest in several laboratories due to their potent pharmacological activities. This review compiles all the available literature data on the synthesis of phosphorus compounds containing chromone and thiochromone rings as well as their available biological properties starting from their appearance up to the end of 2019.

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INTRODUCTION

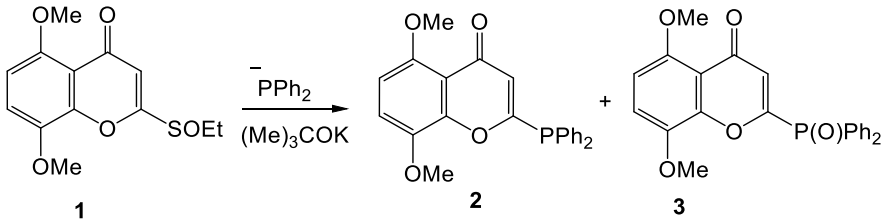
Chromone compounds are a group of naturally occurring compounds that are ubiquitous in nature, especially in vegetables, fruits, flowers, nuts, seeds, and tree bark. Chromone derivatives are also main components in large amounts in the diet of humans because of their abundance in plants and have low toxicity in mammalian.[1,2] Chromones not only have been extracted from natural products, but also synthesized by different chemical methods.[3] In some recent studies to improve the bioactivity of chromones, chemists have found that chromone-linked heterocyclic molecules have an important biological activity, especially at the C-3 position such as antitumor,[4] antimicrobial,[5] antioxidative and calpain inhibitory properties.[6,7] On the other hand, organophosphorus compounds are important intermediates in organic synthesis and have been widely used as pharmaceutical,[8–16] agricultural,[17] and chemical agents.[18–22] Recently, phosphorus heterocycles[23,24] have received considerable interest because of their unique biological activities as antimicrobial[25] and their anticancer effects.[26–29] For many years, the

synthesis of phosphorus compounds containing chromone or thiochromone has been a subject of interest in several laboratories.[30-33] The biological activities of these compounds were investigated; many of them have demonstrated the strongest in *vitro* alkylating activity and cytotoxic effect.[34] The present survey includes all the available literature data on methods developed for the synthesis of phosphorus compounds containing chromone and thiochromone rings as well as their biological properties starting from their appearance up to the end of 2019. The reported methods for the synthesis of phosphorus compounds containing chromone rings were described according to their structures.

2. Synthetic approach

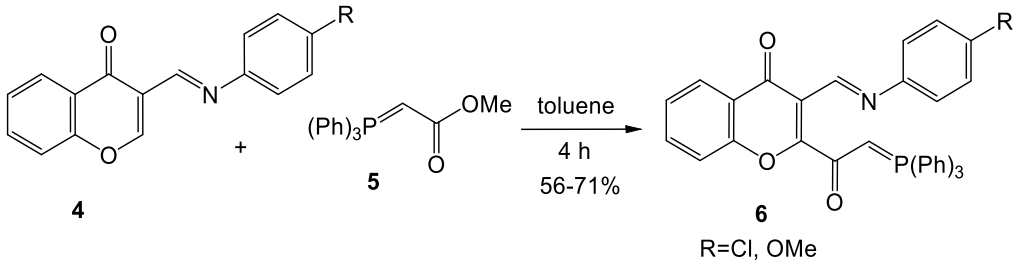
2.1. Synthesis of chromonyl phosphines, phosphoranes and phosphates

Bantick and Suschitzky,[35] reacted 5,8-dimethoxy-2-ethylsulfinochromone (**1**) with diphenylphosphine anion in the presence of potassium *tert*-butoxide to give the corresponding derivatives **2** and **3**. Their structures were established by NMR and mass spectrometry data of the crude reaction mixture as **2** and **3**, which decomposed during attempts of isolation (Scheme 1).



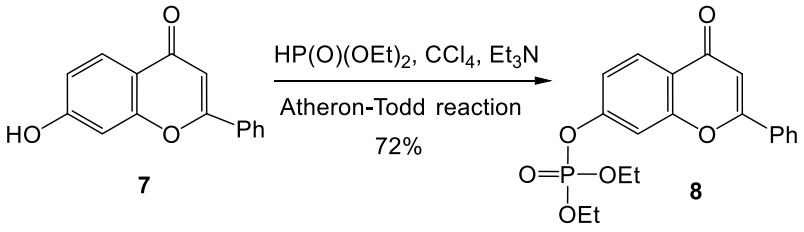
Scheme 1

When equimolar amounts of 3-[(arylimino)methyl]-4*H*-chromen-4-one (**4**) and carbomethoxymethylene-triphenylphosphorane **5** were heated under reflux in dry toluene for 4 hours, a colourless crystalline chromonyl phosphorane **6** was formed (Scheme 2).[36]



Scheme 2

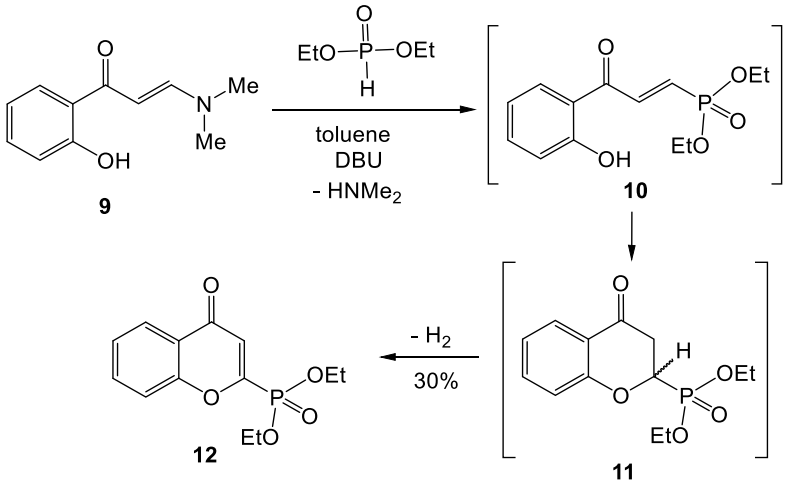
Diethyl 2-phenyl-4-oxo-4*H*-chromen-7-yl phosphate (**8**) was synthesized from 7-hydroxy-2-phenyl-4-oxo-4*H*-chromene (**7**), diethyl phosphite and carbon tetrachloride in the presence of triethylamine under Atheron-Todd reaction conditions (Scheme 3).[37]



Scheme 3

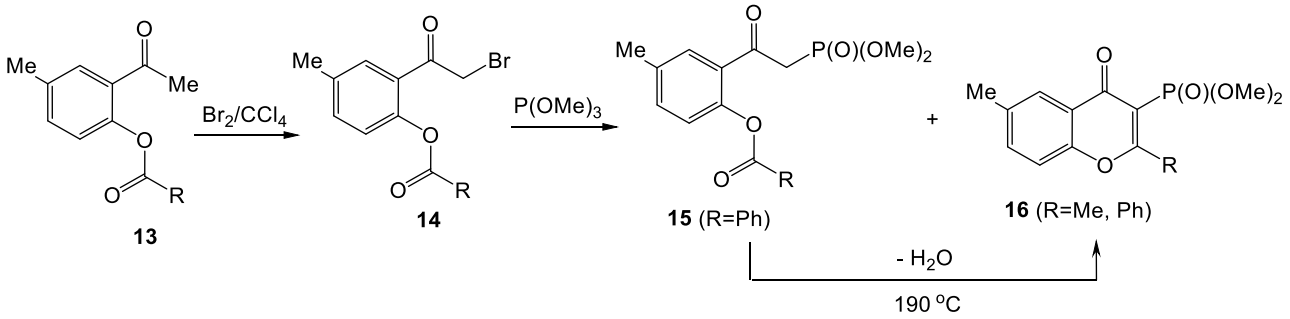
2.2. Synthesis of chromonyl phosphonates

When (2*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one (**9**) was allowed to react with diethyl phosphite in toluene containing a few drops of DBU as a basic catalyst, the reaction took place under thermal condition to give the diethyl (4-oxo-4*H*-chromen-2-yl)phosphonate (**12**) in low yield 30% (Scheme 4).[38]



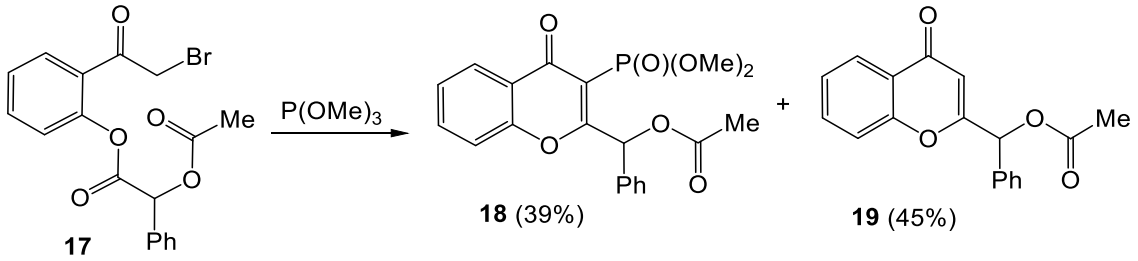
Scheme 4

Dimethyl (6-methyl-2-alkyl(aryl)-4-oxo-4*H*-chromen-3-yl)phosphonate (**16**) was obtained *via* bromination of the *ortho*-ketoester derivative **13**, followed by heating with trimethyl phosphite under Arbuzov reaction conditions (Scheme 5). The by-product **15** (R=Ph) was isolated, which underwent further cyclization into the final product **16** after its heating at 190 °C for 5 hours with 47% yield (Scheme 5). Compound **16** (R=Me) exhibited detectable activity against *S. aureus* and its alkylating property was determined by the *in vitro* Preussmann test which displayed high alkylation activity toward NBP.[39,40]



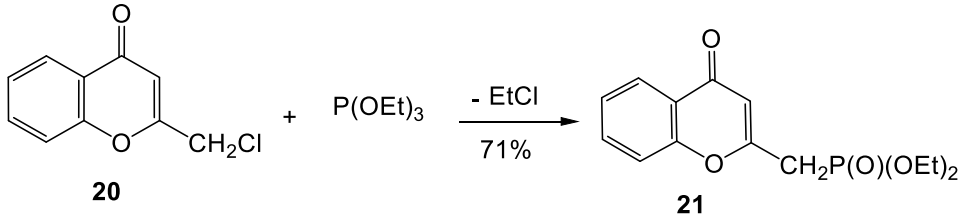
Scheme 5

The reaction of the α-bromoketone derivative **17** with trimethyl phosphite was studied. Two products of the Perkow and Arbuzov type were isolated.[41] The compound **17** underwent cyclization to give a mixture of diastereoisomers which subsequently, either lose dimethyl phosphate to yield the Wittig-type product **19**,[42] or undergo 1,2-*trans*-elimination of water on a chromatography column to give the 3-phosphono-chromone derivative **18** (Scheme 6).[43]



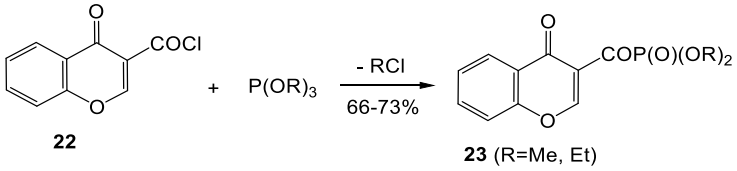
Scheme 6

Mouysset *et al.*,[44] prepared the diethyl ester of chromone-2-methanephosphonic acid **21** in good yield starting from 2-chloromethylchromone (**20**) and triethyl phosphite under Arbuzov reaction conditions (Scheme 7).



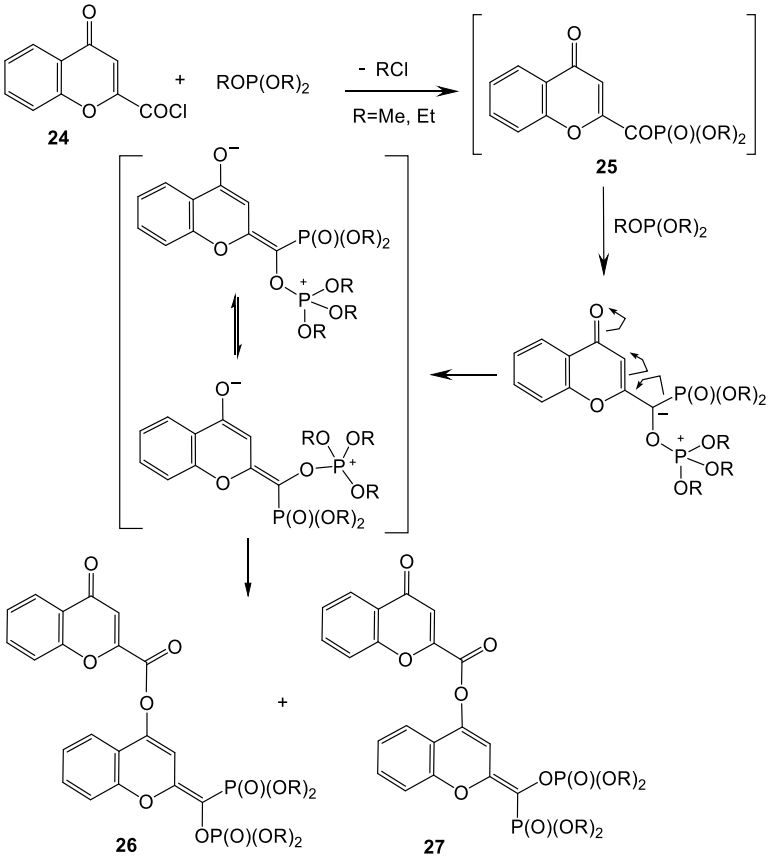
Scheme 7

Similarly, reaction of chromone-3-carboxylic acid chloride (**22**) with trialkyl phosphite yielded the corresponding chromonyl phosphonates **23** (Scheme 8).[31]



Scheme 8

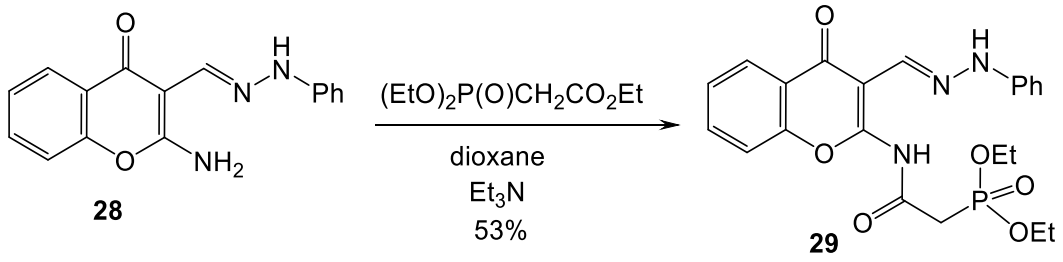
Kostka and Modranka,[31] observed that the reaction of chromone-2-carboxylic acid chloride (**24**) with trialkyl phosphite was complicated and afforded two isomeric phosphonic-phosphate compounds namely (*E*)-2-(dialkylphosphonato,dialkylphosphato)methylene-4-[(4-oxo-4*H*-chromen-2-yl)carbonyloxy]-2*H*-chromene (**26**) and their *Z*-isomers **27** in 87% yield (Scheme 9). They suggested that a second equivalent of trialkyl phosphite attacked the oxygen atom of the carbonyl group of the ketophosphonic intermediate **25** (analogous to that formed from the 3-substituted derivative of chromone (Scheme 9). At 40 ºC, a ratio between the products was 3:1, which increased to 6:1 when the temperature of reaction was increased to 60 ºC. This suggested that the formation of **26** is kinetically favoured (Scheme 9).



Scheme 9

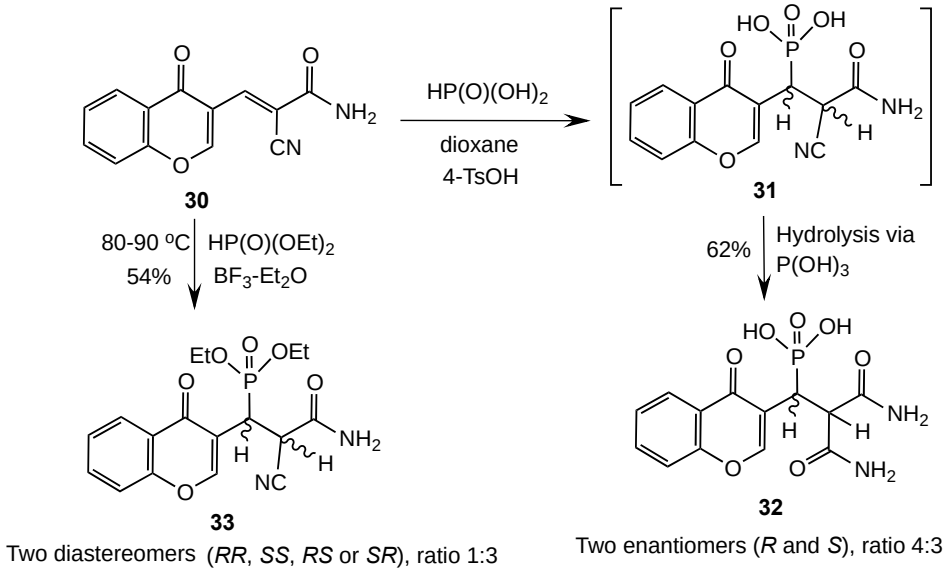
When compound 2-amino-3-formylchromone phenylhydrazone (**28**) was heated under reflux with triethyl phosphonoacetate in dry dioxane containing a few drops of triethylamine, it gave diethyl [2-oxo-2-{3-

[(2-phenylhydrazinylidene)methyl]-4-oxo-4*H*-chromen-2-yl)amino}ethyl]phosphonate (**29**) (Scheme 10). Several attempts were done to cyclize compound **29** under different basic conditions. Unfortunately, these attempts failed.[45]



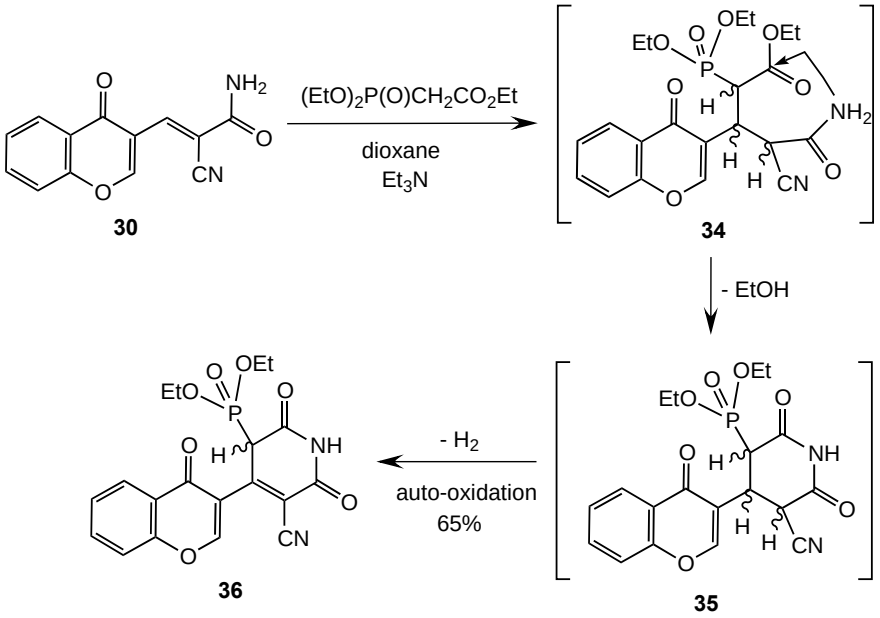
Scheme 10

Because of 2-cyano-3-(4-oxo-4*H*-chromen-3-yl)prop-2-enamide (**30**) has several electrophilic and nucleophilic centres, it can be utilized as key intermediate for the synthesis of some phosphorus compounds containing a chromone ring *via* its reaction with some phosphorus reagents such as phosphorous acid and its ester. Thus, compound **30** reacted with phosphorous acid in dry dioxane containing a catalytic amount of 4-toluenesulfonic acid to give the unisolable intermediate **31** which was formed *via* phospha-Michael addition reaction. This intermediate underwent partial hydrolysis of the nitrile group due to presence of strong acidic medium (H_3PO_3 and 4-TsOH) affording the isolated product **32** in yield 62% (Scheme 11). Likewise, treatment of compound **30** with diethyl phosphite was carried out at 80–90 °C in the presence of $BF_3{\cdot}Et_2O$ as a catalyst for 10 hours. After removing the excess of diethyl phosphite, the diethyl chromonyl phosphonate **33** was isolated in yield 54% as two diastereomers (Scheme 11).[46]



Scheme 11

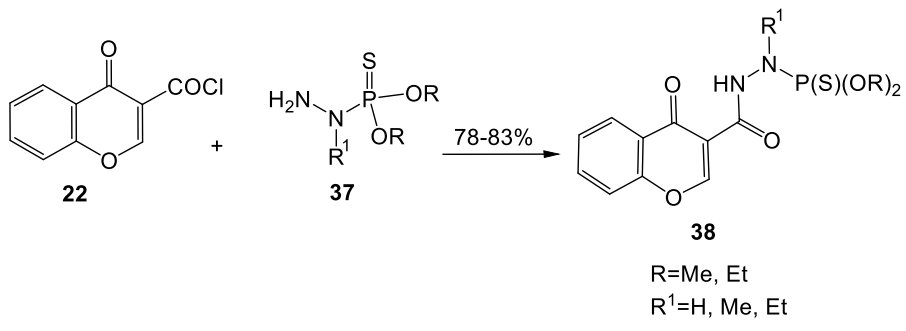
Also, equimolar amounts of compound **30** and triethyl phosphonoacetate were added in dry dioxane containing a few drops of triethylamine as a catalyst, then heated under reflux. The isolated product was identified as diethyl [5-cyano-1,2,3,6-tetrahydro-2,6-dioxo-4-(4-oxo-4*H*-chromen-3-yl)pyridine-3-yl]-phosphonate (**36**) (Scheme 12). The suggested mechanism of the reaction indicated that the propagation of the reaction took place through a nucleophilic attack of active methylene carbon on β-carbon of compound **30** (CH=C–C=O), followed by heterocyclization *via* removal of ethanol molecule to form the unisolable intermediate **35**. The latter intermediate underwent auto-oxidation affording the final product **36** (Scheme 12).[46]



Scheme 12

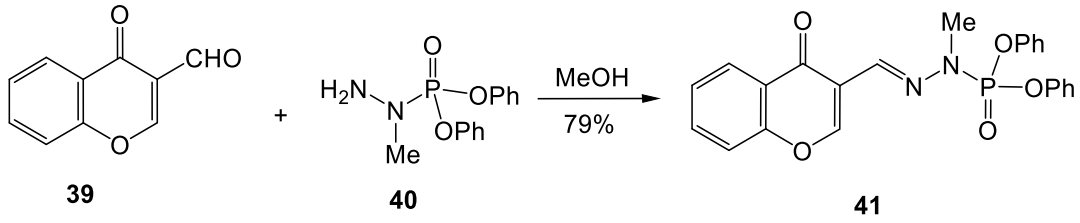
2.3. Synthesis of phosphorohydrazides and phosphorohydrazones of chromones

Treatment of chromone-3-carbonyl chloride (**22**) with phosphorohydrazide **37** gave the corresponding chromonyl phosphorohydrazones **38** (Scheme 13). Compound **38** (R=R^1=Et) demonstrated *in vitro* antitumor activity against p388 leukemia as well as antineoplastic activity with methotrexate using L120 murine leukemia.[47,48]



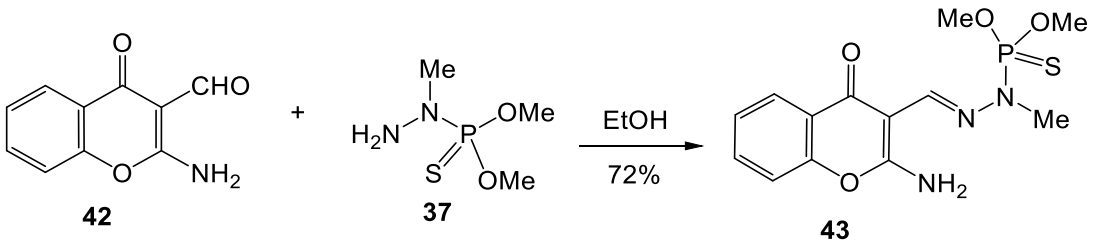
Scheme 13

(*E*)-3-{[(Diphenoxyphosphoryl)methylhydrazono]methyl}-4*H*-chromen-4-one (**41**) was obtained by the reaction of equimolar amounts of 4-oxo-4*H*-chromen-3-carboxaldehyde (**39**) and phosphorohydrazide **40** in anhydrous methanol (Scheme 14). The X-ray crystallographic analysis suggested that the chromone methyl hydrazone moiety is planar and the two phenoxy rings are inclined at angles of 21.29° and 89.33°.[47,49,50]



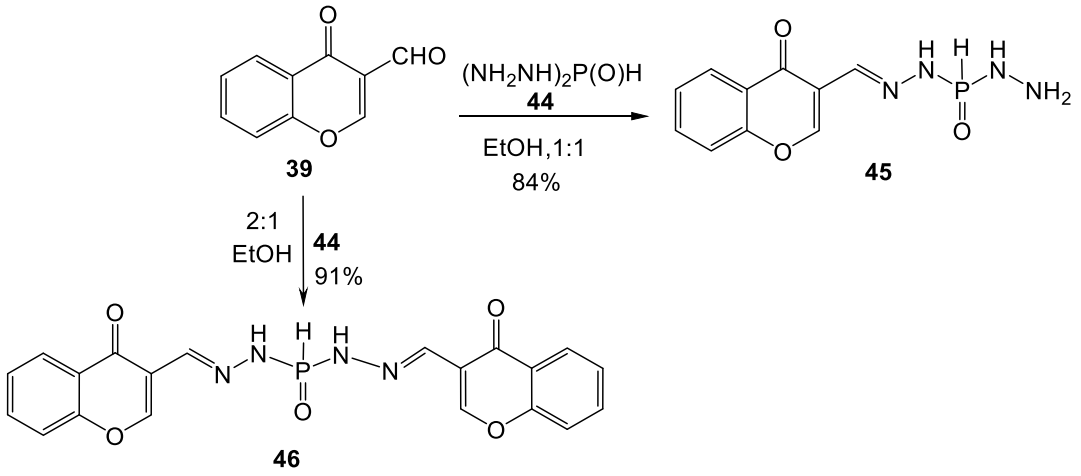
Scheme 14

Similarly, the chromonyl phosphorohydrazone **43** was prepared by treating of the 2-amino-3-formyl-chromone (**42**) with phosphorohydrazide **37** in dry ethanol (Scheme 15). The cytotoxicity index of compound **43** was higher on drug resistant HL-60 ADR cells in comparison to HL-60. Compound **43** showed ability to induce cytochrome translocation from mitochondria to cytosol.[50]



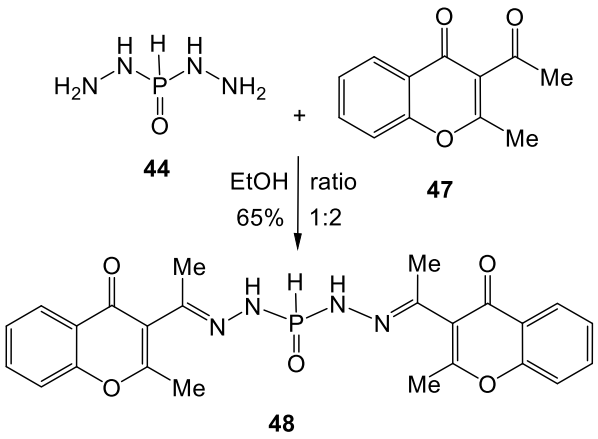
Scheme 15

Condensation of 4-oxo-4*H*-chromene-3-carboxaldehyde (**39**) with phosphonic dihydrazide (**44**) was carried out in the ratio 1:1 and 2:1 in boiling ethanol to give N`-[(4-oxo-4*H*-chromen-3-yl)methylene]-phosphonic dihydrazide (**45**) and N^1,N^5-bis[(4-oxo-4*H*-chromen-3-yl)methylene]phosphonic dihydrazide (**46**), respectively, in excellent yields (Scheme 16).[51]



Scheme 16

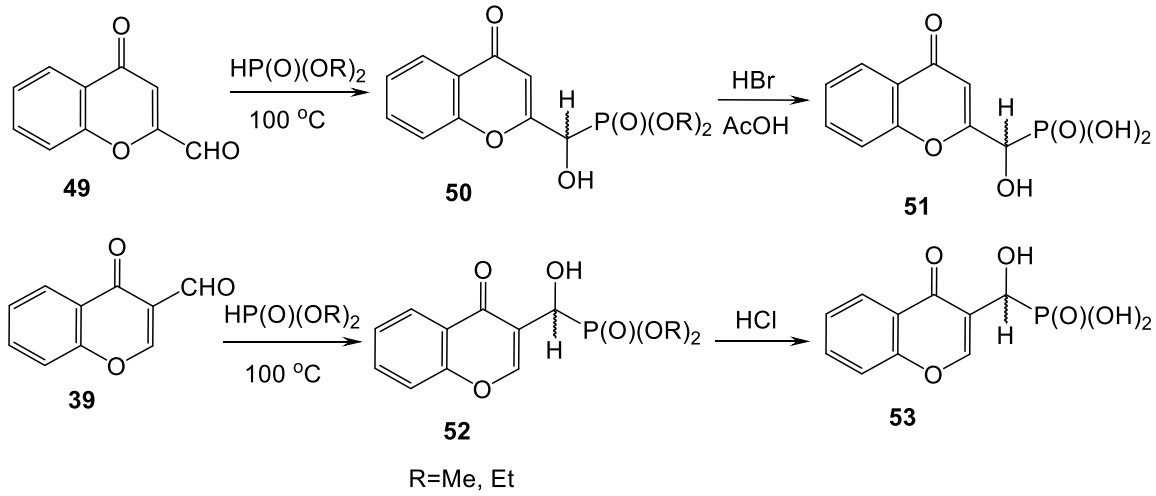
Also, condensation of phosphonic dihydrazide (**44**) with 3-acetyl-2-methylchromone (**47**) in absolute ethanol gave the corresponding phosphonic dihydrazone **48** as yellow crystals in 65% yields (Scheme 17).[52]



Scheme 17

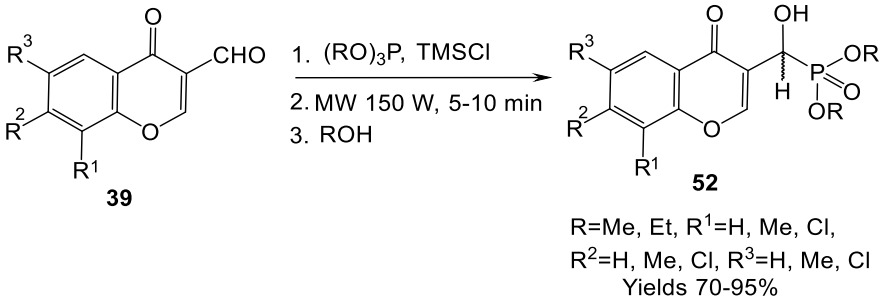
2.4. Synthesis of chromonyl α-hydroxyphosphonates

2-Formylchromone (**49**) and 3-formylchromone (**39**) were treated with dialkyl phosphite at 100 ºC with no solvents to furnish the chromonyl 2-hydroxymethanephosphonate **50** and chromonyl 3-hydroxy-methanephosphonate **52**, respectively, with 48-78% yields (Scheme 18).[30] The best results were obtained with dimethyl phosphite. Dialkyl esters **50** and **52** underwent hydrolysis in aqueous solution of HCl or acetic acid solution of HBr, yielding the corresponding phosphonic acids **51** and **53**, respectively (Scheme 18).



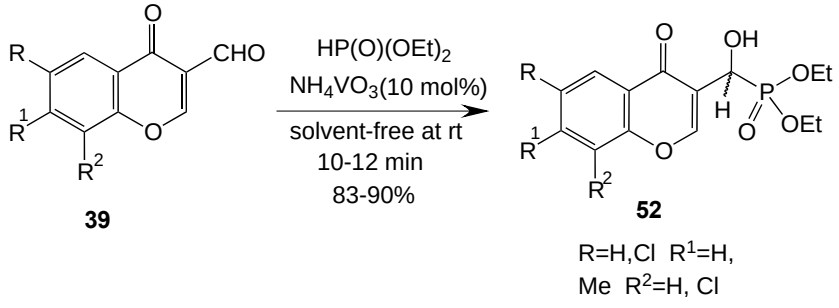
Scheme 18

The chromonyl α-hydroxyphosphonates **52** were also prepared by treatment of substituted 3-formylchromones **39** with trialkyl phosphite in the presence of TMSCl under solvent-free conditions using commercial microwave oven (BPL, 800 T, 2450 MHz) in 70-95% yields (Scheme 19).[53]



Scheme 19

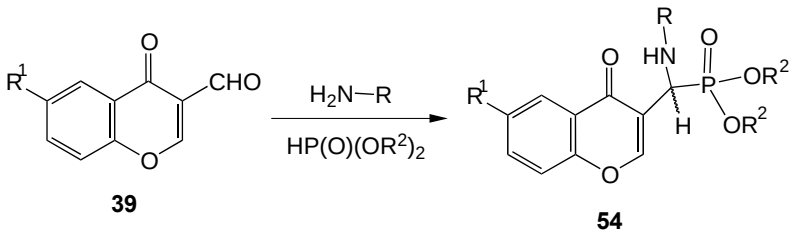
The reaction of substituted 3-formylchromones **39** with diethyl phosphite in the presence of NH_4VO_3 as effective catalyst gave the corresponding chromonyl α-hydroxyphosphonates **52** in high yields (Scheme 20).[54]



Scheme 20

2.5. Synthesis of chromonyl α-aminophosphonates

Some substituted-3-formylchromones **39** reacted with some aliphatic and aromatic amines and dialkyl phosphite in one-pot under Kabachnik-Fields reaction conditions. These reactions were performed in the absence of catalyst and its presence such as $BF_3{\cdot}Et_2O$, $ZnCl_2$, $AlCl_3$ and rhodium-boron nitride to yield the corresponding chromonyl α-aminophosphonates **54** in 62−100% yields (Scheme 21).[32,33,55,56] Compounds **54** (R^1=H and R= 3-$NO_2C_6H_4$, 4-BrC_6H_4) recorded good antimicrobial activities against *B. cereus*, *M. luteus, E. coli* and *C. albicans.* Also, they were found to be less toxic to the brine shrimp and may have more valuable biological application.[34] Moreover, when R^1=Me and R=Et, CH_2Ph, 4-ClC_6H_4 showed high inhibitory activities against *Candida albicans* and so antioxidative properties.[33]

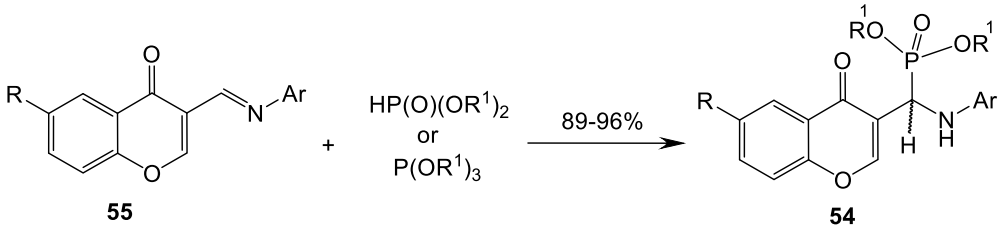


39 **54**

R=Et, CH_2Ph, 4-ClC_6H_4, 4-HOC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$
4-BrC_6H_4, 3-$NO_2C_6H_4$
R^1=H, Me, R^2=Me, Et

Scheme 21

6-Substituted-3-[(arylimino)methyl]-4*H*-chromen-4-one (**55**) was treated with di- or trialkyl phosphite in the presence of solvent or without solvent under Pudovik reaction conditions to afford dialkyl [(arylamino)(6-substituted-4-oxo-4*H*-chromen-3-yl)methyl]phosphonates (**54**) (Scheme 22).[36,57]

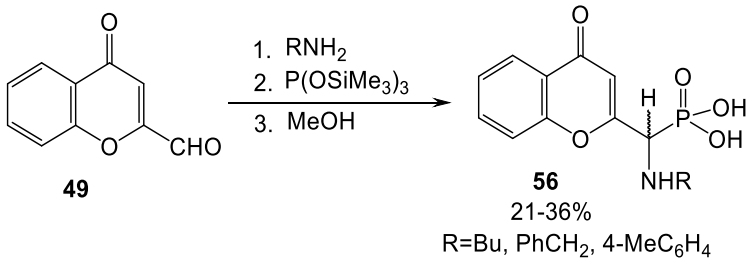


55 **54**

R=H, Me, R^1=Me, Et, Pr
Ar=Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-$NO_2C_6H_4$, 4-BrC_6H_4, 2-$MeOC_6H_4$, 3-$NO_2C_6H_4$, 2-MeC_6H_4

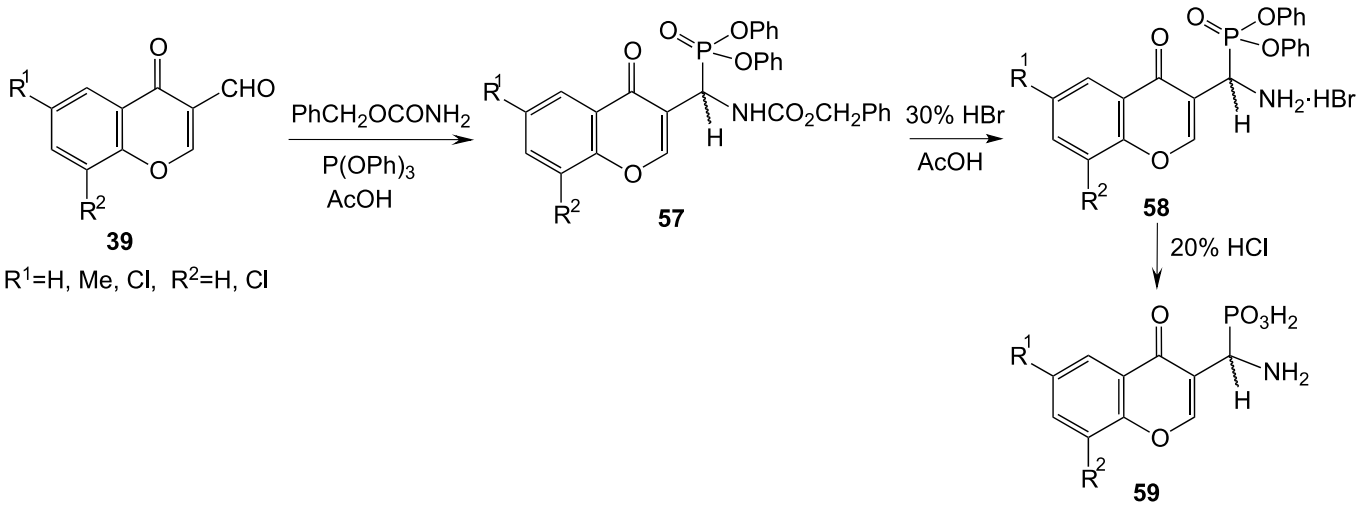
Scheme 22

Similarly, the action of tris(trimethylsilyl)phosphite on aldimine that formed in *situ* from aldehyde **49** and amines, followed by methanolysis of the silylated product, gave the corresponding chromonyl α-amino-phosphonic acid **56** (Scheme 23). The reaction was carried out without isolation of the intermediates and gave the final product as white amorphous solid.[57,59]



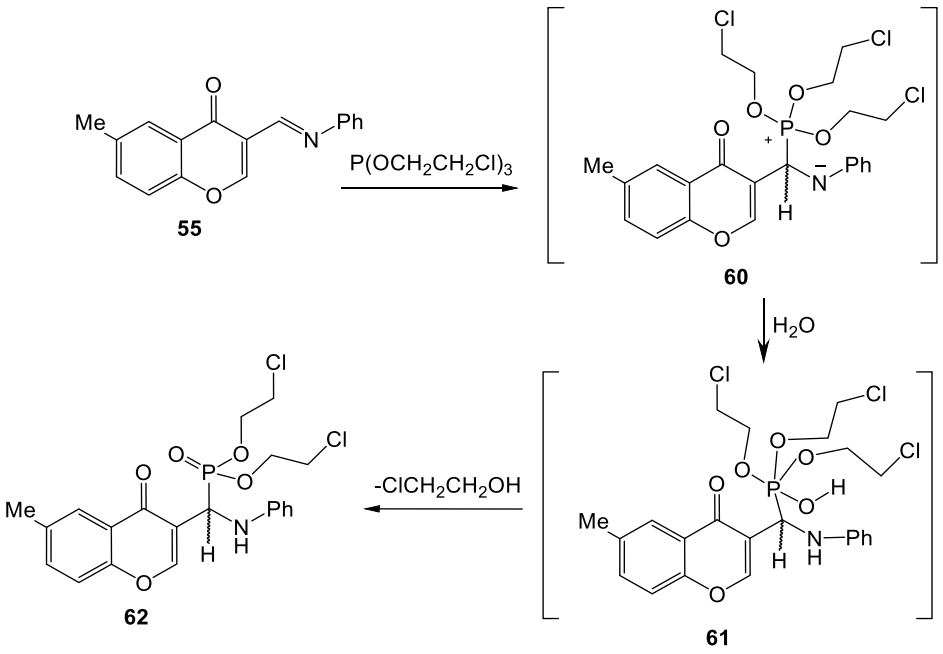
Scheme 23

Furthermore, 3-formylchromones **39** reacted easily with benzyl carbamate and triphenyl phosphite in acetic acid solution to form the *Z*-substituted diphenyl aminophosphonates **57** in high yield (Scheme 24). The latter compounds were deprotected by the effect of hydrogen bromide solution in acetic acid to form the aminophosphonates **58** which were easily hydrolyzed in aqueous 20% HCl into the corresponding chromonyl α-aminophosphonic acids **59** (Scheme 24).[58]

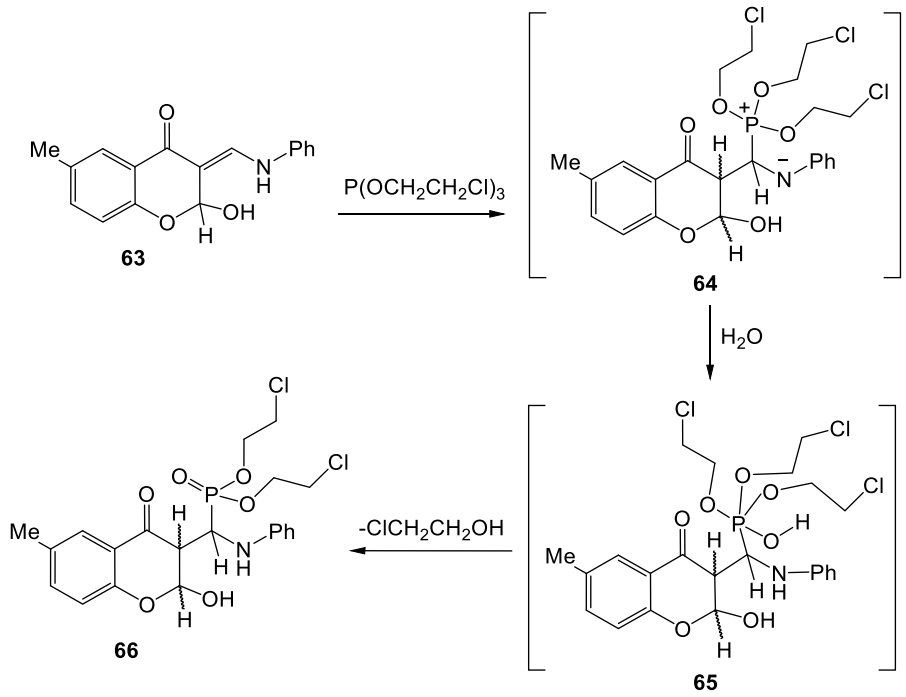


Scheme 24

Reaction of aldimines **55** and **63** with tris(2-chloroethyl)phosphite in the presence of a certain amounts of distilled water, which accelerated the reactions, produced the corresponding α-aminophosphonate derivatives **62** and **66**, respectively (Schemes 25 and 26).[57] A possible mechanism for these reactions could involve a nucleophilic phosphorus attack on the electrophilic carbons of compounds **55** and **63** to give the intermediate dipolar species of type **60** and **64**, respectively, which could be solvated by water present in the reaction media to give transients such as **61** and **65**, respectively. The latter transients decomposed via removal of 2-chloroethanol molecule to afford the final products **62** and **66**, respectively (Schemes 25 and 26).[57]

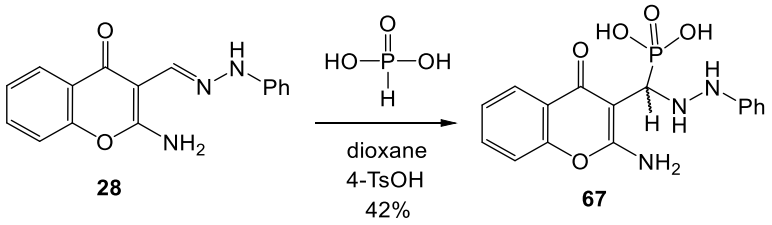


Scheme 25



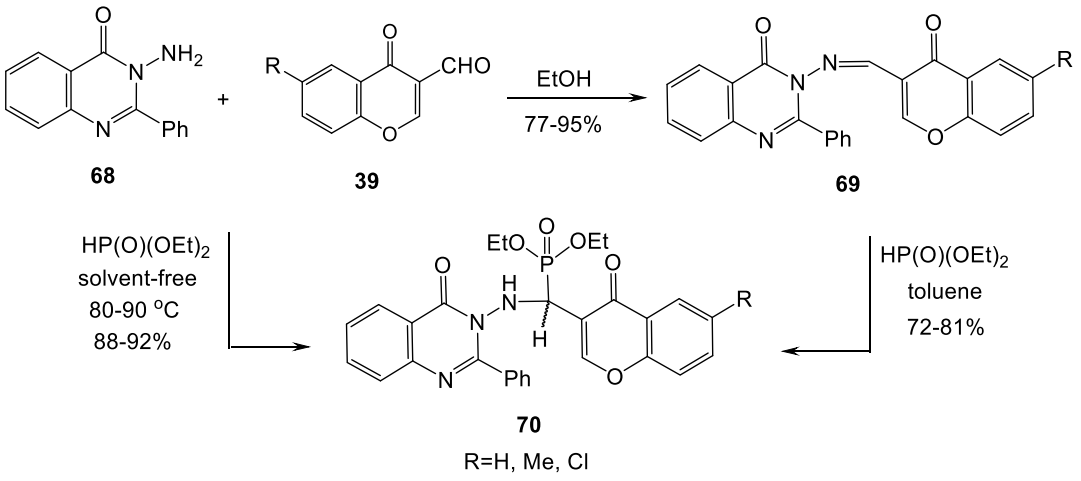
Scheme 26

When the chromonyl phenylhydrazone **28** reacted with phosphonic acid in dry dioxane containing 4-toluenesulfonic acid as a catalyst under Pudovik reaction conditions, the chromonyl α-hydrazino-phosphonic acid **67** was isolated (Scheme 27).[45]



Scheme 27

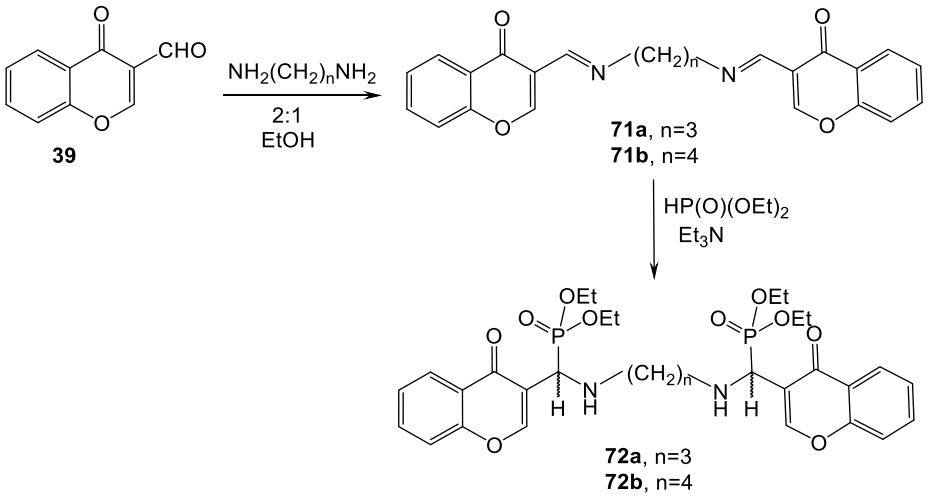
Some synthesized quinazolinone-derived Schiff bases **69** were designed from simple condensation of 3-amino-2-phenylquinazolin-4(3*H*)-one (**68**) with 3-formylchromones **39** in absolute ethanol (Scheme 28). Addition of diethyl phosphite to a solution of quinazolinone-derived Schiff bases **69** in toluene proceeded well under Pudovik reaction conditions. After 3-6 hours, the reactions were completed and the obtained products, that are identified as diethyl {(6-substituted-4-oxo-4*H*-chromen-3-yl)[(4-oxo-2-phenylquinazolin-3(4*H*)-yl)amino]methyl}phosphonates (**70**) with good overall yields 72-81% (Scheme 28). Quite encouragingly, the reaction of compound **68** with 3-formylchromones **39** in the presence of diethyl phosphite was performed in neat condition and the chromonyl α-aminophosphonates **70** were obtained in excellent yields of 88-92% when the three-component reaction was run at 90-100 ºC for 30 minutes under Kabachnik-Fields reaction conditions (Scheme 28).[60] Compounds **70** have no noticeable effect on the colon HCT116, breast MCF-7 and liver HepG2 cancer cells.[60]



Scheme 28

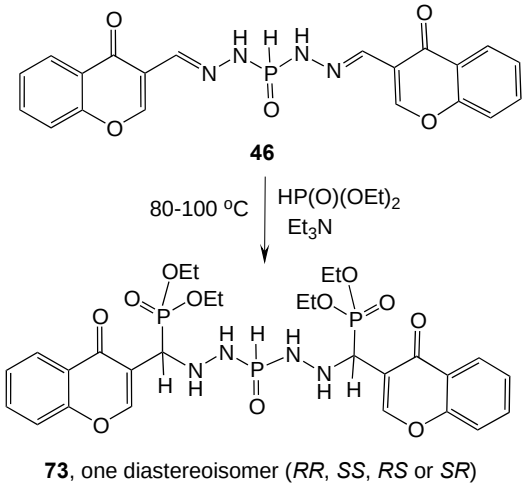
3-{[(4-Oxo-4*H*-chromen-3-yl)methylene]amino}propyl)imino]methyl}-4*H*-chromen-4-one (**71a**) and 3-{[(4-{[(4-oxo-4*H*-chromen-3-yl)methylene]amino}butyl)imino]methyl}-4*H*-chromen-4-one (**71b**) were obtained by condensation of aldehyde **39** with 1,3-diaminopropane and 1,4-diaminobutane, respectively, in dry benzene containing a catalytic amount of 4-toluenesulfonic acid (Scheme 29). The addition of diethyl phosphite to compounds **71a**,**b** was carried out in dry benzene containing a few drops of

triethylamine as catalyst to afford the corresponding bis(α-aminophosphonates) derivatives **72a**,**b**, respectively (Scheme 29).[61]



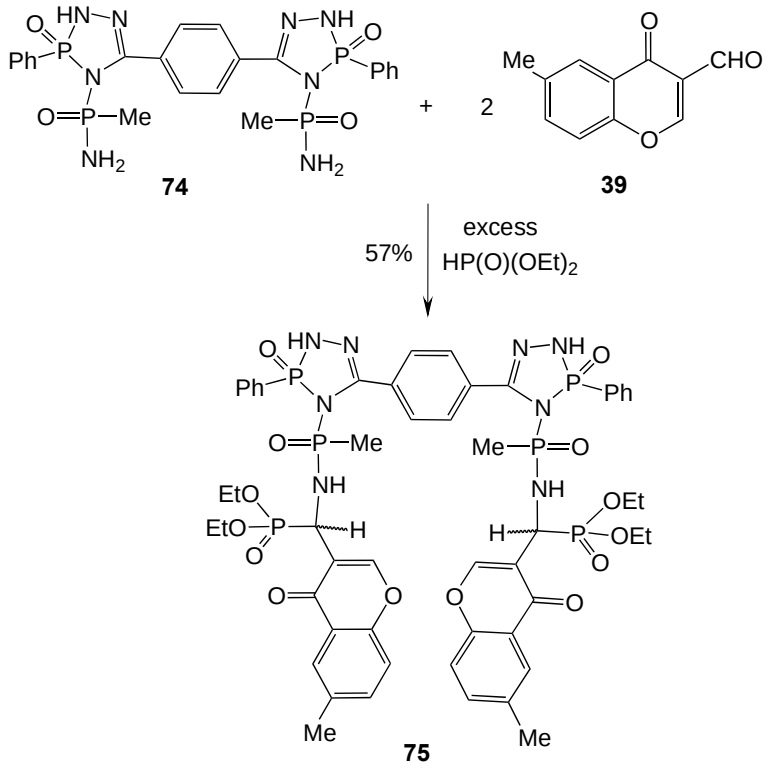
Scheme 29

Similarly, fusing of the bis-hydrazone **46** with diethyl phosphite at 80-100 °C in the presence of a catalytic amount of triethylamine produced N^1,N^5-bis{N-methyl(diethoxyphosphonyl)-1-[(4-oxo-4*H*-chromen-3-yl)}phosphonic dihydrazide **73** as one diastereoisomer (Scheme 30).[61]



Scheme 30

The addition of diethyl phosphite to a mixture of bis-phosphamide **74** and double amounts of 6-methyl-3-formylchromone (**39**) at 80–100 °C in the presence of a catalytic amount of triethylamine gave two diastereomeric forms of 5,5`-(1,4-phenylene)bis-{diethyl[[(3-oxo-3-phenyl-2,3-dihydro-4*H*-1,2,4,3-triazaphosphol-4-yl)methylphosphoryl]amino][6-methyl-4-oxo-4*H*-chromen-3yl)methyl]phosphonate} (**75**) (Scheme 31).[61]



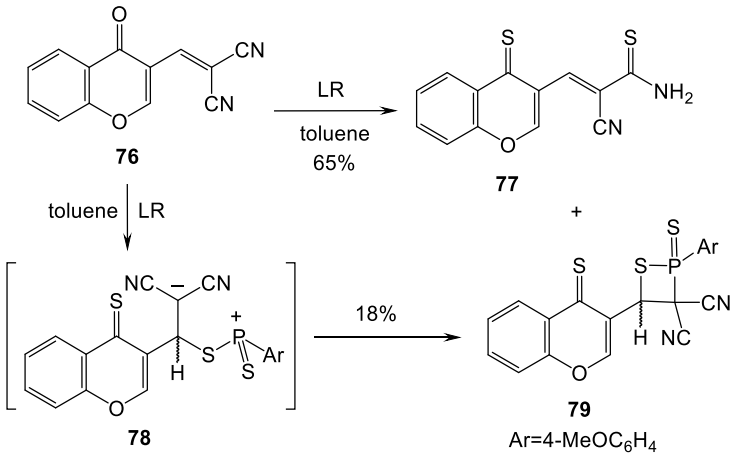
Two diastereomeric forms meso (*R*,*S*) and racemic (*R*,*R* and *S*,*S*)

Scheme 31

2.6. Synthesis of phosphorus heterocycles bearing chromone and thiochromone rings

2.6.1. 1,2-Thiaphosphetane

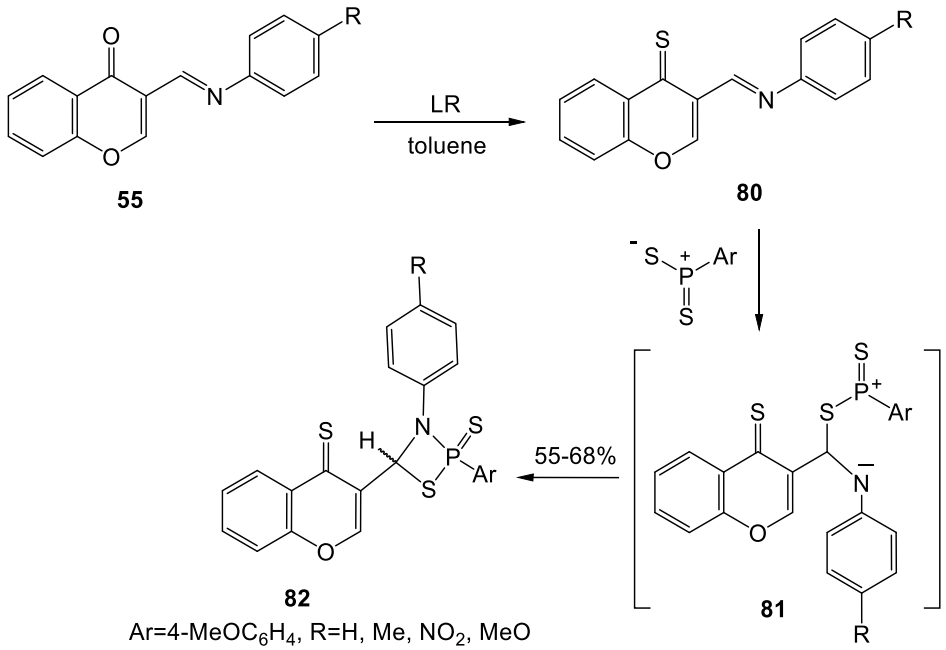
[(4-Oxo-4*H*-chromen-3-yl)methylene]malononitrile (**76**) reacted with Lawesson's reagent (LR) to give a mixture of two products which could be separated by column chromatography. The first product (65%) was 2-cyano-3-(4-thioxo-4*H*-chromen-3-yl)prop-2-enethioamide (**77**) (Scheme 32). The second product was 2-(4-methoxyphenyl)-4-(4-thioxo-4*H*-chromen-3-yl)-1,2-thiaphosphetane-3,3-dicarbonitrile-2-sulfide (**79**) (Scheme 32).[62]



Scheme 32

2.6.2. 1,3,2-Thiazaphosphetidine

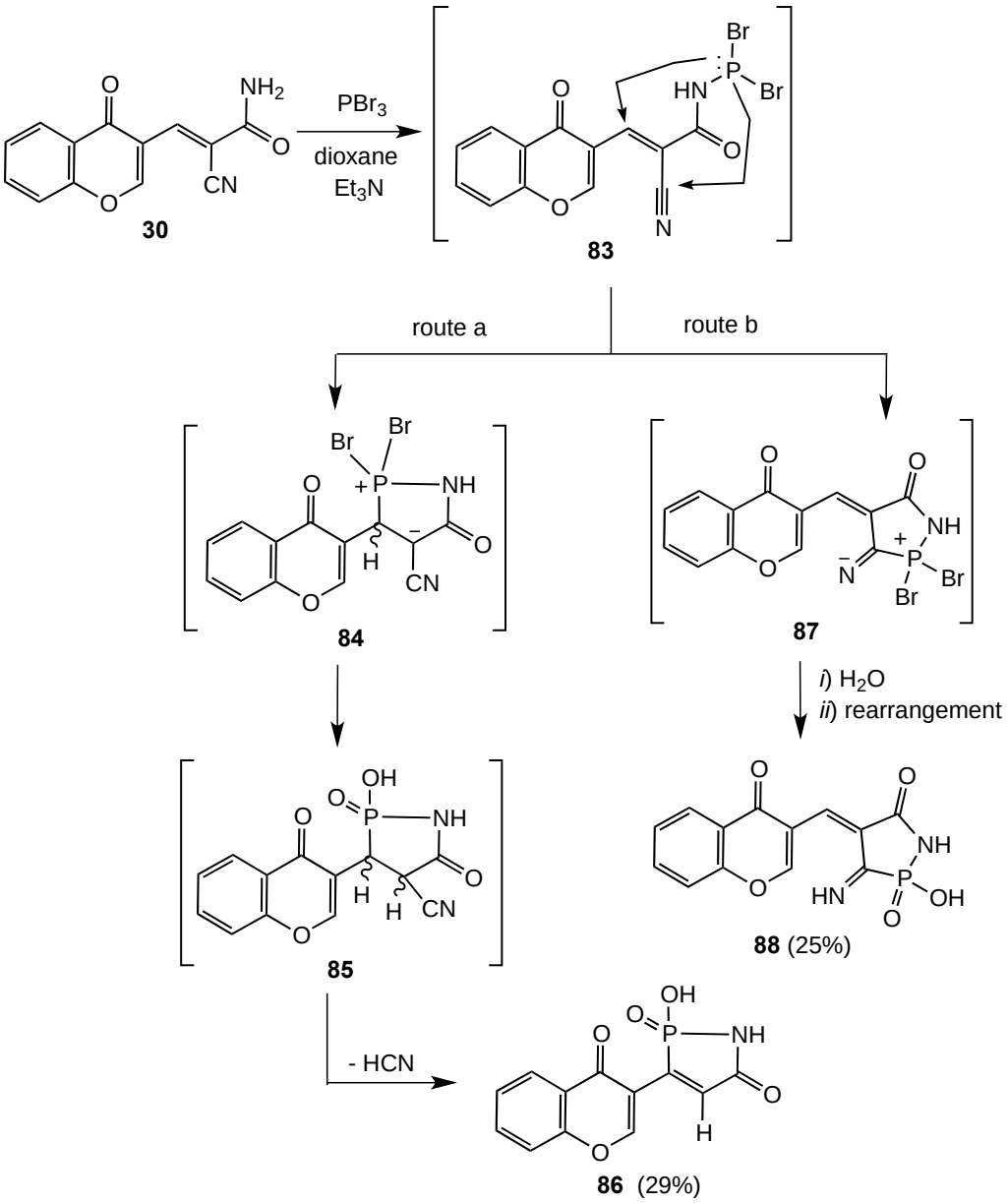
The reactions of 3-(aryliminomethyl)chromones **55** with Lawesson's reagent (LR) were studied. The isolated products were 3-{(*E*)-[4-aryliminomethyl]}-4*H*-chromene-4-thione (**80**) and 3-[3-aryl-2-(4-methoxyphenyl)-2-sulfido-1,3,2-thiazaphosphetidin-4-yl]-4*H*-chromene-4-thione (**82**) (Scheme 33). The product **82** was suggested to occur *via* a nucleophilic attack of the monomeric species of Lawesson's reagent on compound **80** to give the intermediate **81**, followed by ring closure to afford the product **82** (Scheme 33).[62]



Scheme 33

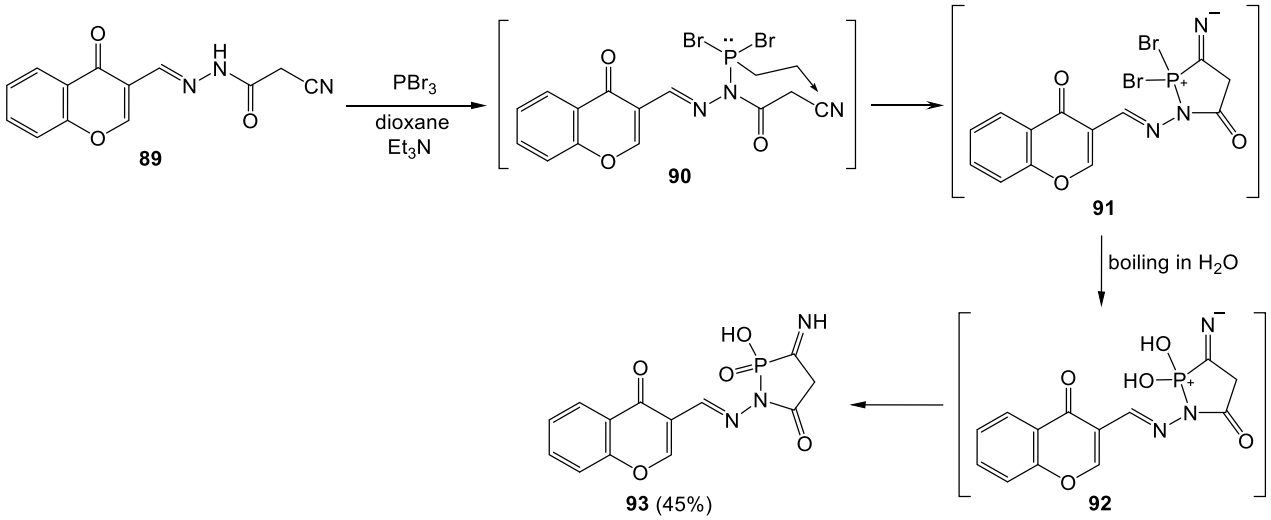
2.6.3. 1,2-Azaphospholes

Treatment of the chromonyl arylidene **30** with phosphorus tribromide in dry dioxane containing a catalytic amount of triethylamine gave the two isomeric products of novel chromonyl azaphospholes **86** and **88** (Scheme 34). The formation of compounds **86** and **88** was assumed to proceed *via* simple condensation reaction to remove hydrogen bromide to give the unisolable intermediate **83**. The latter intermediate underwent two pathways to form the final products. The first pathway was a nucleophilic addition of phosphorus atom to the ethylenic bond forming the unisolable intermediate **84**, which underwent hydrolysis by the air-moisture and rearrangement followed by removal of hydrogen cyanide to yield the isolated product **86**. On contrary, the second pathway was a nucleophilic addition of phosphorus atom to the nitrile group forming the unisolable intermediate **87** that was hydrolyzed by distilled water and rearranged into the isolated product **88** (Scheme 34).[46]



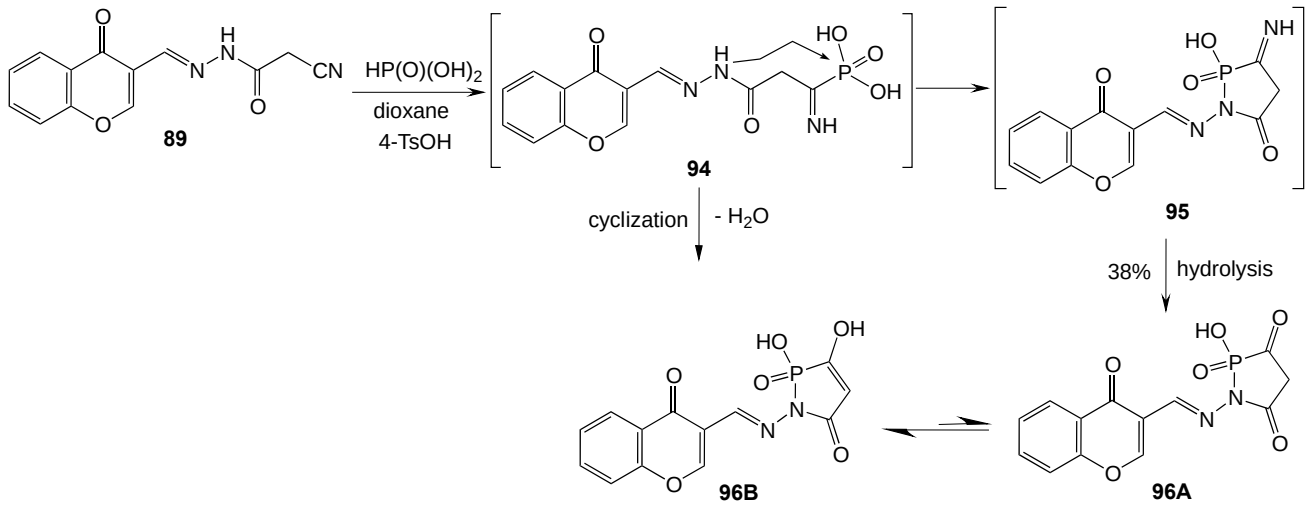
Scheme 34

Similarly, the treatment of chromonyl hydrazone **89** with phosphorus tribromide in dry dioxane containing two equivalent amounts of triethylamine gave 3-{[(2-hydroxy-3-imino-2-oxido-5-oxo-1*H*-1,2-azaphospholidin-1-yl)imino]methyl}-4*H*-chromen-4-one (**93**) in moderate yield (Scheme 35). The mechanism of the formation of product **93**, suggested a nucleophilic substitution on the phosphorus atom to produce the hydrazonyl phosphorus dibromide intermediate **90**. In the latter intermediate, attack of phosphorus atom at the nitrile group was accompanied by formation of the 1,2-azaphospholidine intermediate **91** as oily product which upon boiling in water for 30 minutes led to the formation of the final product **93** (Scheme 35). Compound **93** was more potent as anticancer agent against breast MCF-7 cells (IC_{50}=8.30±0.96 μg/mL) than the reference drug Tamoxifen (IC_{50}=8.50±0.90 μg/mL).[63]



Scheme 35

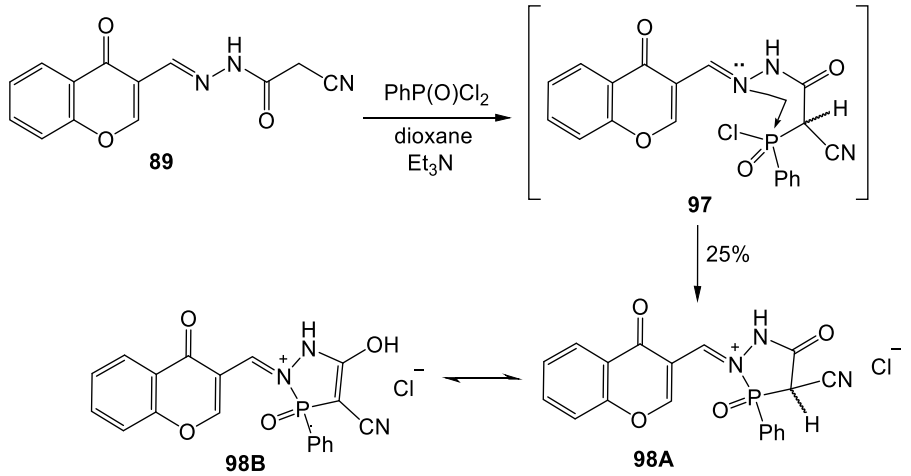
Furthermore, the hydrazone compound **89** reacted with phosphonic acid in dry dioxane in the presence of 4-toluenesulfonic acid as a catalyst to give the 1,2-azaphospholyl chromone derivative **96** in low yield (Scheme 36). The reaction proceeded through the unexpected nucleophilic attack of phosphorus atom at the nitrile group and not the azomethine bond to form the corresponding α-iminophosphonic acid **94** as unisolable intermediate. The latter intermediate underwent heterocyclization *via* removal of water molecule to give the unisolable intermediate **95**. The presence of water and phosphonic acid in the reaction medium promoted the hydrolysis of imino group into the corresponding carbonyl group forming the final product **96**. Compound **96** was existed in two tautomeric forms **96A** (*minor form*) and **96B** (*major form*) because of keto-enol tautomerism (Scheme 36). Compounds **96** was found to be potent inhibitor against expression of VEGF on cancer cells with percentage of inhibition values of 87% as compared with the positive drug, Tamoxifen (95%).[63]



Scheme 36

2.6.4. 1,2,3-Diazaphosphole

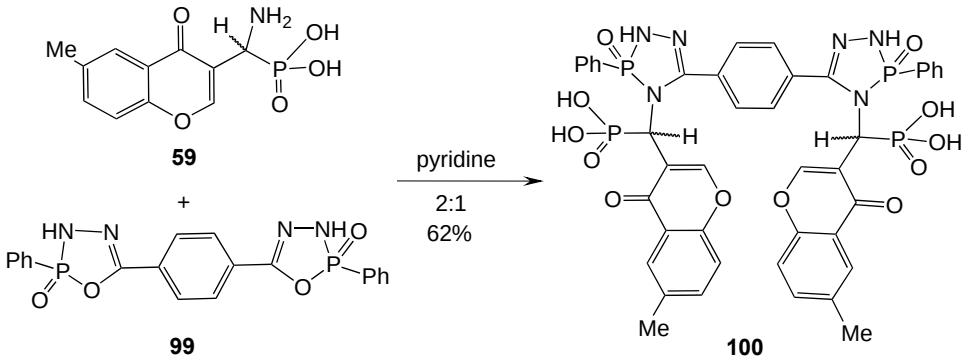
Analogous reaction of the hydrazone **89** with phenylphosphonic dichloride under the same reaction condition did not lead to construction of product like that formed in the case of PBr_3. However, this reaction gave one product identified with the 1,2,3-diazaphospholyl chromone derivative **98** (Scheme 37). This product was formed as an iminium salt and existed in two tautomeric forms **A** and **B** because of keto-enol tautomerism. The proposed mechanism suggested unexpected nucleophilic attack of active CH_2 at phosphorus atom to remove HCl molecule by helping of Et_3N to give the intermediate **97**. This intermediate underwent cyclization *via* a nucleophilic attack of nitrogen atom of azomethine group and not amino group to give the final product **98** in low yield (Scheme 37).[63]



Scheme 37

2.6.5. 1,2,4,3-Triazaphosphole

Ali *et al.*[61] reported that reaction of 1,4-bis{1,3,4,2-oxdiazaphospholyl}benzene **99** with [amino(6-methyl-4-oxo-4*H*-chromen-3-yl)methyl]phosphonic acid (**59**) in dry pyridine provided only one diastereomeric form of 5,5`-(1,4-phenylene)*bis*-[(3-oxo-3-phenyl-2,3-dihydro-4*H*-1,2,4,3-triazaphosphol-4-yl)(6-methyl- 4-oxo-4*H*-chromen-3-yl)]methyl phosphonic acid) (**100**) (Scheme 38).

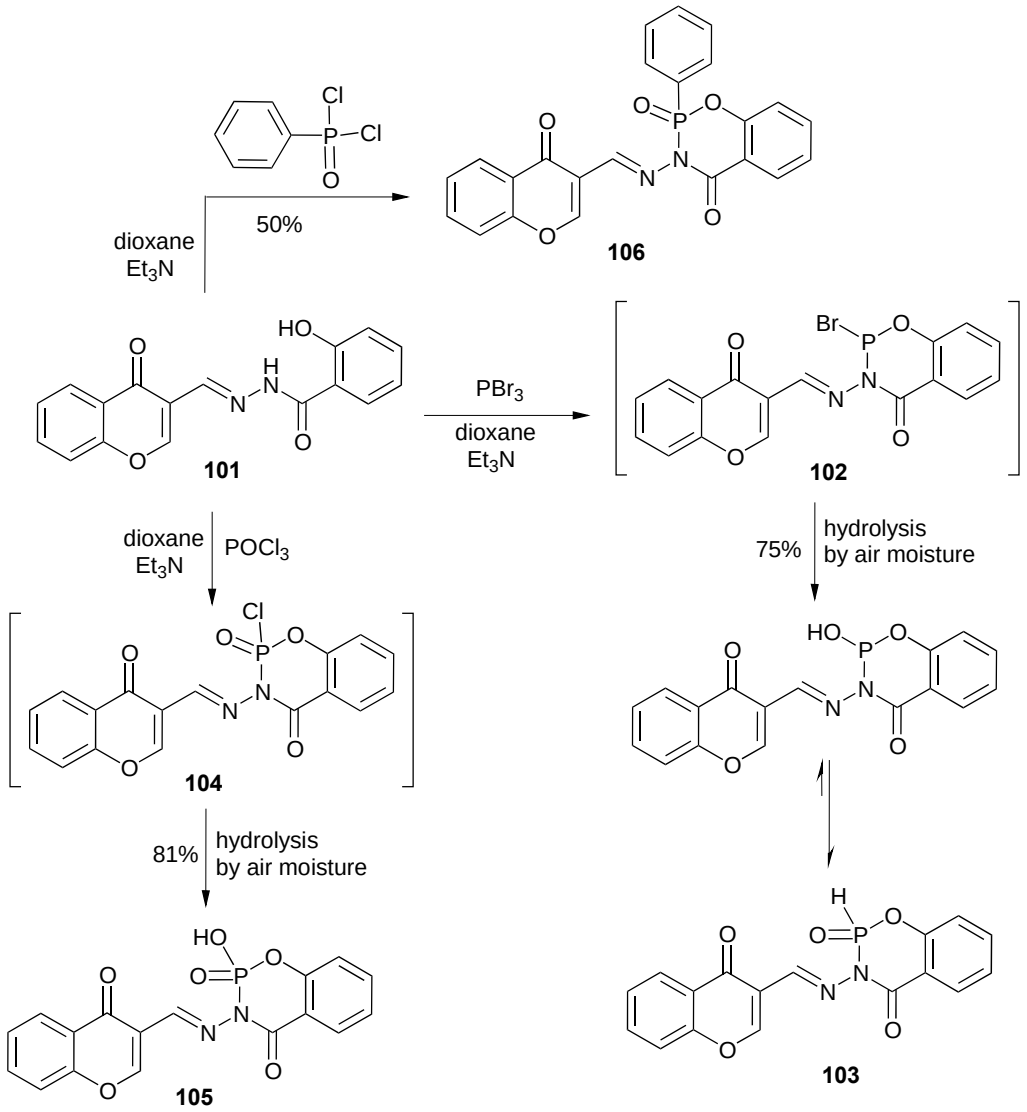


one diastereomeric form meso (*R*,*S*) or racemic (*R*,*R* and *S*,*S*)

Scheme 38

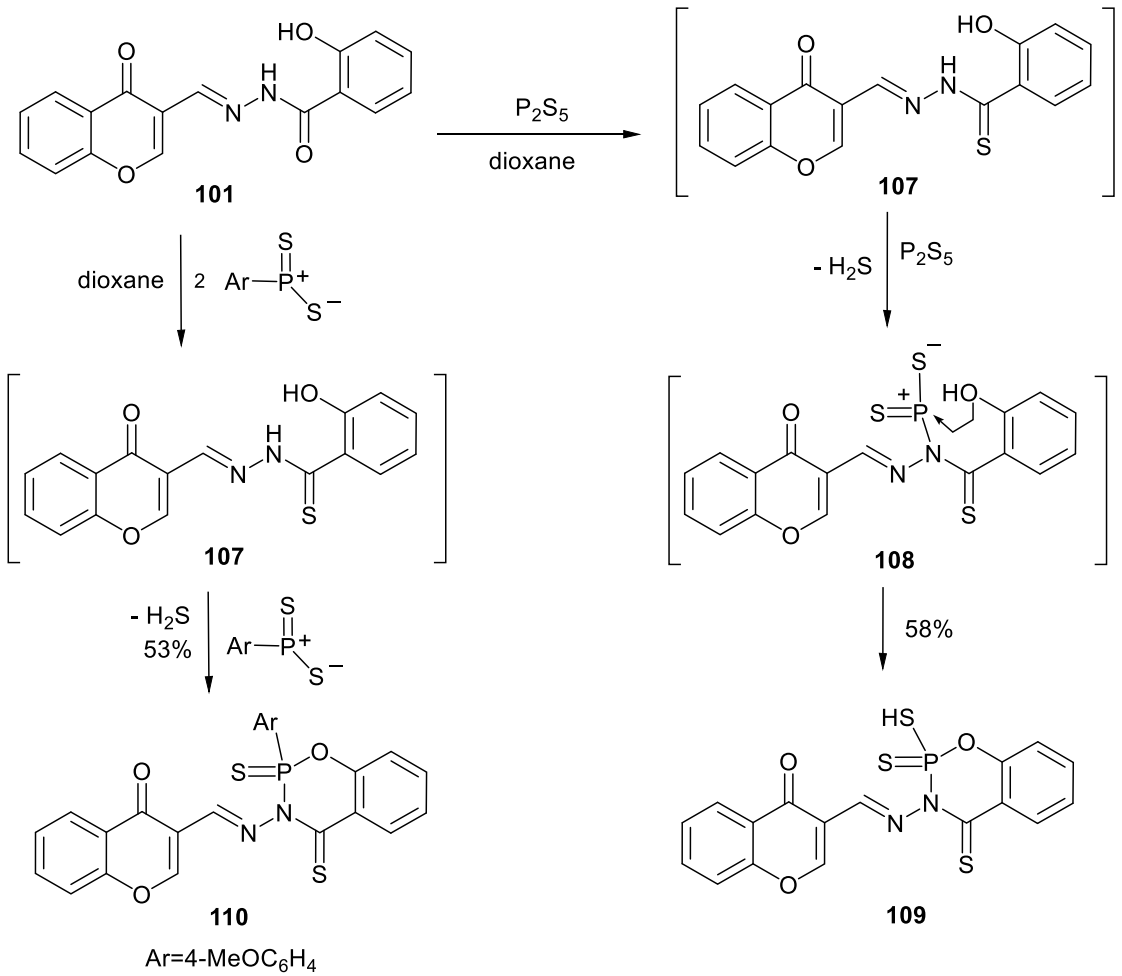
2.6.6. 1,3,2-Oxazaphosphinine

Due to the diversity of the importance of six-membered organophosphorus heterocyclic compounds, the synthesis of 1,3,2-benzoxazaphosphinines *via* the ring-closure reactions of the chromonyl hydrazone **101** with some different phosphorus halide regents was carried out. Thus, addition of phosphorus tribromide, phosphorus oxychloride and phenylphosphonic dichloride to a solution hydrazone **101** in dry dioxane containing two equimolar amounts of triethylamine yielded the corresponding 1,3,2-benzoxaza-phosphininyl chromone derivatives **103**, **105** and **106**, respectively, in good yields (Scheme 39). The suggested mechanism for construction of compounds **103** and **105** took place *via* a nucleophilic attack of NH and OH groups at phosphorus atoms to remove two molecules of triethylammonium halide affording the unisolable intermediates **102** and **104**, which were hydrolyzed by air moisture and washing with water (Scheme 39). The separated products showed moderate cytotoxicity properties against MCF-7 breast cancer cell.[64]



Scheme 39

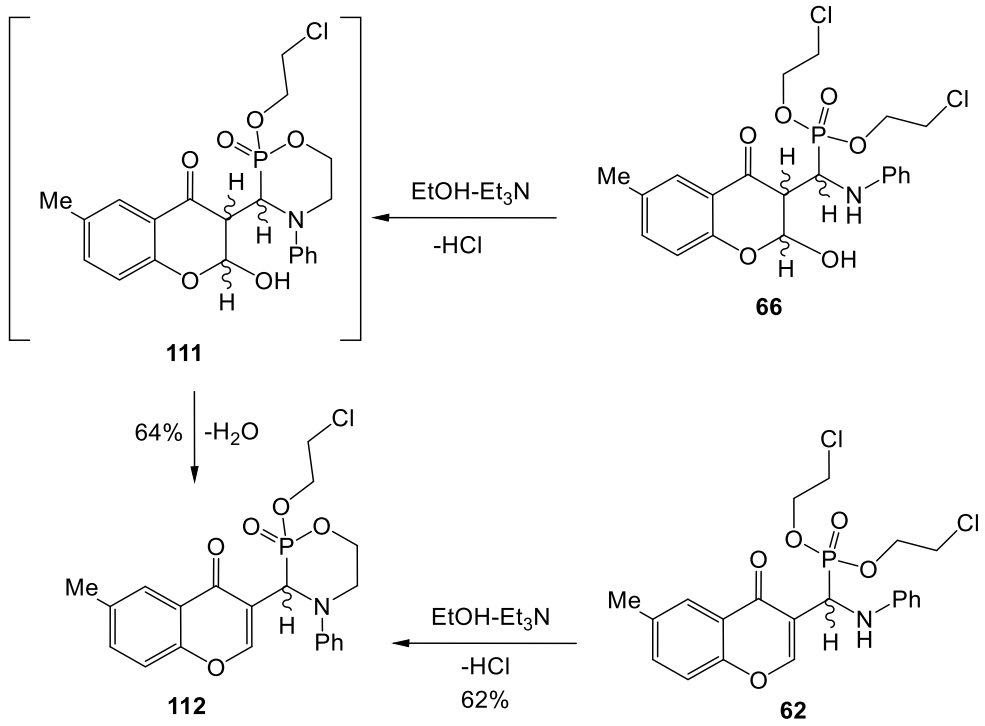
Additionally, the hydrazone **101** could be cyclized with phosphorus pentasulfide (P_2S_5 or P_4S_{10}) and Lawesson's reagent (LR) to result in phosphorus heterocycles. Thus, 3-{[(2-sulfanyl-2-sulfido- 4-thioxo-1,3,2-benzoxazaphosphinin-3(4*H*)yl)imino]methyl}-4*H*-chromen-4-one (**109**) and 3-{[2-(4-methoxy-phenyl)-2-sulfido-4-thioxo-1,3,2-benzoxazaphosphinin-3(4*H*)yl)imino]methyl}-4*H*-chromen-4-one (**110**) were isolated from treatment of hydrazone **101** with phosphorus pentasulfide and Lawesson's reagent, respectively, in dry dioxane under reflux for 8−10 hours (Scheme 40).[64] The explanation for the formation of products **109** and **110** was demonstrated in Scheme 40. The hydrazone **101** reacted with P_2S_5 and LR to give the intermediates **107** which formed *via* thionation of $C{=}O_{amide}$ group. The latter intermediates underwent cyclization *via* its reaction with another molecule of phosphorus reagent to afford the desired product. Compound **110** displayed anticancer activity against MCF-7 breast cancer cell (IC_{50} = 8.60 ± 0.88 μg/mL) which was like that of Tamoxifen. It was found to be potent inhibitor against expression of VEGF with percentage of inhibition values of 85% as compared with the positive drug, Tamoxifen (95%).[64]



Scheme 40

2.6.7. 1,4,2-Oxazaphosphinane

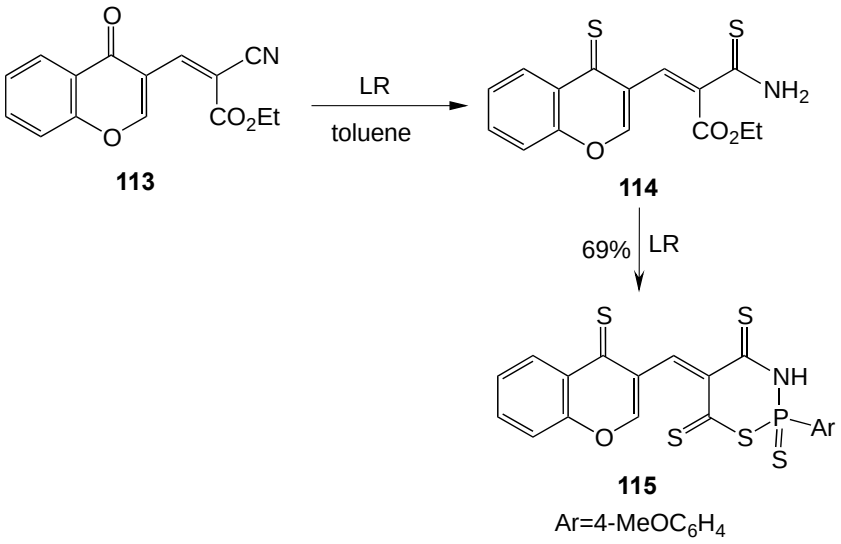
The chromonyl α-aminophosphonates **62** and **66** were heated in absolute ethanol containing a catalytic amount of triethylamine. These reactions afforded only one product formulated as 3-[2-(2-chloro-ethoxy)-2-oxo-4-phenyl-1,4,2-oxazaphosphinan-3-yl]-6-methyl-4-oxo-4*H*-chromen-4-one (**112**).[57] Formation of compound **112** is believed to take place *via* loss of one HCl molecule from **62** and **66** through cyclization process followed by elimination of water from **111**. Hydrogen bonding between OH and NH groups gave stability to systems **62** and **66**, but destruction of this hydrogen bond, after removing the HCl molecule, may facilitate elimination of water (Scheme 41).[57]



Scheme 41

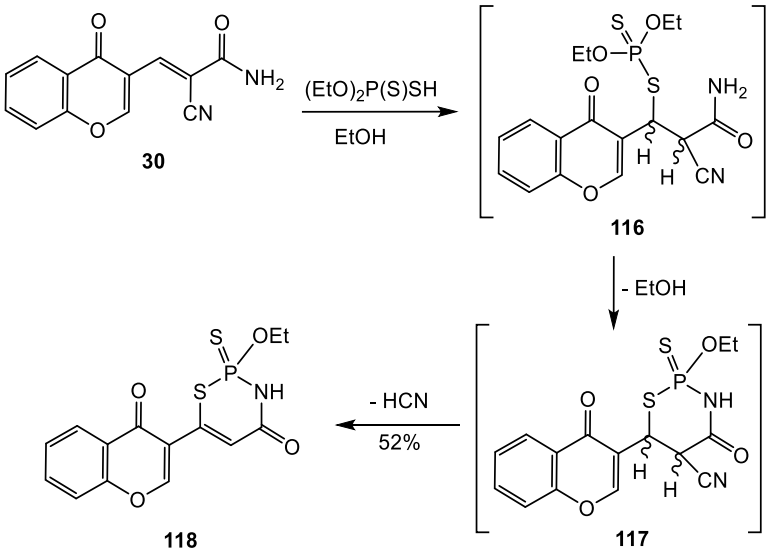
2.6.8. 1,3,2-Thiazaphosphinane

The reaction of ethyl 2-cyano-3-(4-oxo-4*H*-chromen-3-yl)acrylate (**113**) with Lawesson's reagent (LR) was carried out in boiling toluene, giving (2-(4-methoxyphenyl)-5-[(4-thioxo-4*H*-chromen-3-yl)-methylene]-1,3,2-thiazaphosphinane-4,6-dithione-2-sulfide (**115**) as a sole product in pure form (Scheme 42). In this reaction, the chromonyl thiazaphosphinane **115** was believed to be formed *via* the thioamidoacrylate intermediate **114** with elimination of ethanol molecule when it reacted with another molecule of LR (Scheme 42).[62]



Scheme 42

Compound **30** reacted with *O*,*O*-diethyldithiophosphoric acid (formed *in situ*) in dry ethanol to afford the chromonyl thiazaphosphinine **118** (Scheme 43). A conceivable mechanism for the formation of **118** was proposed in Scheme 43. The reaction proceeded through sulfur-Michael addition of SH group at exocyclic CH=C to form the unisolable intermediate **116**, that subsequently underwent intramolecular cyclization *via* removal of ethanol molecule, followed by elimination of hydrogen cyanide molecule (Scheme 43).[46]

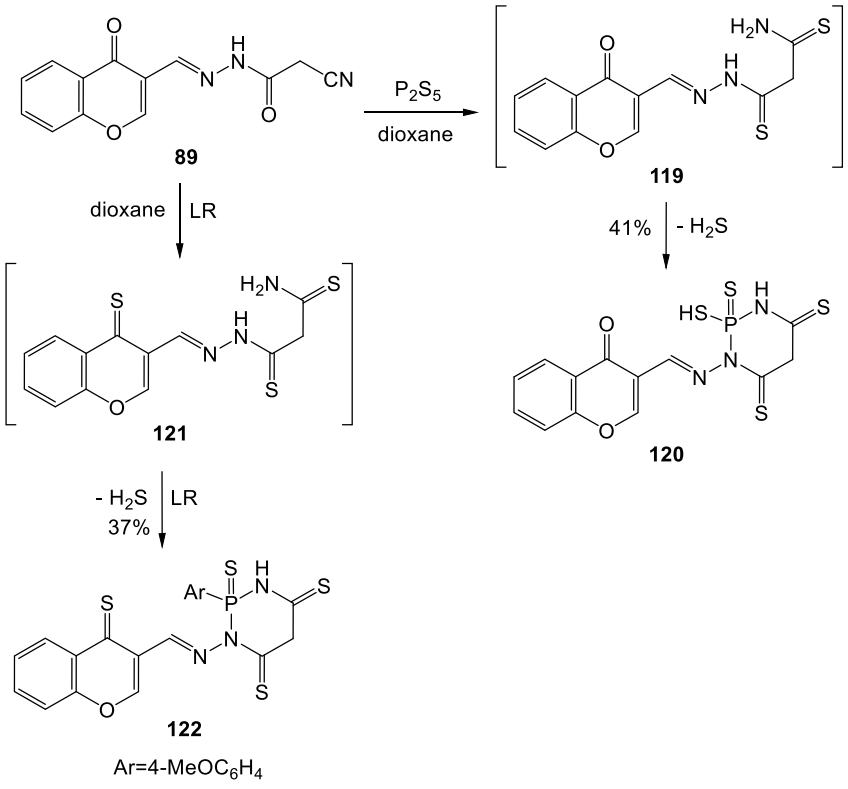


Scheme 43

2.6.9. 1,3,2-Diazaphosphinine

Two of the most known thionation reagents are phosphorus pentasulfide (P_2S_5) and Lawesson's reagent (LR). They underwent cyclization reactions with substrates having two functional groups to form

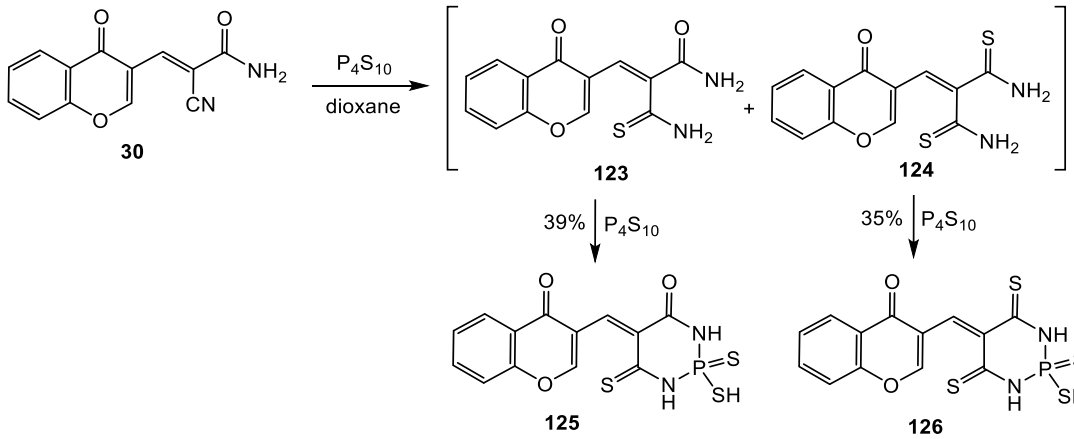
phosphorus or sulfur heterocycles. Thus, the hydrazone **89** reacted with equivalent amounts of each phosphorus pentasulfide and Lawesson's reagent in refluxing dioxane containing a few drops of triethylamine for 4−10 hours. The formed products were a novel class of 1,3,2-diazaphosphinyl-chromones **120** and **122**, respectively (Scheme 44).[64] As shown in Scheme 44, the first stage of the interaction of hydrazone **89** with P_2S_5 and LR probably involved formation of the intermediate thiocarbamoyl derivatives **119** and **121** *via* hydrolysis of nitrile group and thionation of carbonyl groups. The second stage was undoubtedly cyclization of the latter intermediates by another molecule of phosphorus sulfides forming phosphorus-containing ring according to Scheme 44. It is known that LR is superior over P_2S_5 in thionation process.[65] Thus, the chromone ring was thionated during formation of compound **122** into thiochromone. Compound **122** showed moderate potent anticancer properties (IC_{50}=10.65±1.76 μg/mL) against MCF-7 breast cancer cell near to the standard drug (IC_{50}=8.50±0.90 μg/mL).



Scheme 44

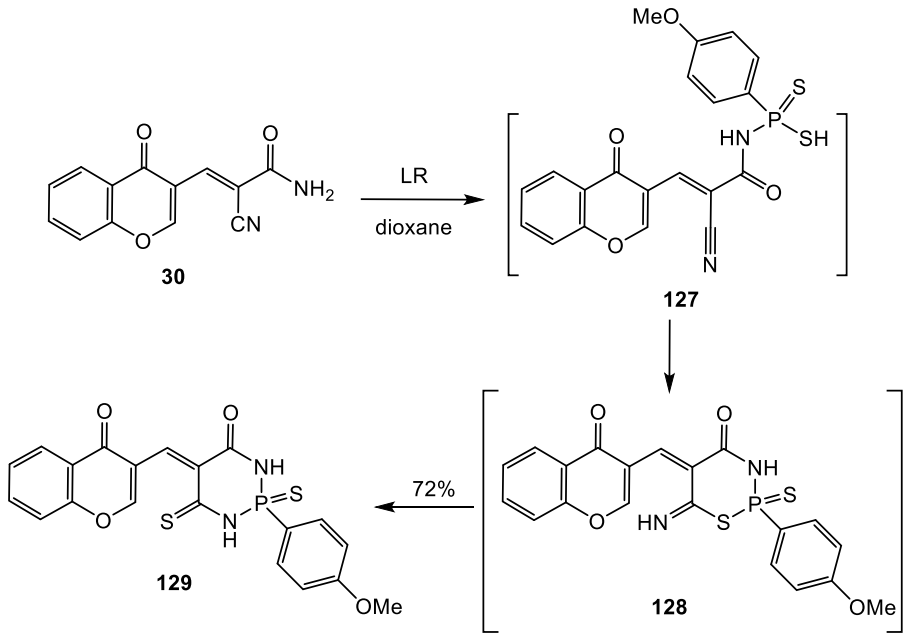
In the same sense, compound **30** reacted with phosphorus pentasulfide in boiling dioxane to give a mixture of two products that could be separated. The first product with yield 39% was identified as 5-[(4-oxo-4*H*-chromen-3-yl)methylidene]-2-sulfanyl-2-sulfido-6-thioxo-1,3,2-diazaphosphinan-4-one (**125**) while the second product was identified as 5-[(4-oxo-4*H*-chromene-3-yl)methylidene]-4,6-dithioxo-2-sulfanyl-2-sulfido-1,3,2-diazaphosphinane (**126**) in 35% yield (Scheme 45). The formation of compounds

125 and **126** could be interpreted as conversion of **30** into the two intermediates **123** and **124** *via* hydrolysis of the nitrile group into thioamide along with sulfuration of amide group for the intermediate **124**. Both intermediates underwent ring closure *via* P_4S_{10} to afford the diazaphosphinanes **123** and **124**, respectively (Scheme 45).[46]



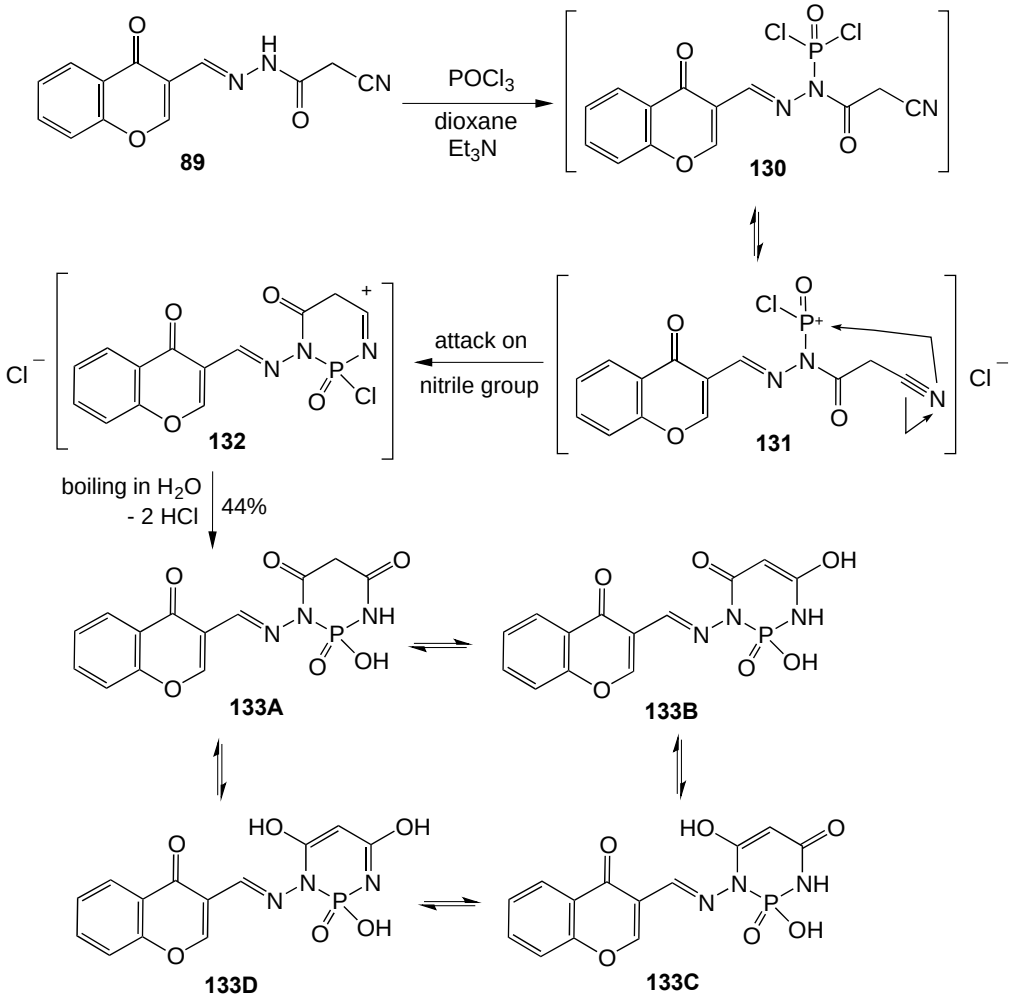
Scheme 45

Moreover, compound **30** reacted with Lawesson's reagent in dry dioxane giving rise a sole product which was identified as 2-(4-methoxyphenyl)-5-[(4-oxo-4*H*-chomen-3-yl)methylidene]-2-sulfido-6-thioxo-1,3,2-diazaphosphinan-4-one (**129**). The reaction proceeded *via* phosphorylation of amide group to give the nonisolable intermediate **127** and its subsequent cyclization due to addition of the SH group at the nitrile group forming the intermediate **128**. The latter intermediate underwent fast Dimroth rearrangement to the final product **129** (Scheme 46).[46]



Scheme 46

When phosphorus oxychloride was added to a solution of hydrazone **89** in dry dioxane containing two equivalent amounts of triethylamine, the 1,3,2-diazaphosphinyl chromone **133** was obtained in 44% yield (Scheme 47). On the basis of the well-established chemistry of phosphorus oxychloride, the reaction of the NH group of hydrazone fragment with $POCl_3$ produced the phosphorodichloridate intermediate **130** that can be also existed in form **131**. This reaction was facilitated in the presence of triethylamine as HCl acceptor. The subsequent nucleophilic substitution of the nitrogen atom of nitrile group on the phosphorus atom produced the intermediate **132**. The final step in the synthesis of **133** was simple hydrolysis *via* attack of water at the carbon and phosphorus atoms of the iminium and elimination of HCl (Scheme 47).[63]

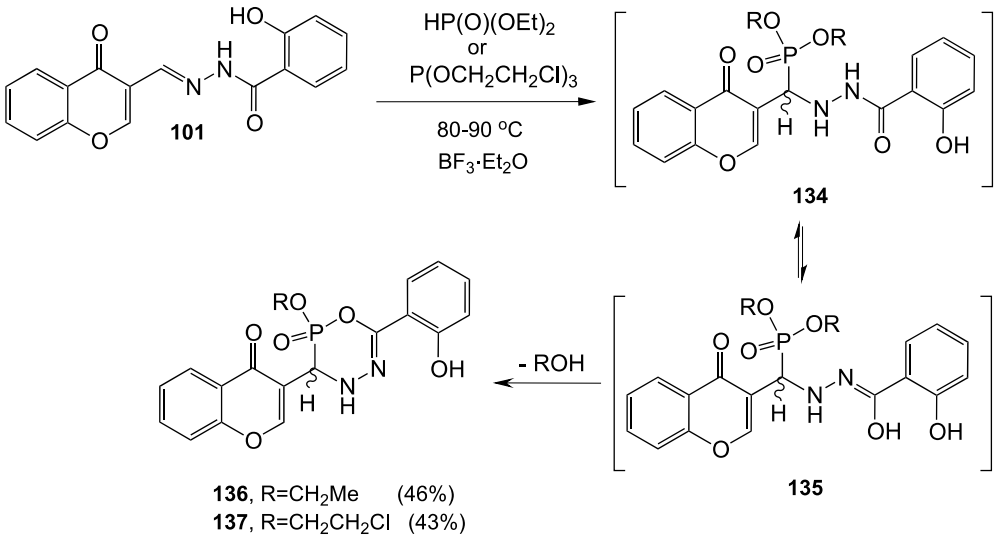


Scheme 47

2.6.10. 1,4,5,2-Oxadiazaphosphinine

When diethyl phosphite and tris(2-chloroethyl)phosphite were allowed to react with hydrazone **101** in the presence of $BF_3{\cdot}Et_2O$ as a catalyst at 80−90 °C under Pudovik reaction conditions, the corresponding 1,4,5,2-oxadiazaphosphininyl chromones **136** and **137**, respectively, were isolated (Scheme 48). The

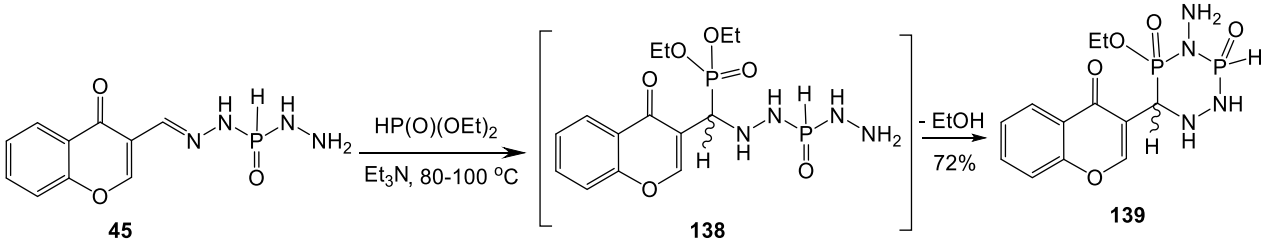
formation of compounds **136** and **137** could be explained *via* phospha-Micheal addition of phosphorus atom of phosphite reagents on the azomethine bond to give the corresponding dialkyl α-hydrazino-phosphonates **134**, which can be existed in forms **135**. The latter unisolable intermediates underwent cyclization *via* nucleophilic attack of OH_{enol} at the phosphonate groups to remove alcohol molecule affording the desired product **136** and **137** (Scheme 48). Compounds **136** (IC_{50} = 11.7 ± 1.50 μg/mL) and **137** (IC_{50} =9.37 ± 1.30 μg/mL) showed anticancer activity against MCF-7 human breast cancer cell lines while they showed moderate activity against VEGF with inhibition percentages of 53 and 56%, respectively.[63]



Scheme 48

2.6.11. 1,2,4,3,5-Triazadiphosphinane

Addition of diethyl phosphite to the azomethine bond of the phosphonic hydrazone **45** in the presence of triethylamine as a catalyst at 80-100 °C gave 3-(4-amino-5-ethoxy-3,5-dioxido-1,2,4,3,5-triazadi-phosphinan-6-yl)-4*H*-chromen-4-one (**139**). The addition resulted in the intermediate **138** (not isolated), which underwent an intramolecular cyclization *via* elimination of ethanol affording the desired product **139** (Scheme 49).[51]

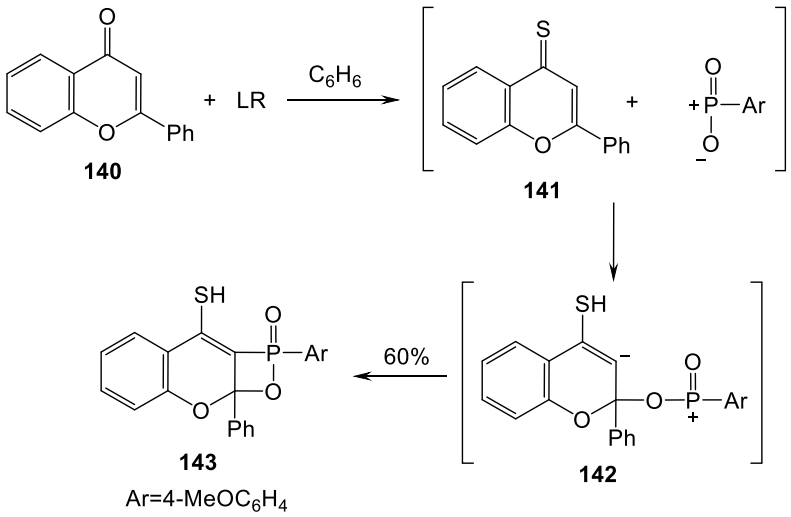


Scheme 49

2.7. Synthesis of phosphorus heterocycles fused with chromone or thiochromone ring

2.7.1. 1,2-Oxaphospheto[4,3-*b*]chromene

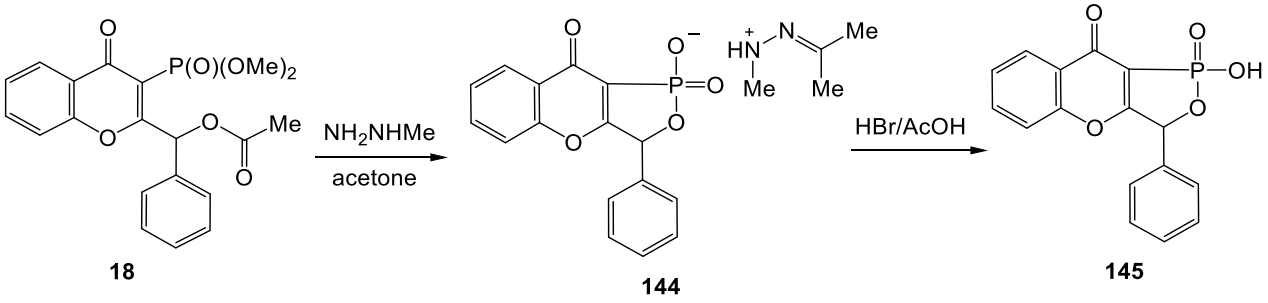
When a mixture of 2-phenylchromone (**140**) and Lawesson`s reagent (LR) in dry benzene was exposed to sunlight, an orange crystalline substance of 1,2a-diphenyl-1-oxido-8-thioxo-2a*H*-1,2-oxaphospheto[4,3-*b*]chromene (**143**) was isolated according to the Scheme 50.[66]



Scheme 50

2.7.2. 2,1-Oxaphospholo[4,5-*b*]chromone

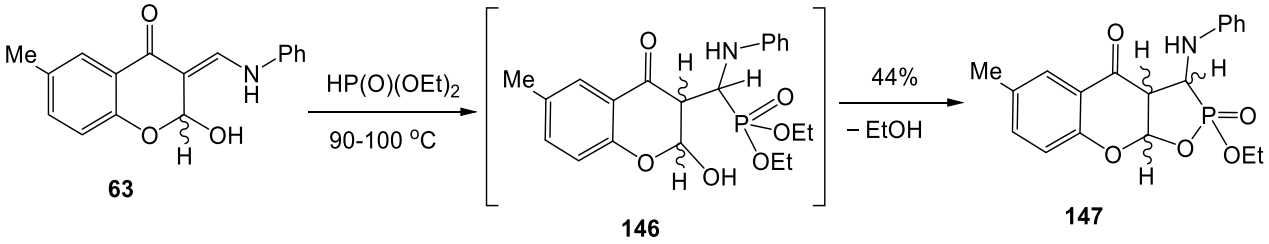
The chromone hydrazonium salt of 1-hydroxy-1-oxido-3-phenyl-1,3-dihydro-1λ^5-2,1-oxaphospholo-[4,5-*b*]-4*H*-chromen-4-one (**144**) and its acid **145** were obtained by reaction of 2-(1-acetoxybenzyl)-3-(dimethoxyphosphoryl)-4-oxo-4*H*-chromene (**18**) with *N*-methylhydrazine in acetone and HBr in AcOH, respectively (Scheme 51).[67]



Scheme 51

Ali[57] studied reaction of 3-(phenylaminomethylene)-2-hydroxy-6-methyl-2,3-dihydro-4*H*-chromen-4-one (**63**) with diethyl phosphite at 90−100 °C. The separated product was formulated as 2-ethoxy-6-methyl-

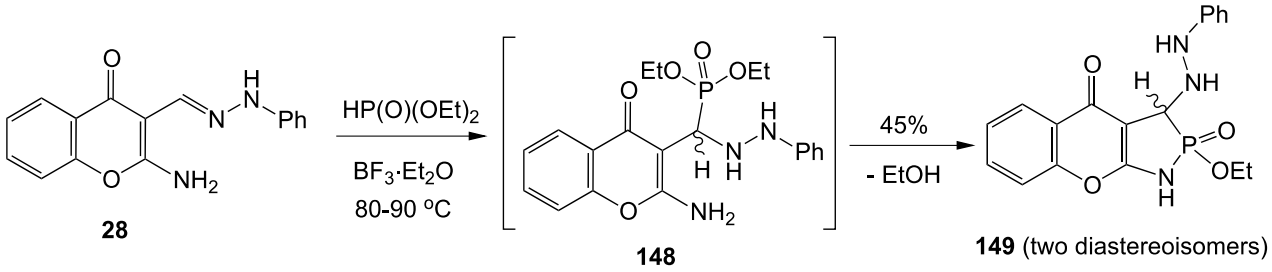
2-oxo-3-phenylamino-2,3,3a,9a-tetrahydro-4*H*-1,2-oxaphospholo[5,4-*b*]chromen-4-one (**147**) (Scheme 52). The formation of compound **147** may be explained as resulting from a nucleophilic attack of the phosphorus atom at the α,β-unsaturated ketone moiety of **63** (Pudovik reaction) to give the unisolable intermediate **146** which underwent cyclization *via* elimination of one molecule of ethanol to give the final product (Scheme 52).



Scheme 52

2.7.3. Chromono[3,2-*d*][1,2]azaphosphole

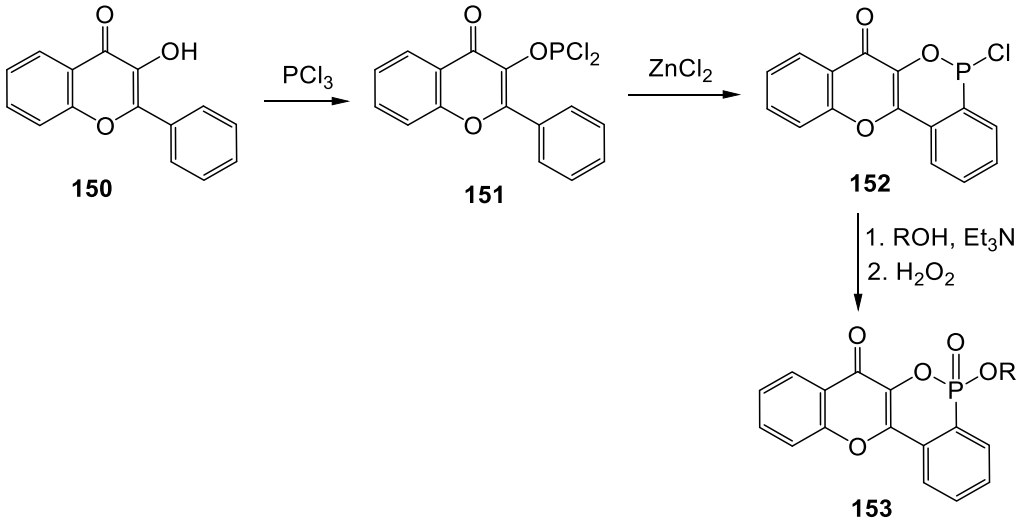
When hydrazone **28** was allowed to react with diethyl phosphite at 80−90 °C in the presence of trifluoroboron etherate as a catalyst under Pudovik reaction conditions for 6 hours gave the unisolable diethyl hydrazinophosphonate **148**, which underwent cyclization *via* removing of ethanol molecule to afford the interesting chromeno[3,2-*d*][1,2]azaphosphole derivative **149** (Scheme 53).[45]



Scheme 53

2.7.4. 1,2-Oxaphosphinino[5,6-*b*]chromone

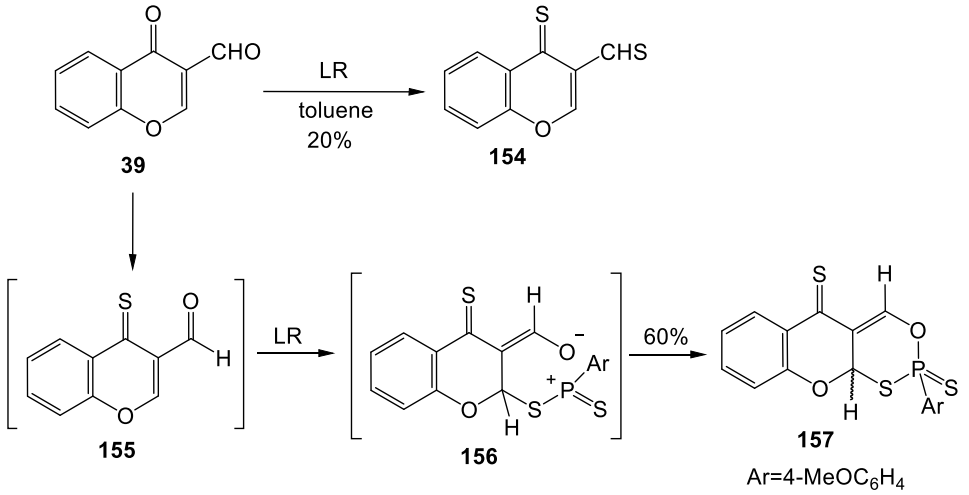
The benzoannulated 1,2-oxaphosphinino[5,6-*b*]chromones **153** were prepared in two steps, starting from 3-hydroxyflavone (**150**). Lewis acid catalyzed electrophilic phosphorylation of **150** with phosphorus trichloride formed phosphorus dichloride intermediate **151**, which on subsequent intramolecular Friedel-Crafts insertion in the presence of $ZnCl_2$ as catalyst formed the six-membered chlorophosphorine **152**. In the second step, compound **152** underwent replacement of halide on reaction with various alcohols in diethyl ether at 25 °C in the presence of Et_3N. Subsequent oxidation with H_2O_2 gave the title compounds **153**, which showed significant activity against bacteria and low activity against fungi (Scheme 54).[68]



Scheme 54

2.7.5. 1,3,2-Oxathiaphosphinino[4,5-*b*]thiochromone

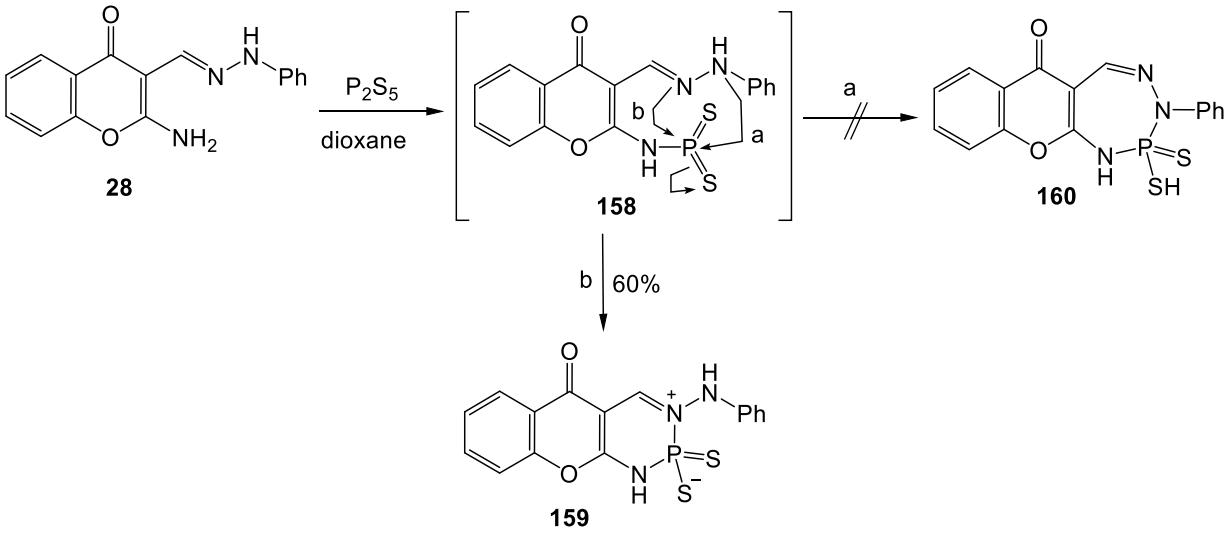
3-Formylchromone (**39**) reacted with Lawesson's reagent (LR) in boiling toluene to give a mixture of two products that were separated by column chromatography. The first product (20%) was 4-thioxo-4-chromene-3-carbothialdehyde (**154**), while the second product (60%) was 2-(4methoxyphenyl)-5*H*-10a*H*-[1,3,2]oxathiaphosphinino[4,5-*b*]chromene-5-thione-2-sulfide (**157**) (Scheme 55).[62]



Scheme 55

2.7.6. Chromono[2,3-*d*][1,3,2]diazaphosphinine

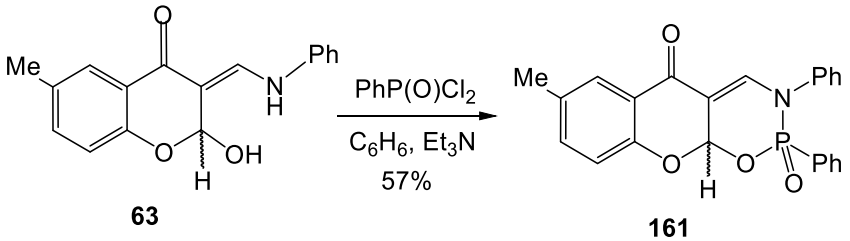
Treatment of hydrazone **28** with phosphorus pentasulfide in dry dioxane did not generate the expected phosphorus heterocycle **160**, but produced the interesting chromono[2,3-*d*][1,3,2]diazaphosphinine-2-sulfide **159** (Scheme 55). The formation of compound **159** did not undergo any thionation of carbonyl group and occurred *via* condensation *via* NH_2 group, followed by a nucleophilic cycloaddition of nitrogen atom of azomethine bond at PS_2 fragment (Scheme 56).[45]



Scheme 56

2.7.7. Chromono[3,2-*e*][1,3,2]oxazaphosphinine

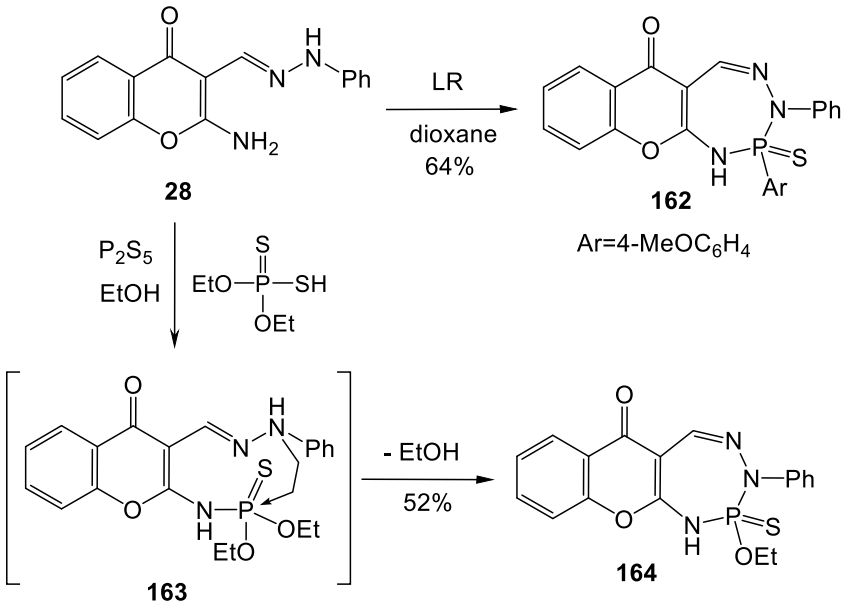
Cyclization of the enaminone **63** with phenyl phosphonic dichloride was performed in dry benzene containing a few drops of triethylamine to produce 2,3-diphenyl-7-methyl-2-oxo-3,10a-dihydro-2*H*,5*H*-chromeno[3,2-*e*][1,3,2]oxazaphosphinin-5-one (**161**) in moderate yield (Scheme 57).[57]



Scheme 57

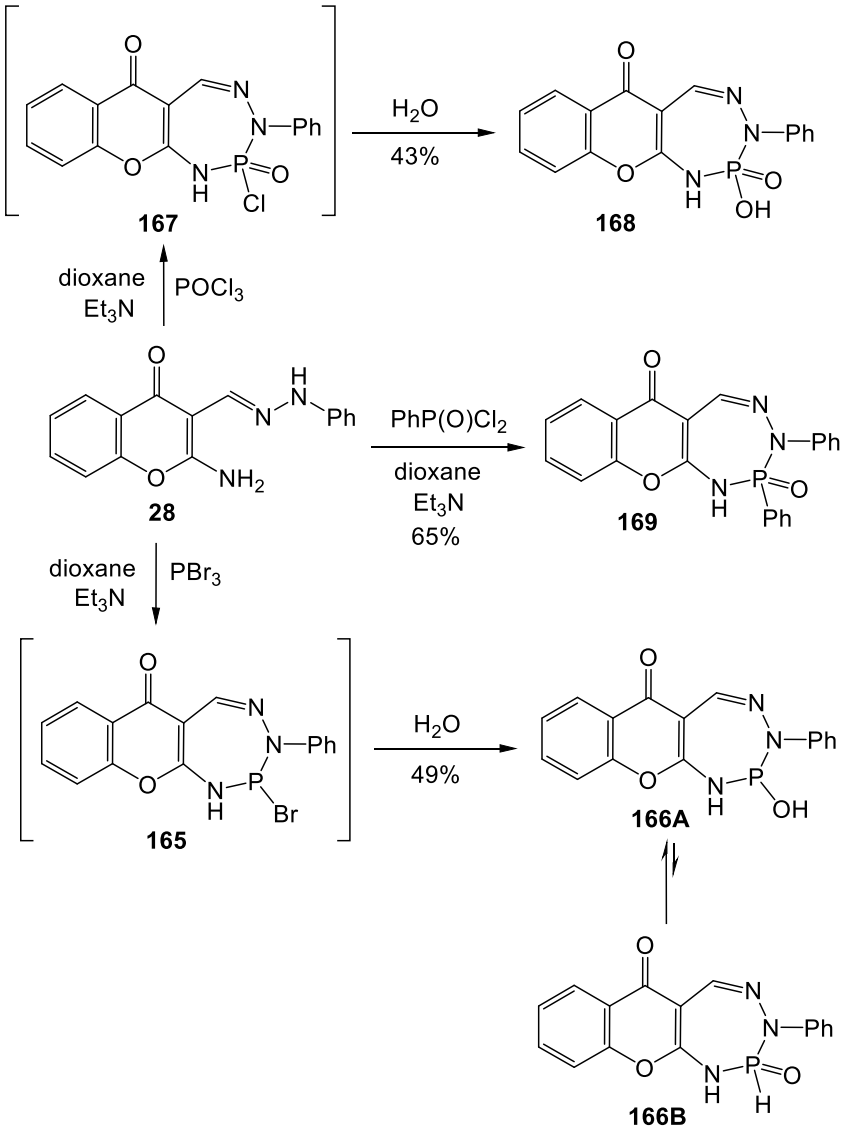
2.7.8. Chromono[2,3-*e*][1,2,4,3]triazaphosphepine

Treatment of hydrazone **28** with Lawesson's reagent and *O*,*O*-diethyldithiophosphoric acid in dry dioxane produced the corresponding chromono[2,3-*e*][1,2,4,3]triazaphosphepine-2-sulfides **162** and **164**, respectively (Scheme 58). The separated products did not undergo any thionation of carbonyl groups and occurred *via* cyclization of phosphorus atoms with mobile hydrogen of NH_2 and NHPh (Scheme 58).[23] Compounds **162** and **164** had significant cytotoxic effects against the Hep-G2, breast MCF-7 and colon HCT-116 human cancer cell lines. Their IC_{50} values ranged between 1.56 and 12.4 μg/mL in comparison to doxorubicin (IC_{50}= 0.426-0.469 μg/mL).[45]



Scheme 58

Addition of some phosphorus halides such as phosphorus tribromide, phosphorus oxychloride and phenyl-phosphonic dichloride to a solution of hydrazone **28** in dry dioxane at room temperature followed by heating under reflux resulted in the chromono[2,3-*e*][1,2,3,4]triazaphosphepin-2-oxides **166**, **168** and **169**, respectively, in moderate yields (Scheme 59). In addition to the expected P−H in form **166B** (phosphorus pentavalent) in compound **166** was not detected which supported its existence in form **166A** (phosphorus trivalent). The former reactions might proceed through cyclocondensation of NH_2 and NHPh with phosphorus halides, followed by hydrolysis providing the final products with loss of hydrogen halide in presence of two equivalent amount of triethylamine (Scheme 59).[45]



Scheme 59

3. CONCLUSIONS

In conclusion, this survey demonstrates the synthesis of phosphorus compounds containing chromone and thiochromone rings. These compounds can be divided into three types depending on the type of phosphorus compound. These types are a side phosphorus group, separated and fused phosphorus heterocycles. The synthetic methods and the biological properties were displayed starting from their appearance up to the end of 2019 that will be a fundamental key in the design of new bioactive agents with improved pharmacological properties.

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