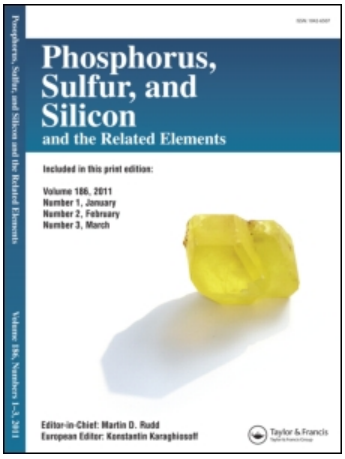

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SYNTHESIS, REACTIONS AND BIOLOGICAL ACTIVITY OF PHOSPHORUS-CONTAINING DERIVATIVES OF CHROMONE AND COUMARIN

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SYNTHESIS, REACTIONS AND BIOLOGICAL ACTIVITY OF PHOSPHORUS-CONTAINING DERIVATIVES OF CHROMONE AND COUMARIN

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Chromone and coumarin derivatives exhibit a wide spectrum of biological activity, including spasmolytic, antiarrhythmic, cardiothonic, antiviral, and anticancer properties. Phosphorus-containing chromone and coumarin derivatives form a novel group of compounds, possessing remarkable cytotoxicity and alkylating and anticancer activity against selected tumor cell lines. Derivatives containing a phosphorus atom at position 2 of a γ-pyrone ring are known to be efficient antibacterial agents.

This review presents methods developed for the synthesis of derivatives of chromone and coumarin that contain a phosphonate moiety. Among them, the reaction of derivatives of 2-hydroxyacetophenone with phosphonic compounds is the one most frequently used. Some analogues were characterized by X-ray crystallography.

Keywords: Alkylating, cytotoxic, and antimicrobial activity; chromone and coumarin derivatives; phosphonic acids

INTRODUCTION

Derivatives of chromone (1-benzopyran-4(4*H*)-one, **1**) and coumarin (benzo-α-pyrone, **2**) exhibit a wide spectrum of biological activity, including spasmolytic, antiarrhythmic, cardiothonic, antiviral, and anticancer properties.[1] Phosphorus-containing chromone and coumarin derivatives represent a novel group of compounds possessing

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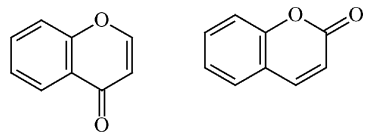


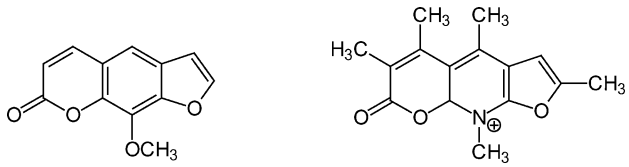
1 **2**

FIGURE 1 The structure of the chromone (**1**) and coumarin (**2**).

remarkable cytotoxicity, alkylating, and anticancer activity against selected tumor cell lines. Derivatives containing a phosphorus atom at position 2 of a γ-pyrone ring are known as efficient antibacterial agents (Figure 1).

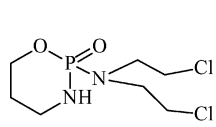
Some coumarin congeners have alkylating properties. Psoralens—the compounds isolated from *Rutacea*, *Umbelliferae*, and *Leguminosae*—constitute the only class of agents known to induce interstrand cross links (ICSs) upon photolysis.[2] In this class of naturally occuring aromatic compounds, a furan ring is fused with the coumarin moiety.[3] The most thoroughly studied psoralen analog, 8-methoxypsoralen (**3**), is a fungal metabolite.[4] N-methylazapsoralen (**4**) is a new analog with enhanced light absorption properties and with the greater water solubility (Figure 2).[5] They have been administered for the treatment of diseases associated with autoimmune disorders, organ rejections, and the AIDS-related complex (**3**).

Alkylating reagents have been used as cytostatics for a very long time.[6] They belong to different families of organic compounds; nonetheless, most of them alkylate the nitrogen atom N_7 or the oxygen O_6 of guanine bases in DNA. One can divide alkylating reagents into monofunctional and bifunctional compounds, resulting in mutagenesis or cytotoxicity, respectively. Bifunctional alkylating reagents are able to cross link the strands in double-stranded DNA, in this way hampering the process of replication.[7]



3 **4**

FIGURE 2 The structure of 8-methoxypsoralen (**3**) and N-methylazapsoralen (**4**).



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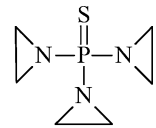

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FIGURE 3 The structure of cyclophosphamide (**5**) and thiotepa (**6**).

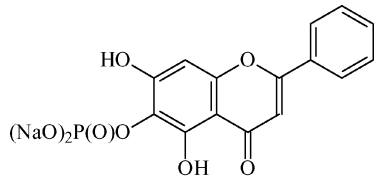
Figure 3 shows two phosphoro-organic alkylating drugs cyclophosphamide (**5**) and thiotepa (**6**). Cyclophosphamide, which has outstanding cytotoxic and immunosuppressor properties,[8] undergoes microsomal activation in liver with participation of oxygenase.[9] Also, its metabolite, acrolein (**5a**), is cytotoxic. Thiotepa (**6**) is converted to its active form, Tepa (**6a**), where oxygen is substituted for sulfur atom.[7]

The alkylating properties of phosphonic esters have been exhaustively described in many studies[10,11] and have been a subject of many patents.[12–14] Derivatives of phosphonic acids also play important biological roles as regulators of growth, inhibitors of metabolic processes, and pesticides[15] or drugs[16] including antibiotics[17,18] that are either synthetic or isolated from *Streptomyces fradiae, S. viridochromogenes*, *S. wedmorensis* (fosmidomycin,[19] fosfomycin[20]), or *Bacillus subtilis* (rhizotocin[21]). Also chromone and coumarin derivatives of phosphoric acid are biologically important. For example, the sodium salt of phosphoric derivative of 5,7-dihydroxy-4-oxo-2-phenyl-4*H*-chromen-6-yl (baicalein)[22] (**7**) has antiallergic properties, while Coroxon (**8**, 3-chloro-7-hydroxy-4-methy-lcoumarin diethyl phosphate) and Coumithoate (**9**, phosphorothioic acid O,O-diethyl-7,8,9,10-tetrahydro-6-oxo-6H-dibenzo[b,d]pyran-yl-ester), are inhibitors of cholinesterase[23] (Figure 4).

There are only a few reports in the literature on biological application of phosphonic analogues of chromone and coumarin, which were tested for their alkylating, cytotoxic,[24] anticancer,[25] and antibacterial[26] properties. In this review, the methods for their synthesis and biological properties will be presented.

SYNTHESIS OF PHOSPHONIC DERIVATIVES OF CHROMONE

There is only a limited number of phosphonic derivatives of chromone, where the phosphorus atom is directly connected with the benzo-pyran



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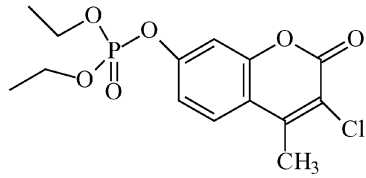

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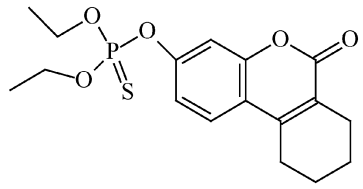

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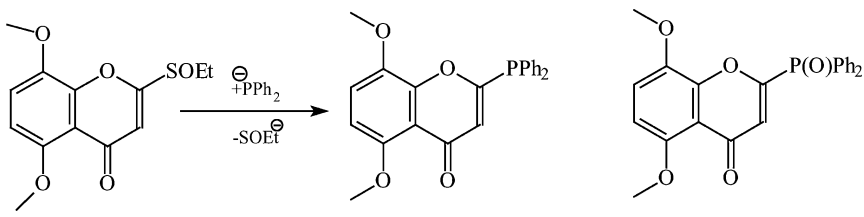
FIGURE 4 The structure of Baicalein (**7**), Coroxon (**8**), and Coumithoate (**9**).



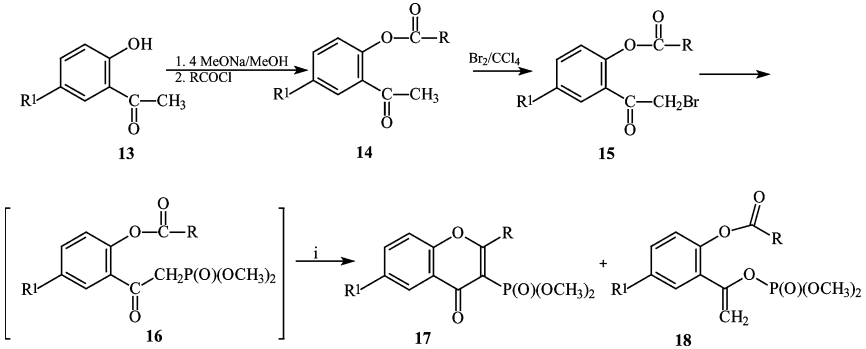
10 11 12

SCHEME 1

ring. In 1981, Bantick and Suschitzki[27] caused 5,8-dimethoxy-2-ethylsulfinochromone **10** to react with diphenylphosphin anion in the presence of potassium tert-butanolate to yield derivatives **11** and **12** (Scheme 1).

Their structure were established only from NMR and mass spectroscopy (MS) data of the crude reaction mixture as **11** and **12**

decomposed during attempts at isolation. Much more successful was a method developed by Kostka et al.[28] based on dervatives of 2′-hydroxyacetophenone. The method was further used after minor modification by Budzisz,[23,24] who caused acid chlorides to react with the sodium salt of 2′-hydroxyacetophenone (**13**) (Scheme 2), followed by bromination and condensation of the resulting **15** with trialkyl phosphite to form Arbuzov's **17** and Perkov's **18** products.



SCHEME 2 R^1 = H, CH_3, R = CH_3, Ph, i: cyclization on a chromatography column.

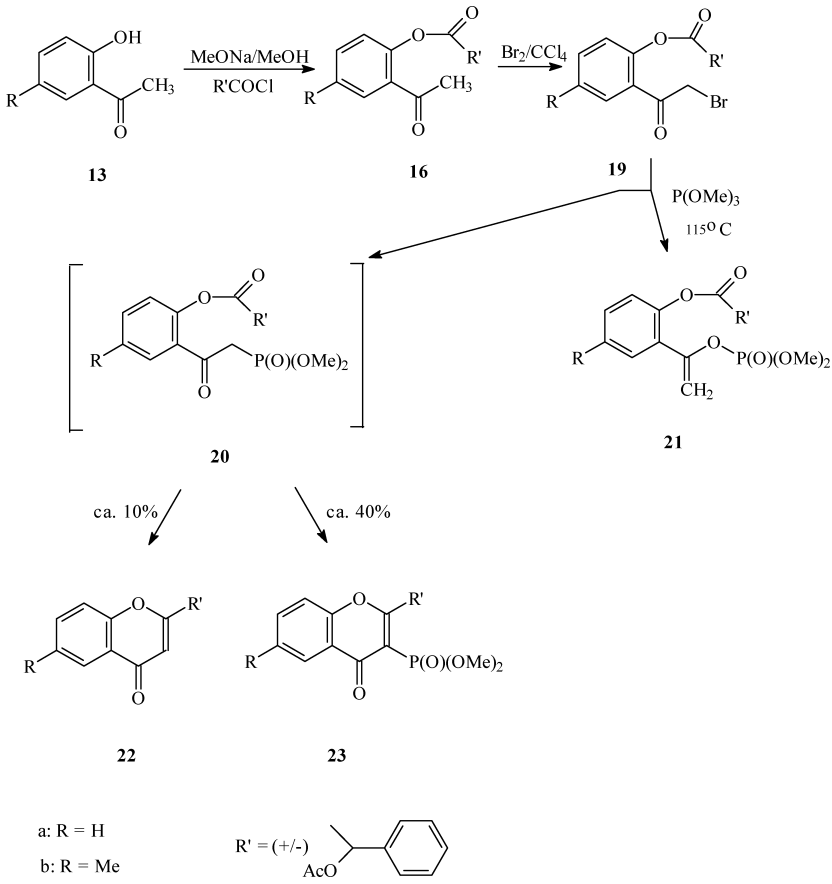
Typically, the product is isolated with ca 40% yield. If R = Ph, the intermediates **16** can be isolated with good yield. On the other hand, if an appropriate derivative of mandelic chloride is used,[24] chromone **22** without the phosphonic moiety is also formed (Scheme 3).

The proposed mechanisms of formation of compounds **22** and **23** are presented in Scheme 4. Substituents in the benzene ring do not affect the outcome of the reaction. According to Cram and Abdelhafez[29] the biggest substituent occupies the position *trans* to the phosphonic moiety, resulting in Arbuzov's product **23**.

Perkov's-to-Arbuzov's product ratio depends on many factors such as reaction temperature, halide, solvent, and carbonyl component used. Perkov's product is preferred at lower temperatures[30,31] in nonpolar solvents.[32]

Strong alkylating and anticancer properties of derivatives **23** were found in vivo for the two mouse cell lines L1210, P388.[24]

In the early 90th, Kostka and Modranka[33] caused 2-formylchromone (**24a**) and 3-formyl-chromone (**24b**) to react with dialkyl phosphites at 100°C with no solvents and obtained chromone-2- (**25a**) and chromone-3-hydroxymethanephosphonic acids (**25b**) and esters with

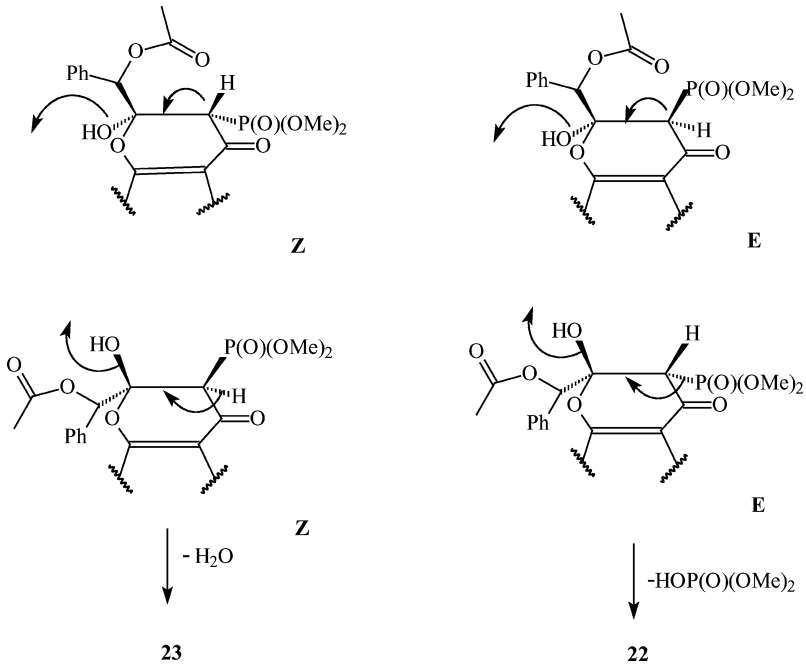


SCHEME 3

48–78% yield. The best results were obtained with dimethyl phosphite (Scheme 5).

Reaction of chromone-3-carboxylic acid chloride (**26a**) with trialkyl phosphites furnished compounds **27a** (Scheme 6).[34]

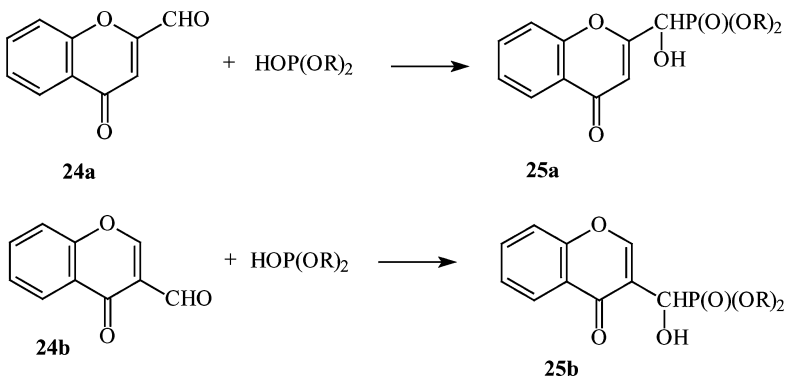
The authors noticed that the reaction of chromone-2-carboxylic acid chloride (**26b**) is more complicated and provides two isomeric phosphonic-phosphate compounds (E)-2(dialkyl-phosphonato, dialkylphosphato)methylene-4[(4-oxo-4*H*-1-benzopyran-2-yl)-carbonyl oxy]-2*H*-1-benzopyran (**28**) and their isomer (Z) **29** in 87% yield. They propose that a second equivalent of trialkyl phosphite attacks the oxygen atom of the carbonyl group of the ketophosphonic intermediate **27b** (analogous to that formed from the 3-substituted derivative of chromone) (Scheme 7). At -40°C, a ratio **28**:**29** of **3:1** was observed,



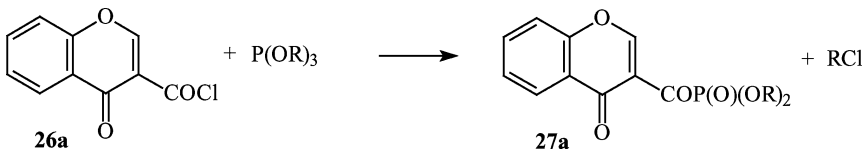
SCHEME 4

which increased to 6:1 when the temperature of reaction was elevated to 60°C. This suggests that the formation of **28** is kinetically favored.

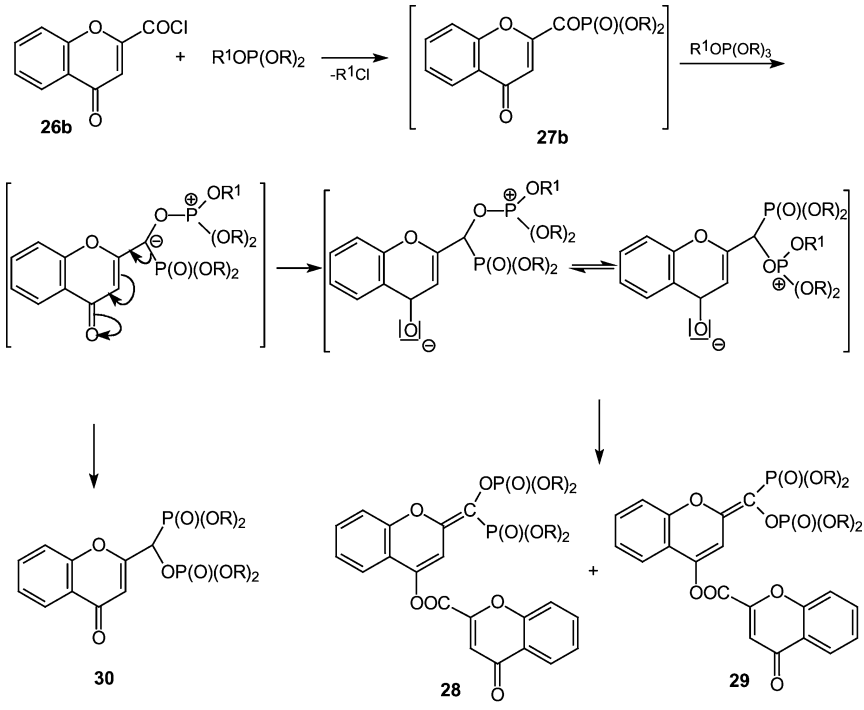
Mouysset et al. synthesized the diethyl ester of chromone-2-methanephosphonic acid (**32**) in good yield starting from 2-chloromethylchromone (**31**) (Scheme 8) and triethyl phosphite.[35]



SCHEME 5 R = Me, Et, i-Pr, Bu, Ph.

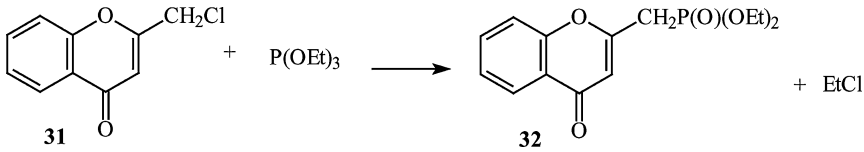


SCHEME 6



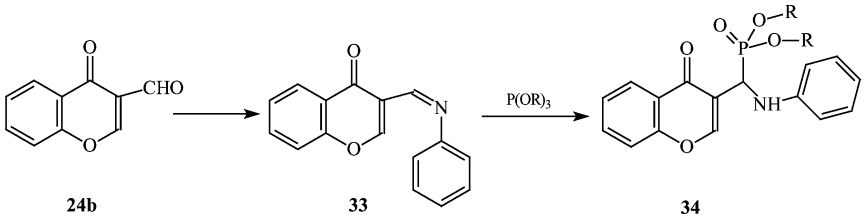
R = CH_3–, C_2H_5–, R^1= $(CH_3)_3Si$–

SCHEME 7



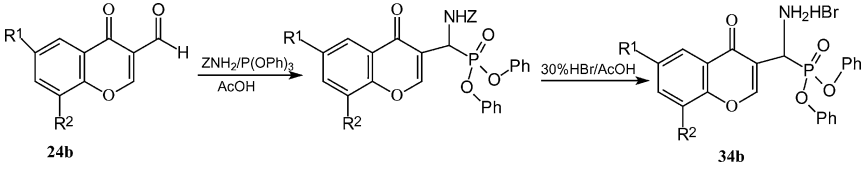
SCHEME 8

Khidre and coworkers obtained several α-aminophosphonic derivatives of chromone (**34**) (ca 55% yield) in the reaction of 3-(phenyliminomethyl)chromone (**33**) with dialkyl- or trialkyl phosphite (R=Me, Et, i-Pr).[36] Compound **33** was synthesized from **24b** and amines (p-chloroaniline, p-anisidine) in the presence of p-toluenosulfonic acid, which was used as a catalyst (Scheme 9).



SCHEME 9 R = Me, Et, i-Pr.

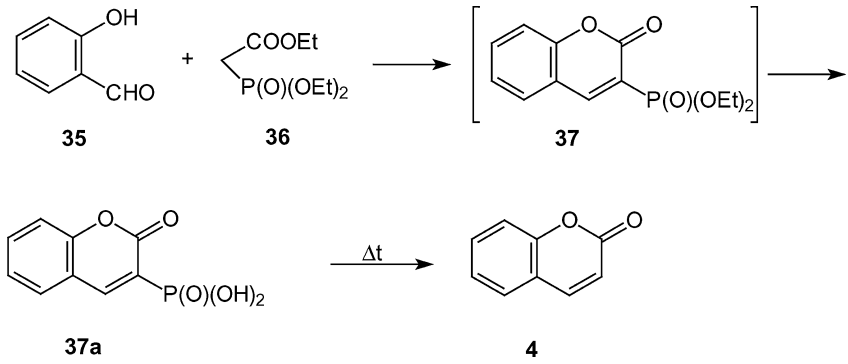
Boduszek et al.[37] obtained hydrobromides (**34b**) of analogous α-aminophosphonic derivatives of chromone using triphenyl phosphite and acetic acid (90–100°C, 84–89% yield). Their hydrolysis provided the corresponding acids in 90% yield (Scheme 10).



SCHEME 10 R_1 = H, Cl, Me, R_2 = H, Cl, Z = $PhCH_2OCO$.

SYNTHESIS OF PHOSPHONIC DERIVATIVES OF COUMARIN

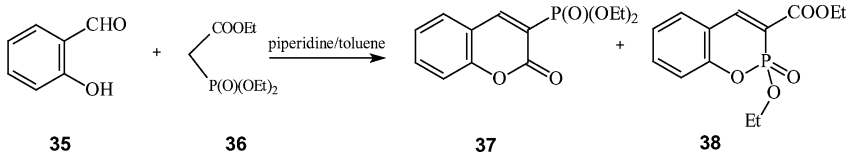
Phosphonic derivatives of coumarin with the phosphorus atom directly connected with the benzopyrane ring were reported for the first time by Robinson and Addison,[38] who obtained the diethyl ester of coumarin-3-phosphonic acid in the reaction of salicylic aldehyde (**35**) with (diethoxyphosphonyl)acetic acid ethyl ester (**36**). The ester was thermally unstable and at elevated temperature decomposed to coumarin **4** (Scheme 11). During the past years, many authors tried to use different derivatives of salicylic aldehyde and different phosphonic components employing



SCHEME 11

a range of catalysts and changing reaction conditions. However, their efforts led predominantly to derivatives **37**.[39–41] Compound **37** was the only product of reaction performed in THF/Pyridin in the presence of $TiCl_4$.[37]

Reaction of salicylic aldehyde with triethylphosphonate in the presence of piperidine in refluxing toluene (Scheme 12) provided diethyl coumarin-3-phosphonate (**37**) in 70% yield.[42] The main product was accompanied by a new heterocyclic compound 1,2-benzo-phosphorinane-3-ethylcarboxylate (**38**) formed with 9% yield.

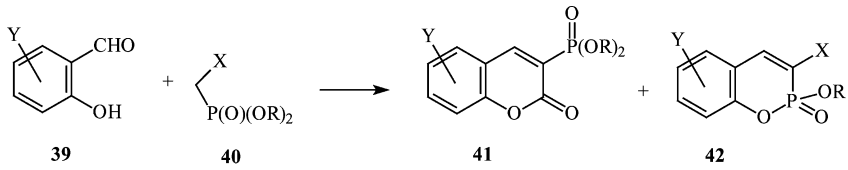


SCHEME 12

Bojilowa and coworkers analyzed the ratio of products **41**:**42** as the effect of substituents in salicylic aldehyde (**39**) and in the phosphonic components **40**, and also changing reaction time, solvent, and catalysts (Scheme 13). The data are presented in Table I.

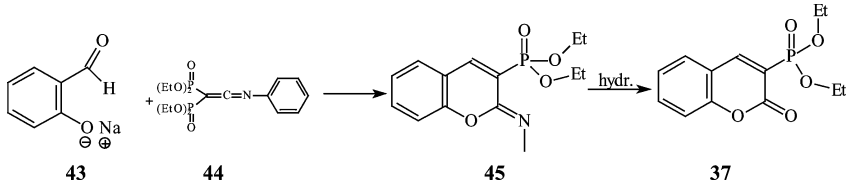
Analysis of the data indicates that both products **41** and **42** are formed when the raction is carried out in solution, in the presence of a base (method A, A_1, A_2, A_3, C and D). Otherwise, (methods E, F, G, and H) only the coumarin-3-phosphonate (**41**) was isolated.

Bestman and Lehnan[43] caused the sodium salt of salicylic aldehyde to react with N-phenyl-bis(diethylphosphono)ketoimine to yield a phosphonic derivative of coumarin **45**, which further hydrolyzed to **37** (Scheme 14).



Y = H, 5-Br, 5-Cl, 4-NEt_3
R = Me, Et
X = COOEt, $COOSi(CH_3)_3$, CN

SCHEME 13



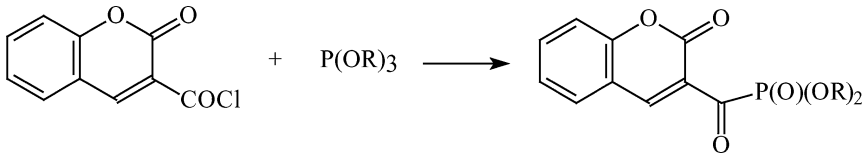
SCHEME 14

In 1985, Vishniakova et al.[44] published the synthesis of phosphonic coumarin derivative **47** by reaction of 3-carboxylcoumarin chloride (**46**) with trialkyl phosphite (Scheme 15).

Reaction of 3-acetylcoumarin (**48**) with di- or trialkylphosphite constitutes another important method for the synthesis of phosphonic derivatives of coumarin (Scheme 16).

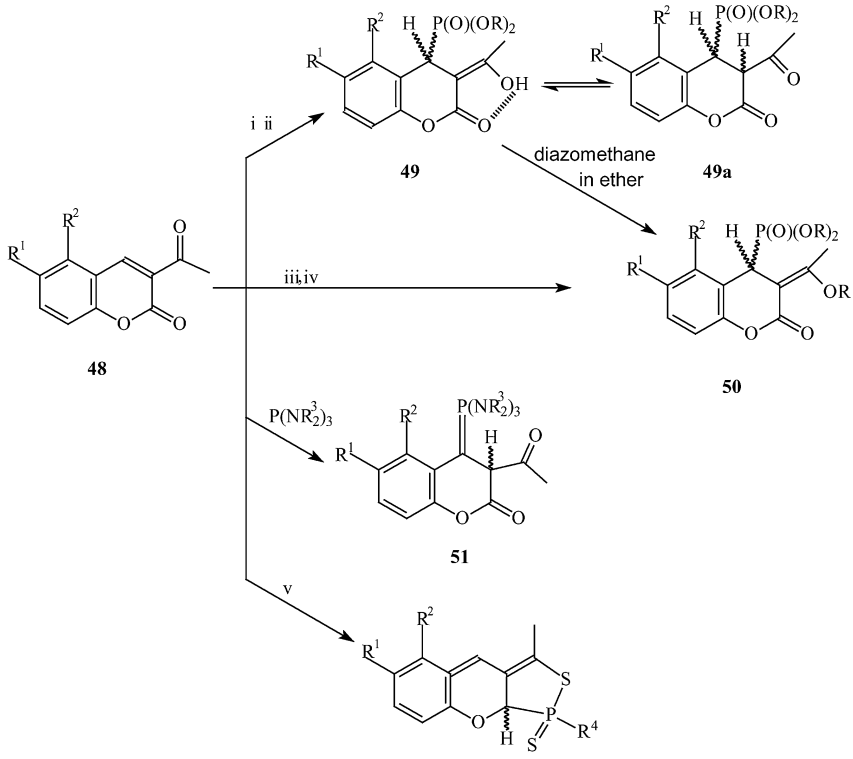
TABLE I Reaction Conditions and Yield of Product **41** and **42**

Method	Reaction conditions	Overall yield (%)	**41**	**42**	**41:42**
A	Toluene (60 ml)/piperidine/Dean-Stark trap	69	45	24	1.8:1
A_1	Toluene (40 ml)/piperidine/Dean-Stark short distance trap	52	17	35	0.5:1
A_2	Toluene (40 ml)/piperidine + acetic acid (2–3 drops)/Dean-Stark short distance trap	38	31	7	4.2:1
A_3	Abs. ethanol (40 ml)/piperidine + acetic acid (2–3 drops)	37	34	3	11.3:1
B	Tetrahydrofuran/titanium tetrachloride/pyridine	49	49	0	49
C	toluene/β-alanine/piperidine acetate/Dean-Stark short distance trap	55	47	8	5.8:1
D	Toluene/piperidine/mol. siev 4A, reflux, 3 h	60	42	18	2.3:1
E	Toluene/mol. siev 4A, reflux, 3 h	34	34	0	
F	Without solvent; alumina (Al_2O_3), 25°C, 1 h	33	33	0	
G	Without solvent; Na 13X-zeolite, 25°C, 10 min	45	45	0	
H	Without solvent; florsil, 25°C, 48 h	37	37	0	



46 **47**

SCHEME 15



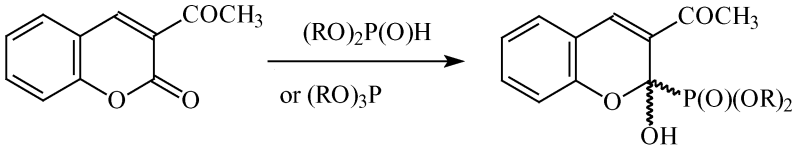
52

R = Et, Me, iPr
$R^1 = R^2 = H$
R^4 = $PhOCH_3$, toluene
i: $HP(O)(OR)_2$, R = CH_3, Et, 100°C without solvent 5 h [56]
ii: $HP(O)(OR)_2$, toluene[57]
iii: $P(OR)_3$, dry toluene, ~8 h[44]
iv: $P(OR)_3$, 100°C, without solvent, R=Me, Et.
v: Lawesson reagent

SCHEME 16

When the reaction was carried out at 100°C (without solvent) for 5 h, only one isomer **49** was obtained, in equilibrium with **49a**. If the reaction was performed at elevated temperature with toluene used as a solvent, compounds **49** or **50** were obtained. Compound **51** was synthesized by Abdou[44] using triaminophosphine and 3-acetylcoumarin **48** ($R = -CH{=}CH_2)_2$ in methylene chloride at 5°C. The reaction is exothermic, and the product was obtained in 82% yield. When di- or trialkylphosphites were used, compounds **50** were obtained with a good yield of 72%.

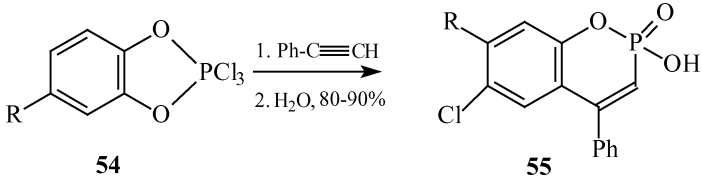
Fahmy et al.[45] made a range of compounds of general formula **52** (60–85% yield) using 3-acetylcoumarin and Lawesson reagent in boiling toluene. Dimethyl-(3-acetyl-3-hydroxy-2*H*-benzopyran-2yl) phosphonate **53** was obtained when 3-acetylcoumarin and trialkyl or dialkyl phosphite (reagent ratio 1:10) without solvent were heated at 100°C for 8 h. The structure of the products was confirmed using spectroscopic methods (IR, NMR, and MS) and elemental analysis (Scheme 17).



48 **53**

SCHEME 17 $R = CH_3, C_2H_5$.

Mironov and coworkers[46–48] prepared phosphonic analogues of coumarin **55** with the phosphonic moiety in position C-2 of the ring, as confirmed by spectroscopy and X-ray analysis (Scheme 18).

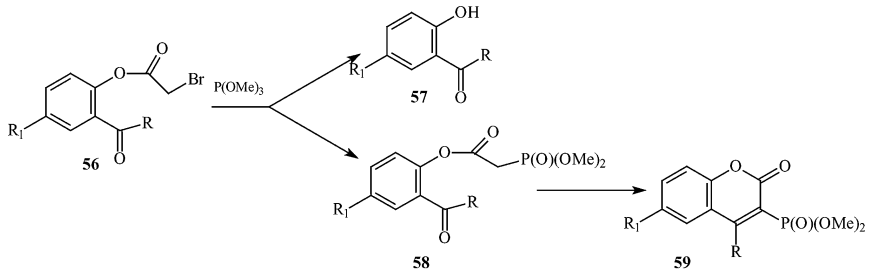


54 **55**

SCHEME 18 R = Cl, Br.

It was found that the presence of substituents in the benzene ring does not affect the structure of the product as the chlorine atom always occupies the *para* position with respect to the oxygen atom in the ring.

In 1998, Kostka[49] reported the synthesis of coumarin derivatives in the reaction of 2′-hydroxya-cetophenone with trialkyl phosphite at 100°C without solvent, followed by chromatographic separation of all products presented in Scheme 19. Analysis of the products confirmed an assumption that α-halogenoesters do not undergo the Perkov rearrangement.[50]



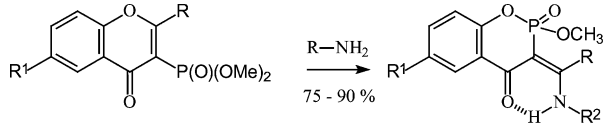
56 57 58 59

R_1 = H, CH_3, NHPh, OCH_3, $N(CH2)_4$; **57**: R = CH_2CH_3, CH_2CH_2Ph **58**: R = Ph, CH_3

SCHEME 19

If substituent R means substituted amine, the reaction provides only compound **58**, which does not cyclize to coumarin **59**. Compounds **59** showed strong alkylating properties in Preussmann's in vitro test.[51] Some of them exhibit cytotoxicity against the two cell lines NALM-6 and HL-60.

Phosphonic analogues of coumarin can also be obtained by rearrangement of chromone phosphonic derivatives **17** upon treatment with amines (Scheme 20).



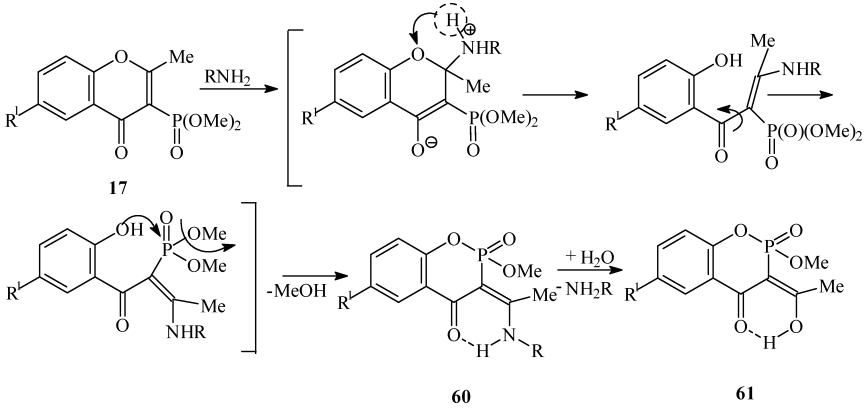
17 **60**

R= CH_3, Ph, R^1=CH_3, H, R^2= CH_3 , CH_2CH_2OH, CH_2Ph,

SCHEME 20

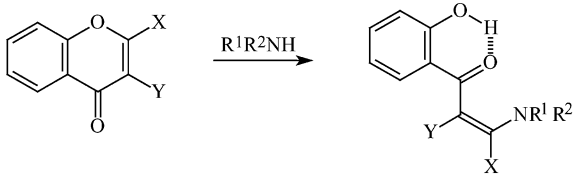
In the products obtained with 75–90% yield, the phosphonic moiety replaces the carbonyl group in position 2 of the coumarin ring. In a first step, the chromone ring opens upon addition of the amine, followed by cyclization into **60** with departure of the methoxyl group.[52] Their

structures were confirmed by X-ray crystallography.[53] The mechanism of rearrangement is depicted in Scheme 21.



SCHEME 21 R = CH_3, CH_2CH_2OH, CH_2Ph, $R^1 = CH_3$, H.

It was found that compounds **60** possessing a methyl group at position C-6 inhibit the growth of *Staphylococcus aureus* and *Bacillus subtilis*[24] and have cytotoxic and alkylating activity.[22] The reaction presented in Scheme 20 is not general, and often the opening of the chromone ring, leading to enamine **62**, is not followed by cyclization[54,55] (Scheme 22).



X, Y = alkyl (R), COOH, COOR, CN, CHO, R^1, R^2 = H or alkyl

SCHEME 22

CONCLUSION

It is well documented that the derivatives of chromone and coumarin possessing the P—C bond have important alkylating properties, as well

as cytotoxic and/or antibacterial activity. Among the methods for synthesis of phosphonic derivatives of chromone and coumarin presented in this review, the reactions of phosphonic esters with carbonyl compounds are the most general. Their efficiency is usually good. It depends on the type of phosphonic ester, and on solvent and temperature of the process. Since demand for new analogues of this class with enhanced biological activity is increasing, search for new methods continues.

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