بسم الله الرحمن الرحيم

((وَلْتَكُنْ مِنْكُمْ أُمَّةٌ يَدْعُونَ إِلَى الْخَيْرِ
وَيَأْمُرُونَ بِالْمَعْرُوفِ وَيَنْهَوْنَ عَنِ الْمُنْكَرِ
وَأُولَئِكَ هُمُ الْمُفْلِحُونَ))

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Ain Shams University
Faculty of Education
Department of Chemistry

Synthesis, Spectral Characterization and Biological Evaluation of Some Novel Organophosphorus Compounds

A thesis submitted
by

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شكر

شاكرة المولى عز وجل على عظيم نعمه وجليل عطاياه وأعظمها نعمة العلم وعطية الإسلام .

يطيب لي أن أتوجه بخالص الشكر إلى الأستاذ الدكتور/ **الحسين على رضا محمد**..... أستاذ الكيمياء العضوية ، كلية التربية ، جامعة عين شمس ... الذى كان له دوره المتميز فى الإشراف واقتراحاته وحفزه المستمر وتوجيهاته البناءة فى مراجعة الرسالة.

يطيب لي أن أتوجه بخالص الشكر إلى الدكتور/ **صلاح عبد الغفار عبد العزيز** أستاذ الكيمياء العضوية المساعد، كلية التربية ، جامعة عين شمس ...على تشجيعه وحفزه المستمر و دوره المتميز فى مراجعة الرسالة.

كما أتقدم بخالص الشكر إلى الدكتور/ **طارق السيد على إسماعيل** أستاذ الكيمياء العضوية المساعد ، كلية التربية ، جامعة عين شمس ... الذى كان له دوره المتميز فى الإشراف من خلال المساعدة فى الجزء العملي و تفسير النتائج وتوجيهاته الدائمة فى كل مراحل إخراج هذه الرسالة .

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سومية محمد عبد الكريم

Contents

Abstract

Synthesis, Spectral Characterization and Biological Evaluation of Some Novel Organophosphorus Compounds

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Facile synthetic methods of novel azolyl, azinyl and azepinyl linked to phosphonate and α-aminophosphonate groups were achieved. Chromonyl α-aminophosphonates and γ-pyranyl phosphonates were also prepared. The methodologies depend on ring-opening and ring-closure (RORC) of chromone ring *via* effects of nitrogen and carbon nucleophiles under mild reaction conditions. Structure of all the synthesized compounds were established by elemental analysis and spectral measurements. All the synthesized compounds were evaluated for their antimicrobial activities and antioxidant properties.

Keywords: Chromone, Kabachnik-Fields, α-Aminophosphonate, Phosphonate, Nucleophiles, Antimicrobial, Antioxidant.

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Aim of the work

- Synthesis of some new chromonyl α-aminophosphonates with modified method.
- Synthesis of novel substituted azoles, azines, azepines and pyrans linked to α-aminophosphonate and phosphonate groups.
- Applying strategy of ring-opening and ring-closure (RORC) on chromonyl α-aminophosphonate *via* its reaction with different nitrogen and carbon nucleophiles.
- Spectral characterization of the novel products with different chemical and spectral tools such as elemental analysis, Infrared, mass spectrometry, ^{1}H-, ^{13}C- and ^{31}P-NMR spectra.
- Evaluation of antimicrobial activity and antioxidant properties of the synthesized compounds.
- Discussion of the results of biological evaluations to study the relationship between the structure and activity.

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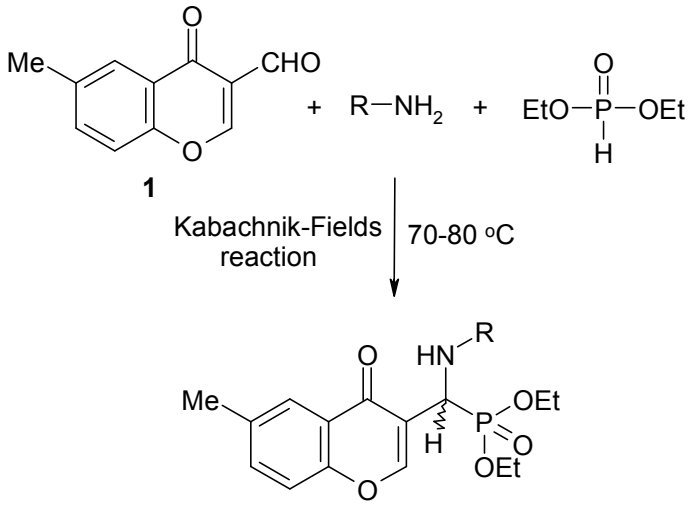
Somaia M. Abdel-Kariem

Summary

Part I: Synthesis and biological evaluations of a series of novel azolyl, azinyl, pyranyl, chromonyl and azepinyl phosphonates

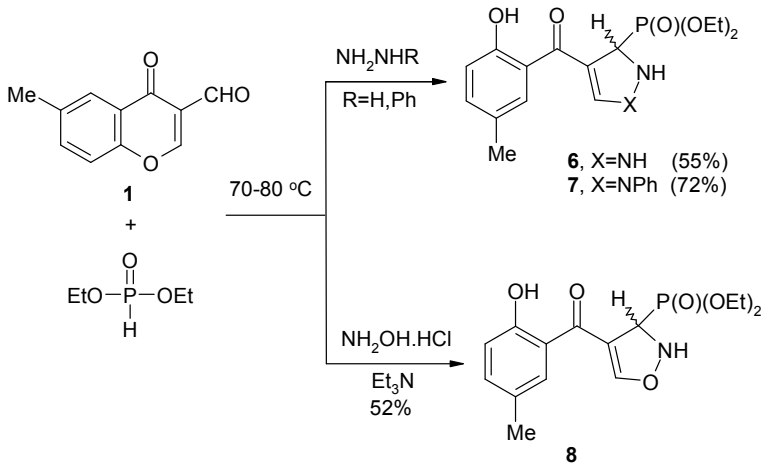
6-Methyl-3-formylchromone (**1**) was allowed to react with ethylamine, benzylamine, 4-chloroaniline and 4-hydroxyaniline in the presence of diethyl phosphite at 70−80 °C under Kabachnik−Fields reaction conditions to produce the corresponding chromonyl α-amino-phosphonates **2**−**5** in 62−100% yields (Scheme 1).



2, R=Et (100 %) **3**, R=CH_2Ph (75 %)
4, R=4-ClC_6H_4 (70 %) **5**, R=4-HOC_6H_4 (62 %)

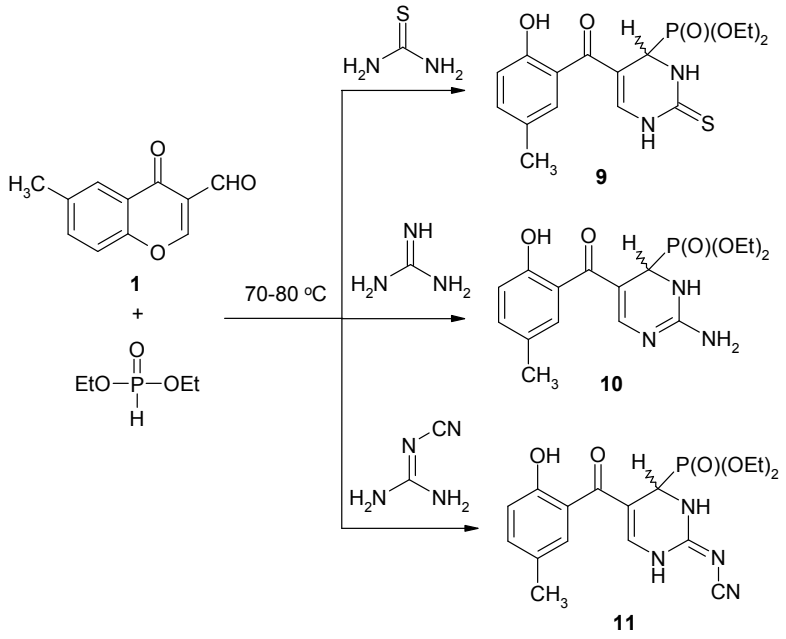
Scheme 1

When 6-methyl-3-formylchromone (**1**) was treated with hydrazine hydrate, phenyl hydrazine and hydroxylamine hydrochloride in the presence of diethyl phosphite at 70−80 °C afforded the corresponding novel azolyl phosphonates **6**−**8**, respectively, as cyclic α-aminophosphonates (Scheme 2).



Scheme 2

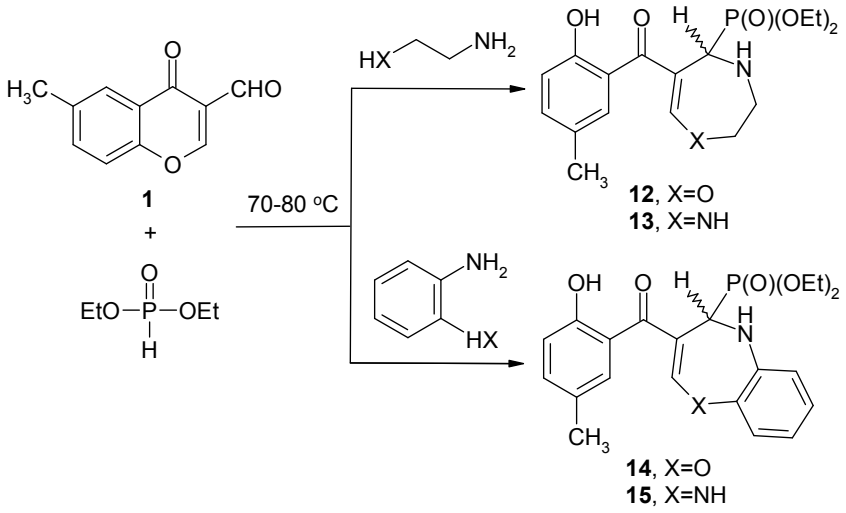
Similarly, fusion of the aldehyde **1** with thiourea, guanidinium carbonate and cyanoguanidine in the presence of diethyl phosphite at 70−80 °C yielded the pyrimidinyl phosphonates **9**−**11**, respectively (Scheme 3).



Scheme 3

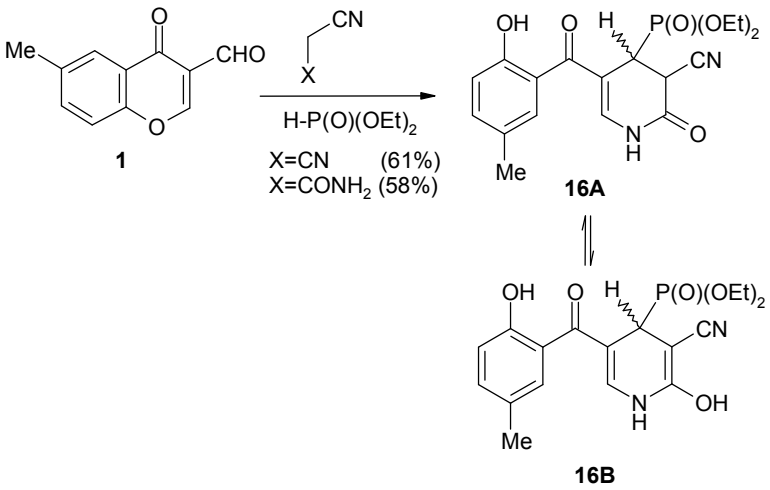
Furthermore, treatment of aldehyde **1** with ethanolamine, ethylenediamine, 2-aminophenol and 1,2-phenylenediamine in the presence of diethyl phosphite at 70−80 °C furnished the corresponding

phosphonate derivatives of seven-membered heterocycles **12**−**15**, respectively (Scheme 4).



Scheme 4

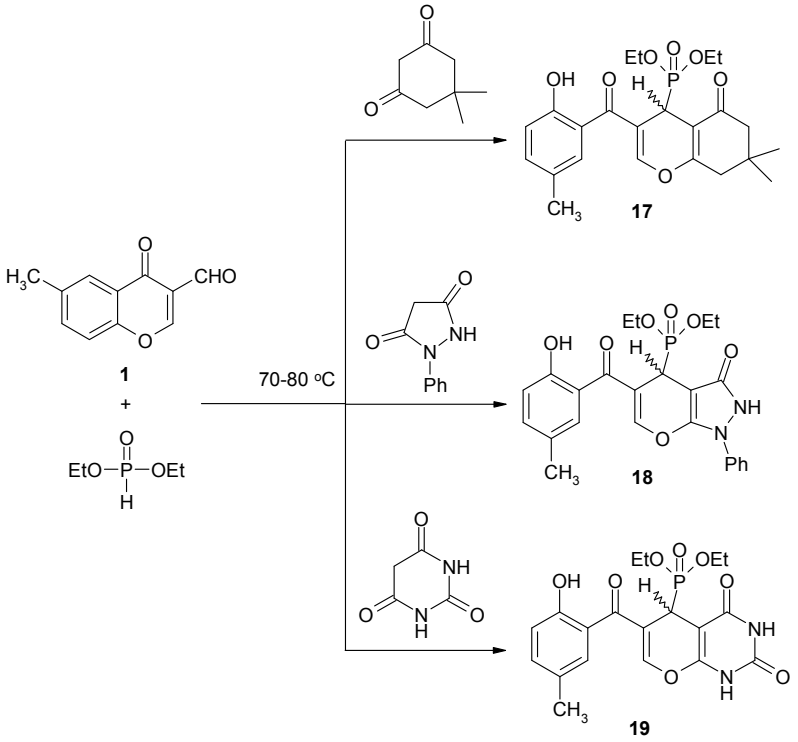
On the other hand, a simple fusion of 6-methyl-3-formyl-chromone (**1**) with malononitrile or cyanoacetamide in the presence of diethyl phosphite and few drops of triethylamine at 70−80 °C afforded the γ-pyridinyl phosphonate **16** in moderate yields (Scheme 5).



Scheme 5

Heating of 6-methyl-3-formylchromone (**1**) with dimedone, 1-phenylpyrazolidin-3,5-dione and barbituric acid in the presence of

diethyl phosphite and few drops of triethylamine at 70−80 ^{o}C afforded the γ-pyranyl phosphonates **17**−**19**, respectively (Scheme 6).



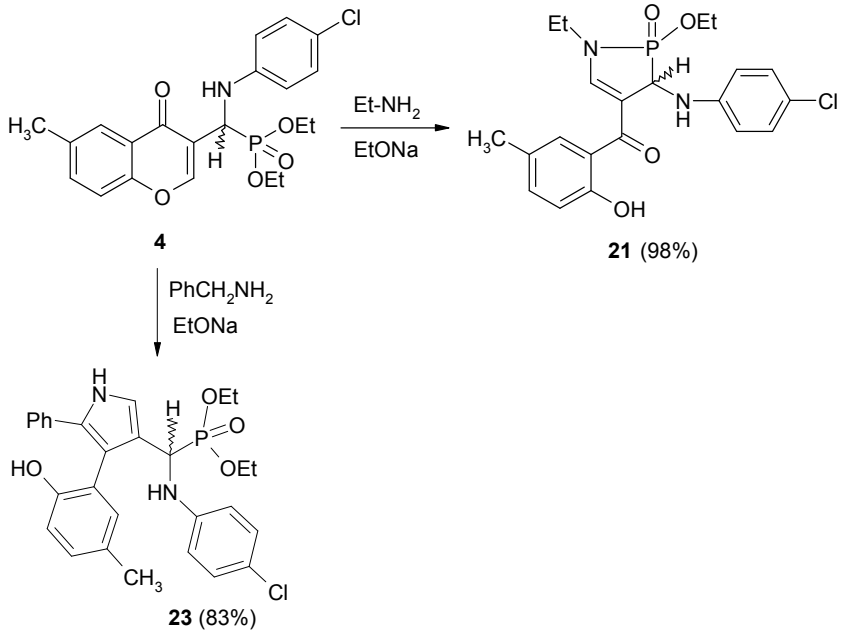
Scheme 6

<u>Part II:</u> Cleavage of chromonyl α-aminophosphonate with nitrogen and carbon nucleophiles: a synthetic approach and biological evaluations of a series of novel azoles, azines and azepines containing α-aminophosphonate and phosphonate groups

The chemical reactivity of diethyl [(4-chlorophenylamino)(6-methyl-4-oxo-4*H*-chromen-3-yl)methyl]phosphonate (**4**) towards some nitrogen and carbon *mono*- and *bi*-nucleophiles in ethanolic sodium ethoxide was investigated.

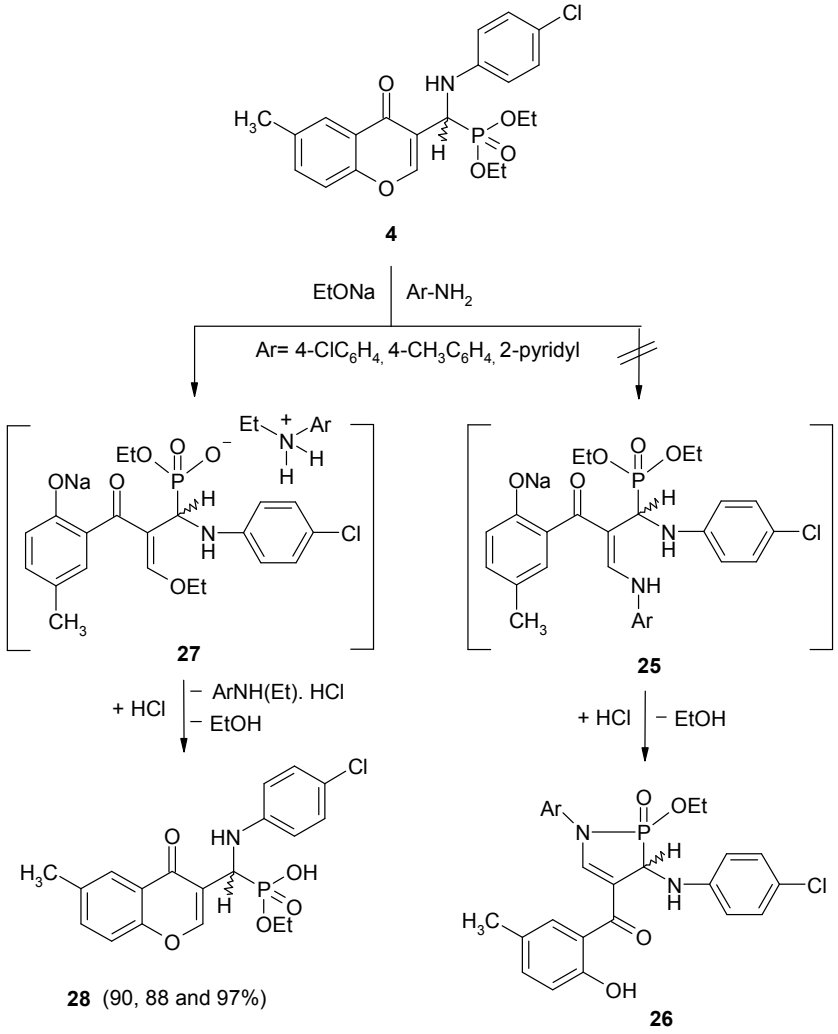
At first, reaction of compound **4** with ethylamine in ethanolic sodium ethoxide under reflux gave 3-(4-chlorophenylamino)-2-ethoxy-1-ethyl-4-[(2-hydroxy-5-methyl phenyl)carbonyl]-2-oxido-2,3-dihydro-1*H*-1,2-azaphosphole (**21**) as cyclic α-aminophosphonate

(Scheme 7). While, treatment of compound **4** with benzylamine under the same basic reaction conditions gave the pyrrolyl α-amino-phosphonate **23** (Scheme 7).



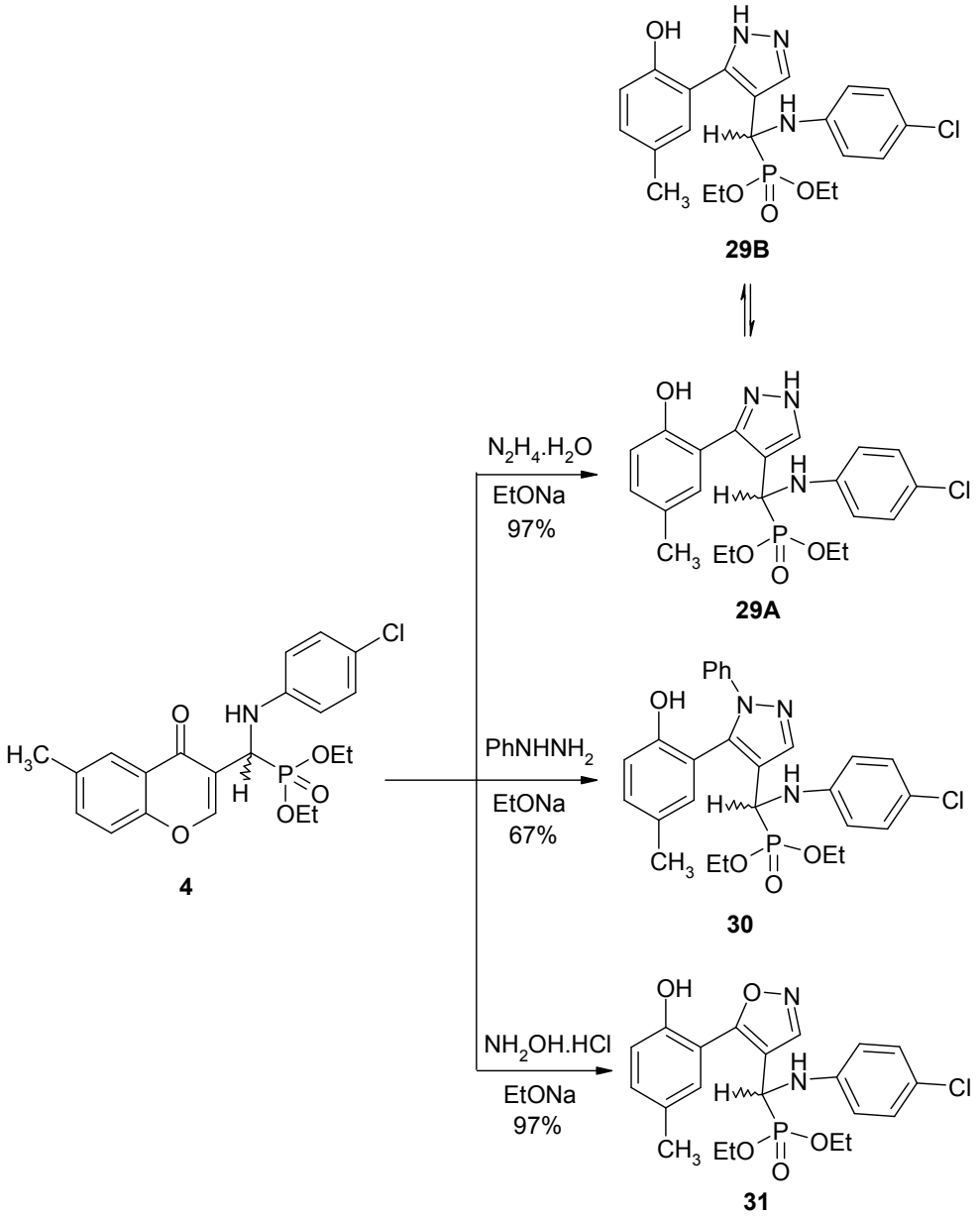
Scheme 7

Analogous reactions of the chromonyl α-aminophosphonate **4** with aromatic amines did not lead to construction of products which are similar to that formed in case of aliphatic amines. However, all the used aromatic amines gave only one product identified with mono ethyl {(4-chlorophenylamino)(6-methyl-4-oxo-4*H*-chromen-3-yl)methyl}phosphonate (**28**) in high yields (Scheme 8).



Scheme 8

When compound **4** was treated with hydrazine hydrate in ethanolic sodium ethoxide under reflux afforded the corresponding pyrazolyl α-aminophosphonates **29A**,**B** (Scheme 9). Similarly, treatment of compound **4** with phenyl hydrazine and hydroxylamine hydrochloride under the same basic reaction conditions gave the corresponding pyrazolyl α-aminophosphonate **30** and isoxazolyl α-aminophosphonate **31**, respectively (Scheme 9).



Scheme 9

Also, the chromonyl α-aminophosphonate **4** was reacted with thiourea, guanidinium carbonate and cyanoguanidine as 1,3-*bi*-nucleophiles in ethanolic sodium ethoxide to yield the corresponding pyrimidinyl α-aminophosphonates **32**−**34**, respectively (Scheme 10).