Synthesis of Biologically Active α-Aminophosphonates

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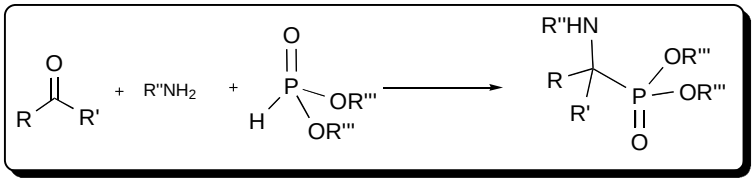
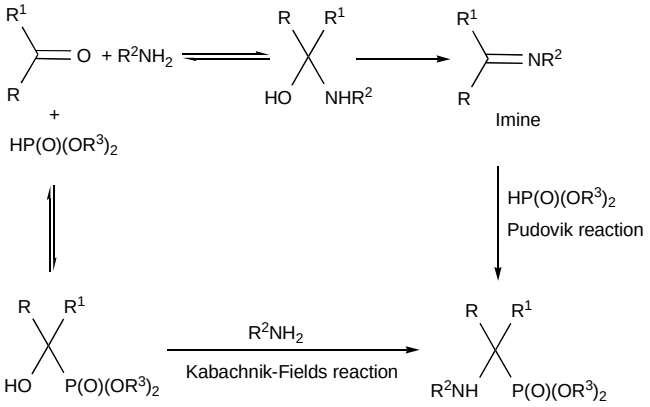
Abstract: Highly convergent Synthesis of α-aminophosphonates were most conveniently achieved using organophosphorus chemistry. Synthesis of α-aminophosphonates were accomplished by three-component coupling of carbonyl, amine and hydrophosphoryl compounds. These aminophosphonates exhibited promising antimicrobial, antioxidant and anticancer activity. Some recent developments and applications to the synthesis of biologically active α-aminophosphonates are also included.



Keywords: α-Aminophosphonates, antimicrobial activity, antioxidant activity, anticancer activity.

INTRODUCTION

α-Aminophosphonates have been the focus of attention in recent years because of their structural analogy to the corresponding α-aminoacids as well as heterocyclic phosphonates [1] and ω-aminophosphonates [2], which have found a wide range of applications in agricultural and medicinal chemistry [3-6]. Some phosphonates exhibit antifungal [7], antibacterial [8] and anticancer activity [9]. In addition, α-aminophosphonates have broad application due to their peptide mimics [10], antibiotics [11], herbicides [12], pharmacological agents [13] and enzyme inhibitors [14]. Hence, several approaches [15] have been developed for the synthesis of α-aminophosphonates. Two main pathways are: (i) Kabachnik–Fields three component reaction, in which a carbonyl, an amine and a di- or tri- alkylphosphite react in a single-pot, and, (ii) Pudovik reaction, where dialkylphos-phites are added to imines (Scheme **1**). In some reports, these reactions were carried out in straight-forward one-pot procedures without any catalysts [16, 17] while, in most cases, it was performed using catalysts, such as $LiClO_4$ [18, 19], $TaCl_5$-SiO_2 [20], $InCl_3$ [21], lanthanide triflate [22] and CF_3COOH [23]. The key step in this synthesis is the nucleophilic addition of amine to carbonyl compound followed by addition of a dialkyl (or) diaryl phosphite to the resulting imine.



Scheme 1:

SYNTHESIS AND BIOLOGICAL ACTIVITY

Schrader [24] proposed that organophosphorus compounds containing the general structure (**A**) may have significant biological activity. All organophosphorus compounds were inherently good phosphorylating agents of enzymes by virtue of the group P-XYZ in the general structure (**A**). Slight variation in the structure can have dramatic effects on the efficiency of bioactivity of organophosphorus compounds. These chemical and biological variable parameters, which were hard to estimate, were involved in deciding the structure-activity relationships of these compounds.

Kategaonkar *et al.* [25] have been Synthesized new substituted α-aminophosphonates **3a–i** *via* tetrazolo

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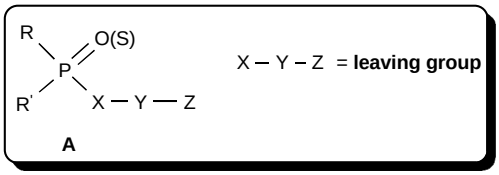


A

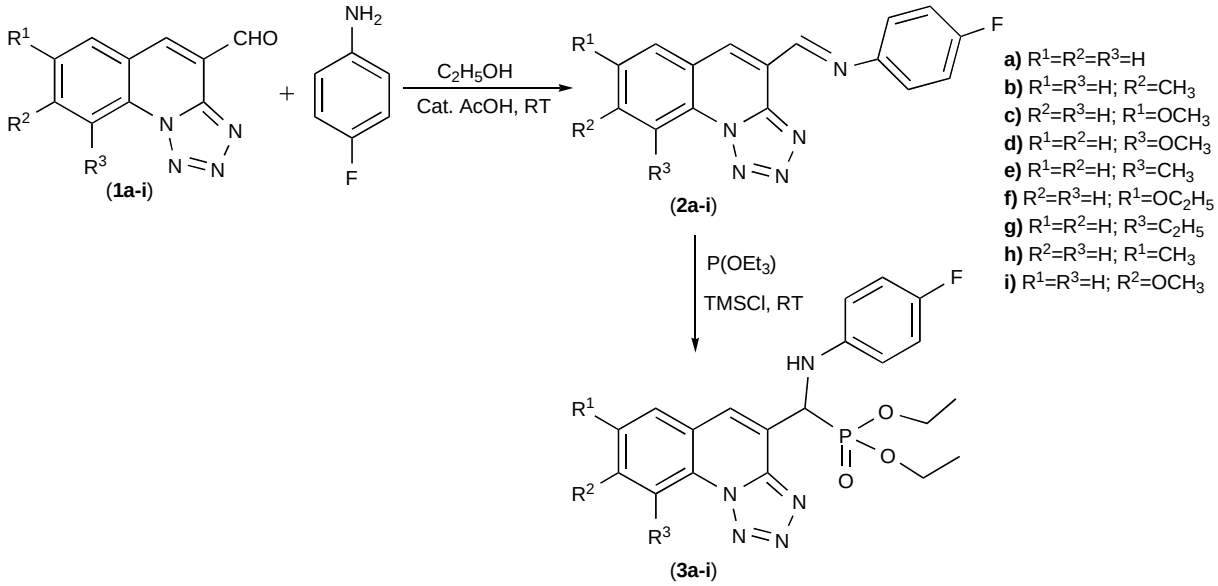
[1,5-a]quinoline derivatives (**1a–i**). The tetrazolo[1,5-a]quinoline imine derivatives (**2a–i**) were prepared by the reaction of tetrazolo[1,5-a]quinoline derivatives with 4-fluoroaniline in ethanol at room temperature using a catalytic amount of acetic acid. The synthesized imines (**2a–i)** were further treated with triethyl phosphite in the presence of TMSCl at room temperature to afford the compounds **3a–i** (Scheme **2**). The time required for this protocol was less than that reported in earlier methods on tetrazolo[1,5-a]quinoline moiety [26]. These α-aminophosphonate derivatives exhibited good to moderate antibacterial and antifungal activity [25].

Badadhe *et al.* [27] reported the synthesis and antibacterial activity of novel substituted *α*-amino-phosphonates. The 1-phenyl-3-(pyridine-4-yl)-1*H*-pyrazole-4-carbaldehyde (**4**) and different substituted anilines **5a–h** in ethanol in the presence of catalytic amount of glacial acetic acid afforded the corresponding imine derivatives **6a–h**. Further treatment with triethylphosphite in the presence of catalytic amount of concentrated HCl at room temperature, afforded the α-aminophosphonates **7a–h** (Scheme **3**). The compounds **7g** and **7h** showed excellent antibacterial activity against Gram-positive bacteria and the compound **7e** showed excellent activity against Gram-negative bacterial strains [27].

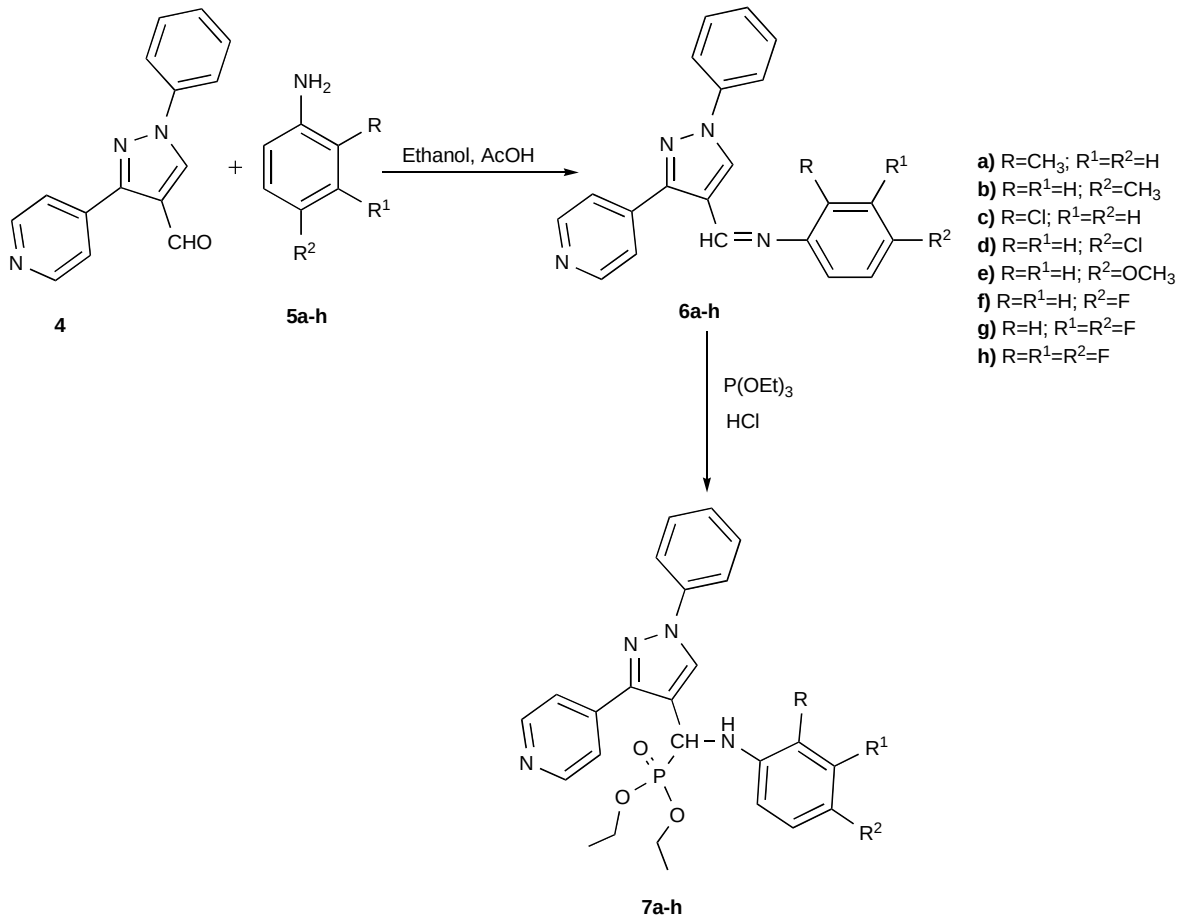
Abdel-Megeed *et al*. [28] developed a convenient method (Scheme **4**) for the synthesis of diphenyl 1-(arylamino)-1-(pyridin-3-yl)ethylphosphonates (**8**). These α-aminophosphonates were evaluated for antimicrobial activity [28] against the growth of Gram-positive, Gram-negative bacteria and fungi. All of them exhibited a remarkable inhibition at low concentration. The compounds showed significant cytotoxicity. Particularly, the liver cancer cell was more sensitive than the breast cancer cell for these compounds [28].

Nizamov *et al.* [29] have been synthesized *O*,*O*-diethyl *α*-(*N*-isobutylamino)-3,7-dimethylocta-2,6-dienylphosphonates (**10**) in two methods. Method A was the Kabachnik–Fields reaction of *E,Z*-citral (**9**) with diethyl phosphite in the presence of isobutylamine to form α-aminophosphonates (Scheme **5**). Method B was the Pudovik reaction of diethyl phosphite with *i*-butyl imines (**9a**) prepared on the basis of *E,Z*-citral with isobutylamine to obtain the same α-aminophosphonates (Scheme **6**). *O*,*O*-diethyl *α*-(*N*-amino)-3,7-dimethylocta-6-enylphosphonates (**12a,b**) were also synthesized [29] from isobutyl/isopropyl amine, diethyl phosphite and (*R,S*)-citronellal (**11**) (Scheme **7**). These α-aminophosphonate derivatives exhibited bacteriostatic activity [29] against *Staphylococcus aureus* and *Bacillus cereus*.

A new class of α-aminophosphonates (**14**) was synthesized [30] by the reaction of equimolar quantities of Schiff's bases (**13**) with diethyl/dimethyl/diphenyl phosphite using tetramethyl-guanidine (TMG) as a catalyst *via* Pudovik reaction (Scheme **8**). They were

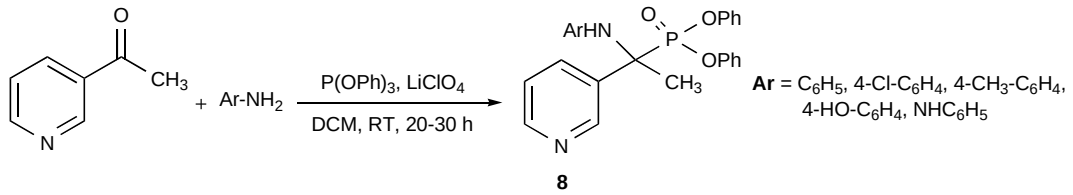


Scheme 2:



4 **5a-h** **6a-h** **7a-h**

Scheme 3:



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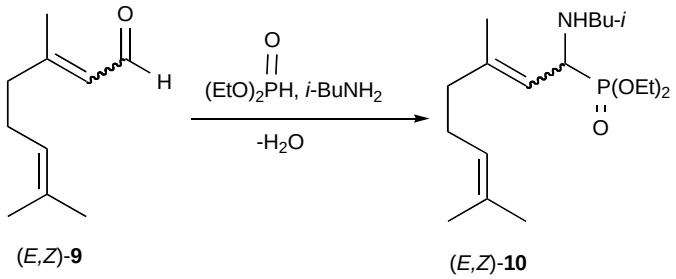
Scheme 4:

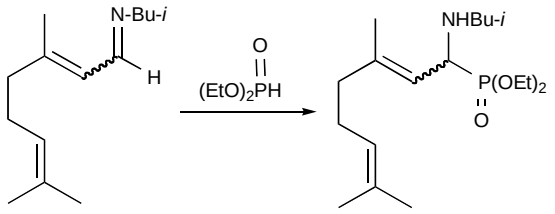


(*E,Z*)-**9** (*E,Z*)-**10**

Scheme 5: Synthesis of α-aminophosphonates (***E,Z*)-10** by the Kabachnik-Fields reaction.

found to possess significant antimicrobial and antioxidant activities [30].

A new series of α-aminophosphonate derivatives (**16**) containing bioactive Indazole moiety was synthesized in two steps [31] In the first step, imine of Indazole moiety (**15)** was synthesized and in the next step it was converted to α-aminophosphonates using chlorotrimethylsilane (TMSCl) and triethyl phosphite (Scheme **9**). Some of the synthesized derivatives were



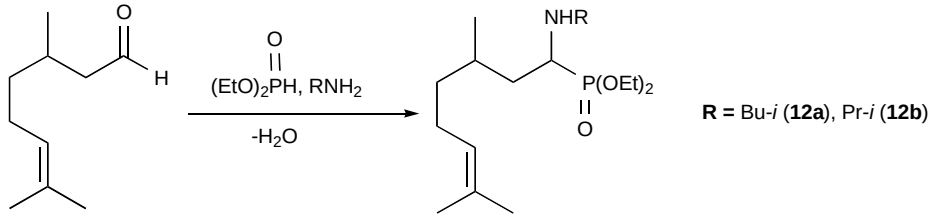
(*E,Z*)-**9a** (*E,Z*)-**10**

Scheme 6: Synthesis of α-aminophosphonates (***E,Z*)-10** by the Pudovik reaction.

evaluated for antibacterial activity, but the overall inhibiting the growth of bacteria was inferior as compared to the standard Gentamycin and Kinamycin drugs [31].

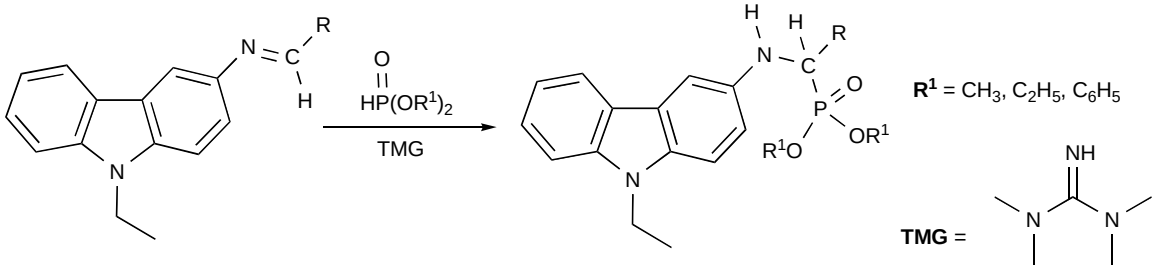
El-Barbary *et al.* [32] have synthesized new α-aminophosphonate derivatives (**18a-c**), by the reaction of 4-amino-6-methyl-3-thioxo-2,3-dihydro[1,2,4]triazin-5(4H)-one (**17**) with various aromatic aldehydes and triethylphosphite (Scheme **10**). Their antimicrobial activity was evaluated against Gram-positive and Gram-negative bacteria. Interestingly *Bacillus subtilis* showed good sensitivity to **18a**.

Prasad *et al.* [33] accomplished [(5-chloro-2-hydroxyphenylamino)-methyl]diethyl phosphonates (**20a-l**) by one pot reaction of equimolar quantities of 2-amino-4-chlorophenol (**19**), various aromatic aldehydes and diethylphosphite *via* Kabachnik-Fields reaction (Scheme **11**). They showed low antibacterial activity against selected bacteria, while compound **20a** exhibited significant antibacterial activity even at lower concentration against both Gram-positive and Gram-negative bacteria.



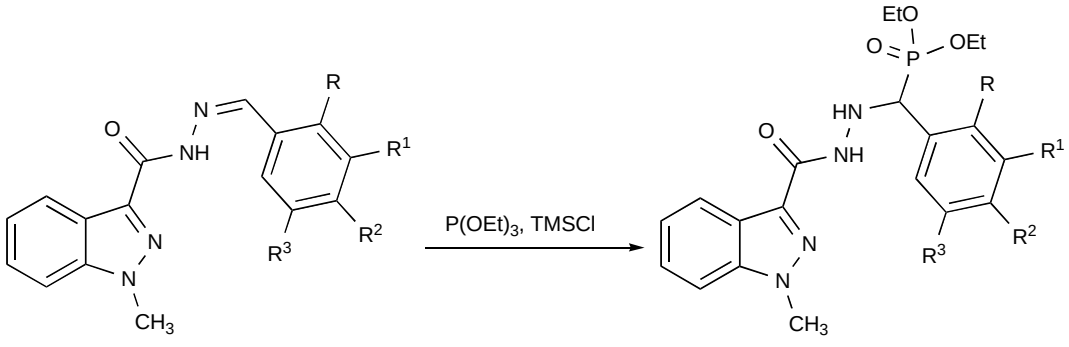
(*R,S*)-**11** **12a,b**

Scheme 7: Synthesis of α-aminophosphonates **12a,b** by the Kabachnik-Fields reaction.



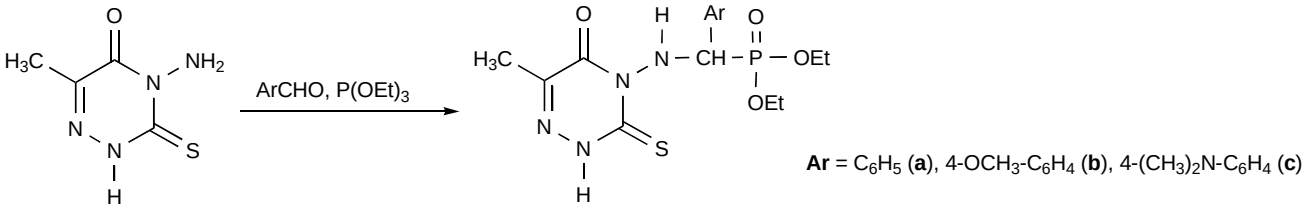
13 **14**

Scheme 8:



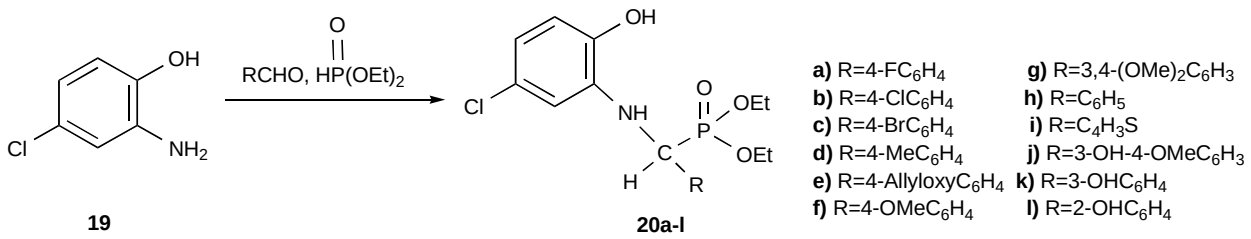
15 **16**

Scheme 9:



17 **18a-c**

Scheme 10:

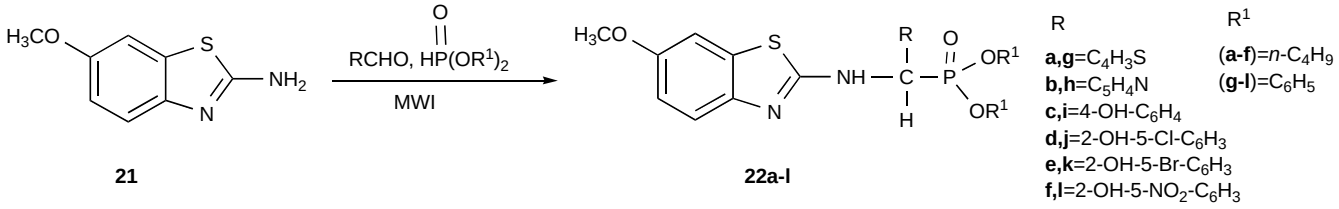


19 **20a-l**

Scheme 11:

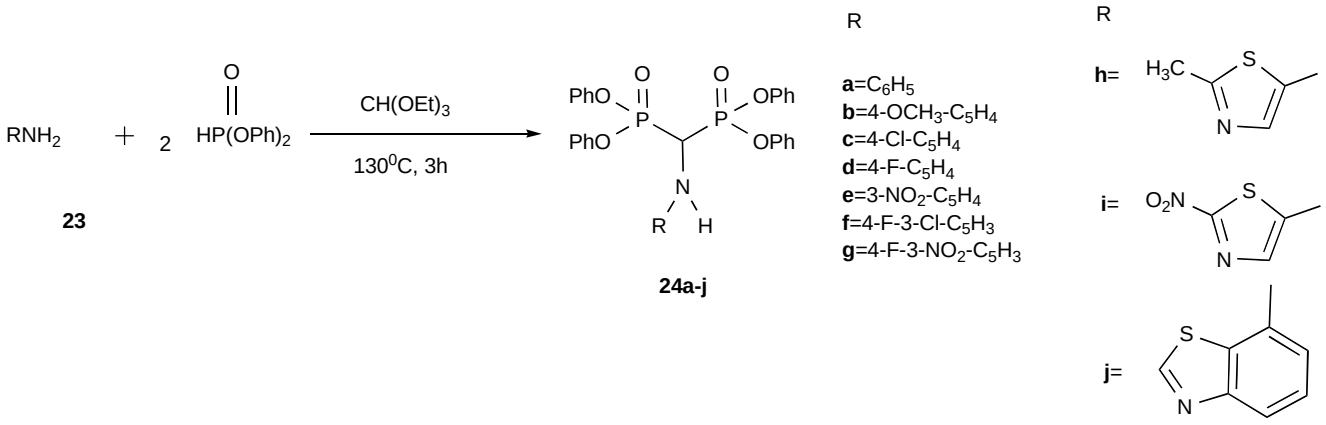
Rao *et al.* [34] reported the synthesis of various α-aminophosphonates (**22a-l**) by the reaction of 2-amino-6-methoxybenzothiazole (**21**), substituted aromatic/heterocyclic aldehydes and dibutyl/ diphenyl phosphites *via* Kabachnik-Fields reaction under microwave irradiation conditions (Scheme **12**). They showed promising antimicrobial, anti-oxidant activities depending on the nature of bioactive groups at the α-carbon.

A new series of novel tetraphenyl(phenylamino)-bisphosphonates (TPM-BPs) (**24a-j**) were synthesized [35] by one pot reaction of various amines (**23**), triethyl orthoformate and diphenyl phosphite (Scheme **13**). The antioxidant activity was evaluated by diphenyl picryl hydrazyl (DPPH), reducing power and lipid peroxidation (LPO) methods. Their inhibitory concentration (IC_{50}) varied according to substitution on the phenyl ring. Vitamin C was used as a standard for antioxidant activity. The scavenging activity of TMP-BPs against



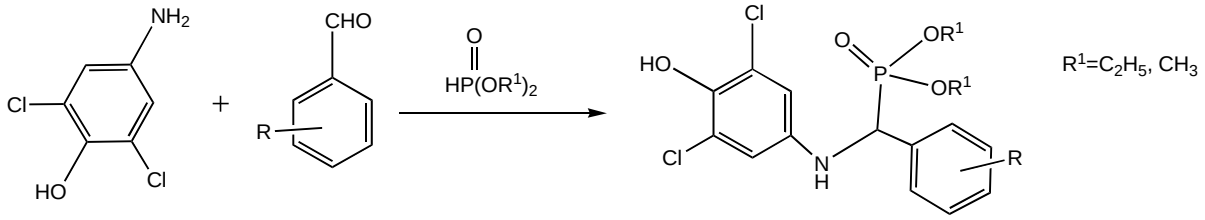
21 **22a-l**

Scheme 12:



23 **24a-j**

Scheme 13:



25 **26**

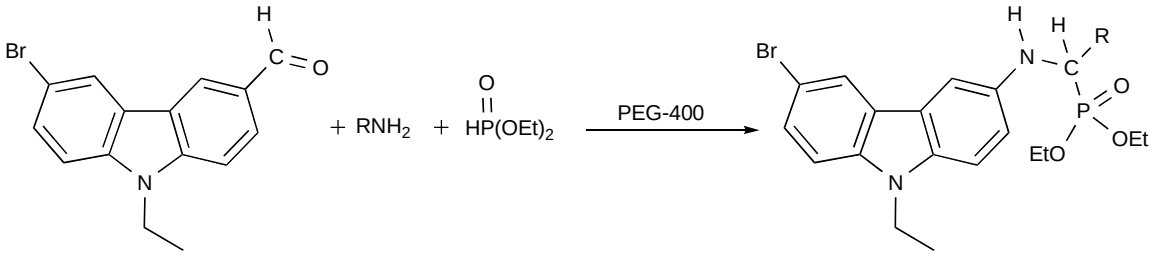
Scheme 14:

DPPH radical was measured adopting the method of Choi *et al*. [36] The tetraphenyl(4-fluoro-3-nitrophenylamino)-methylene bisphosphonate (**24g**) showed the highest antioxidant activity [35].

A simple, inexpensive and eco-friendly method (Scheme **14**) has been reported [37] for a three component reaction of 3,5-dichloro-4-hydroxy phenylamine (**25**), various aromatic aldehydes and diethyl/dimethyl phosphite in the presence of Amberlyst as a catalyst under microwave irradiation condition to afford the α-aminophosphonate derivatives (**26**). Their antioxidant activity against DPPH, nitric oxide (NO) scavenging and reducing power were also studied [37].

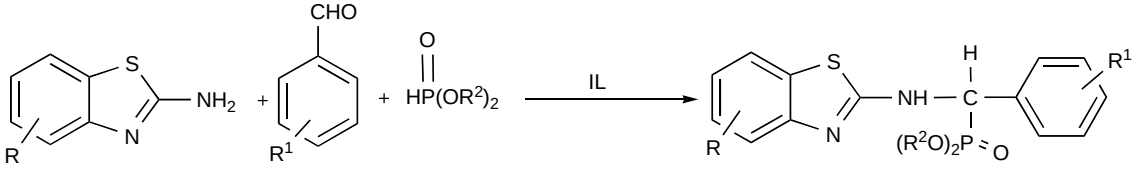
A novel series of carbazole containing α-aminophosphonate derivatives (**28**) was synthesized [38] by three component coupling of 6-bromo-9-ethyl-9*H*-carbazole-3-carbaldehyde (**27**), various aromatic amines and diethyl phosphite using polyethylene glycol (PEG-400) as a green reaction (Scheme **15**). The advantages of this method are simple and mild experimental conditions, avoiding hazardous solvents and toxic organic reagents. The antiproliferative activity of these molecules was evaluated against the cancer cell lines A549, MCF-7 and NCI-N87 [38].

The benzothiazole and fluorine containing α-aminophosphonates (**31a-m**) were synthesized [39] by the reaction of 2-amino-4-methylbenzothiazole/2-amino-6-methoxy-benzothiazole (**29**), 2-/4-fluoro/4-trifluorobenzaldehyde (**30**) and dialkyl phosphite in the presence of [bmim][PF_6] as an ionic liquid medium (IL) *via* Mannich-type addition (Scheme **16**). The



27 **28**

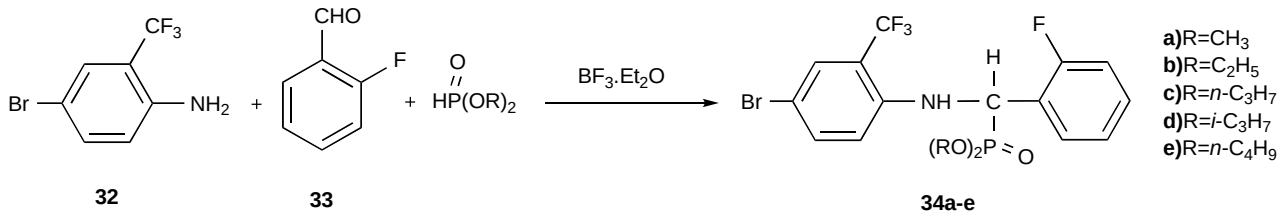
Scheme 15:



29 **30** **31a-m**

a)R=4-CH_3, R^1=2-F, R^2=C_2H_5; **b)**R=4-CH_3, R^1=2-F, R^2=*n*-C_3H_7; **c)**R=4-CH_3, R^1=2-F, R^2=*n*-C_4H_9
d)R=4-CH_3, R^1=4-CF_3, R^2=CH_3; **e)**R=4-CH_3, R^1= 4-CF_3, R^2=C_2H_5; **f)**R=4-CH_3, R^1=4-CF_3, R^2=*i*-C_3H_7
g)R=4-CH_3, R^1=4-CF_3, R^2=*n*-C_4H_9; **h)**R=6-OCH_3, R^1=2-F, R^2=CH_3; **i)**R=6-OCH_3, R^1=2-F, R^2=C_2H_5 **j)**R=6-OCH_3, R^1=2-F, R^2=*n*-C_3H_7; **k)**R=6-OCH_3, R^1=2-F, R^2=*i*-C_3H_7; **l)**R=6-OCH_3, R^1=2-F, R^2=*n*-C_4H_9
m)R=6-OCH_3, R^1=4-F, R^2=C_2H_5

Scheme 16:



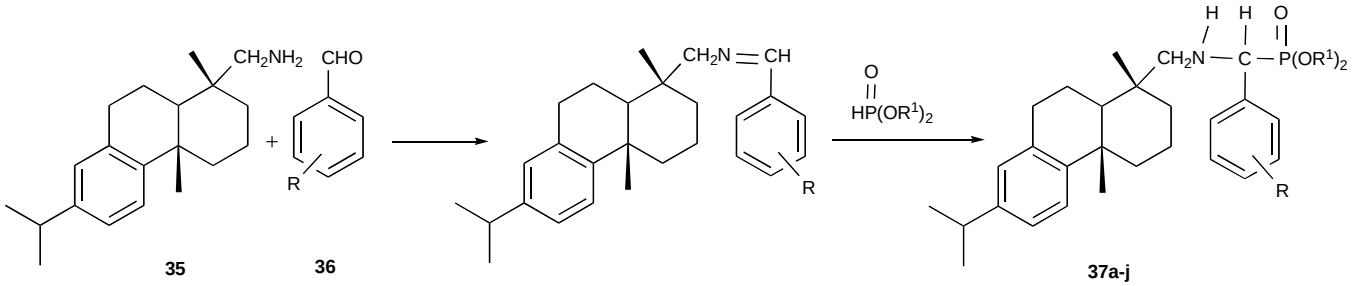
32 **33** **34a-e**

Scheme 17:

compounds were evaluated for their anticancer activity against the cancer cells PC3, A431, A375 and Bcap37 by the MTT method [39]. Usually, when a compound shows a inhibition rate more than 50% at 1 μM or more than 85% at 10 μM, it is considered to be strongly effective. Accordingly compound **31c** was found to have strong activity against PC3 cells and moderate to A431.

An efficient procedure was adopted for the preparation of *N*-(4-bromo-2-trifluoromethylphenyl)-1-(2-fluoro-phenyl)-*O*,*O*-dialkyl-*α*-aminophosphonate derivatives [40] (**34a-e**) through three-component reaction of 2-trifluoromethyl-4-bromoaniline (**32**), *O*,*O*-dialkylphosphite and 2-fluoro-benzaldehyde (**33**) under ultrasonic irradiation, catalyzed by boron trifluoride diethyl ether *via* Mannich-type reaction (Scheme **17**). The antitumor activity of these compounds were assayed by the MTT method [41]. The antiproliferation activity of compound **34c** to PC3 cells at the concentration of 10 lM at 48 h and 72 h were 52.4% and 86.5%, respectively, which is relatively higher than the others.

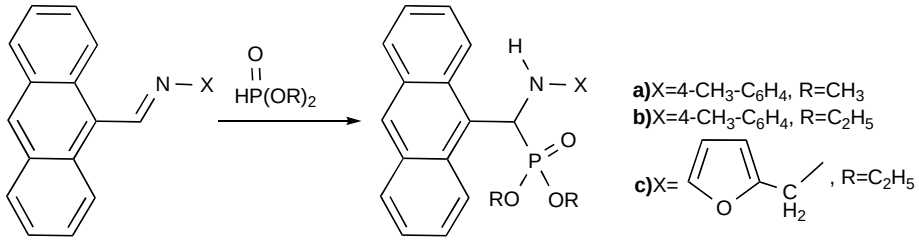
Rao *et al.* [42] reported the synthesis of novel α-aminophosphonates (**37a-j**). The natural product of diterpenic dehydroabietylamine (**35**) and substituted benzaldehydes (**36**) afforded imine derivatives [43], which were further treated with phosphite to afford the **37a-j** (Scheme **18**). Due to high steric hindrance from two reaction components the yields were relatively low (20% – 30%) for phenyl phosphonates, whereas ethyl phosphonates gave higher yields due to less steric hindrance than benzene [44]. Their antitumor activitiy against SMMC7721 liver cancer cells were evaluated by the MTT method [42]. Compounds **37d** and **37f** exhibited higher activities even at very low concentrations, and the inhibition ratios reached 75% and 79% at 0.1 μM, respectively. The inhibition ratio of compound **37i** reached 99% after 72 h incubation.



35 **36** **37a-j**

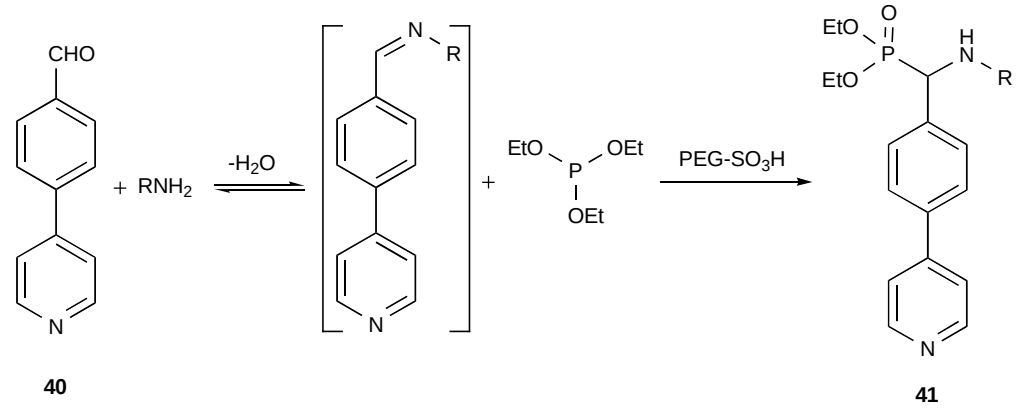
a)R=H, R^1=C_6H_5; **b)**R=4-OCH_3, R^1=C_6H_5; **c)**R=4-Cl, R^1=C_6H_5; **d)**R=4-F, R^1=C_6H_5; **e)**R=3-F, R^1= C_6H_5; **f)**R=4-CF_3, R^1=C_6H_5; **g)**R=2-OH, 4-NO_2, R^1=C_6H_5; **h)**R=2-OH, 4-Cl, R^1=C_6H_5; **i)**R=2-OH, 4-NO_2, R^1=C_2H_5; **j)**R=2-OH, 4-Cl, R^1=C_2H_5

Scheme 18:



38a,b **39a-c**

Scheme 19:

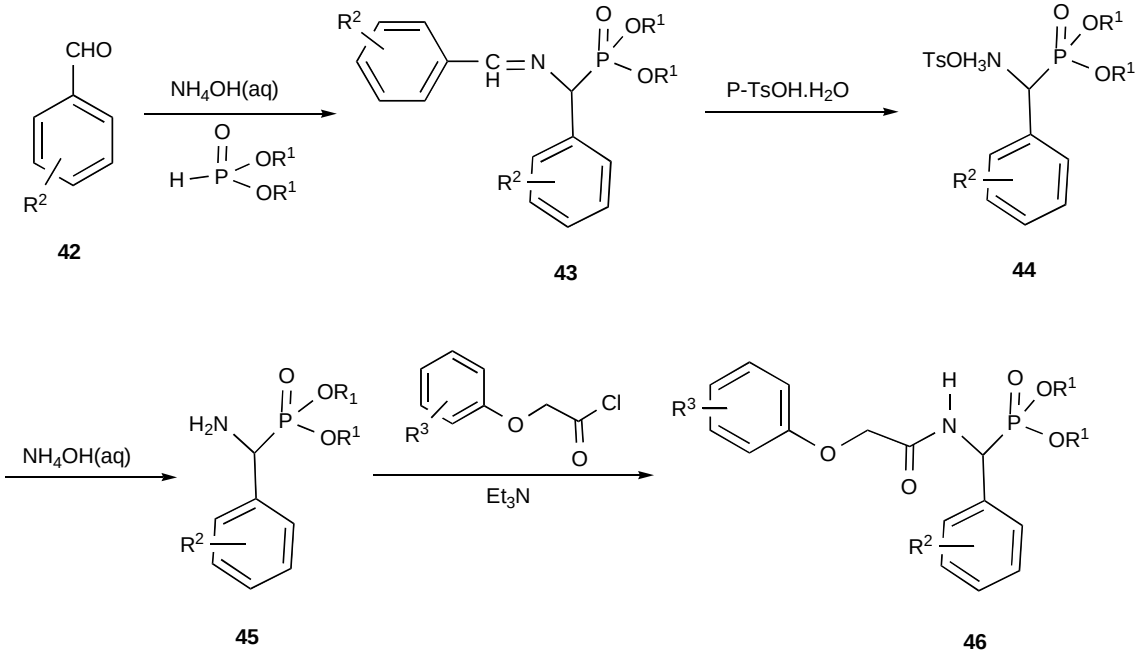


Scheme 20:

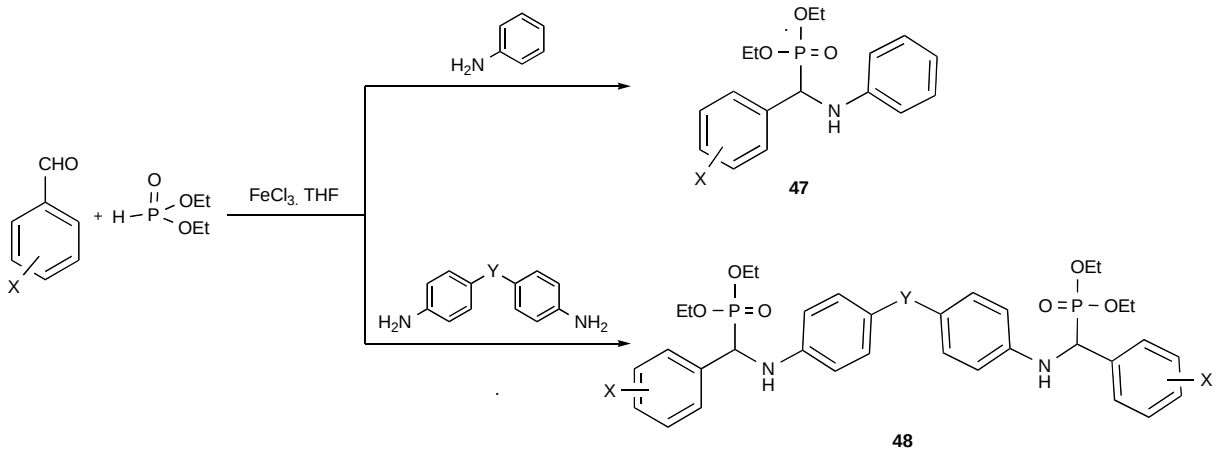
Kraicheva *et al.* [45] reported the synthesis of novel anthracene-containing α-aminophosphonates, [*N*-methyl(dimethoxyphosphonyl)-1-(9-anthryl)]-*p*-toluidine (**39a**), [*N*-methyl(diethoxy- phosphonyl)-1-(9-anthryl)]-*p*-toluidine (**39b**) and [*N*-methyl (diethoxyphos-phonyl)-1-(9-anthryl)]furfurylamine (**39c**). The reaction of 9-anthracenecarboxaldehyde and *p*-toluidine/ furfurylamine afforded imine derivatives **38a,b**. Further treatment with phosphite, afforded the α-aminophosphonates **39a-c** (Scheme **19**). The aminophosphonates and their precursors were evaluated for *in vitro* antitumor activity on a panel of human epithelial cancer cell lines [45].

Reddy *et al.* [46] reported one-pot three-component PEG-SO_3H catalyzed reaction of 4-(Pyridin-4-yl)benzaldehyde (**40**) and various primary amines with triethyl phosphite to give α-aminophos-phonate derivatives **41** (Scheme **20**). The advantages of this method are mild reaction conditions, use of eco-friendly reusable catalyst, easy workup and high product yields. Being an effective and green procedure, this may be the method of choice for commercial production of α-aminophosphonates. They showed moderate antitumor activity [46] on human chronic myeloid leukemia cells (K 562), human colon carcinoma cells (Colo 205) along with non cancerous human embryonic kidney cells (HEK 293).

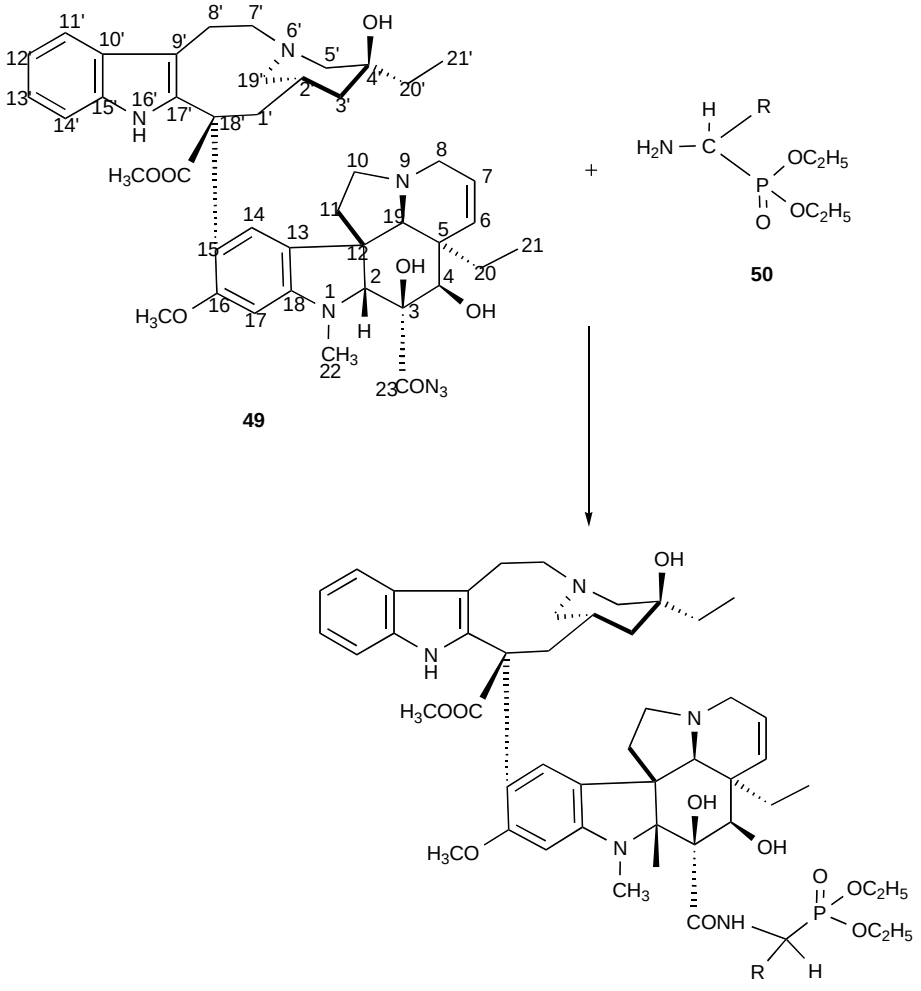
A new series of *O*,*O'*-dialkyl{[2-(substituted phenoxy)acetamido](substituted phenyl)methyl} phosphonates **46** was synthesized by Ning *et al.* [47] *via* the reaction of functionalized α-aminophosphonates **45** with various substituted phenoxyacetic chloride

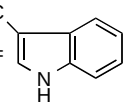


Scheme 21:



Scheme 22:



a)R= H; **b)**[a] & **c)**[b]R=  ; **d)**[c], **e)**[a] & **f)**[b] R= CH_3; **g)**[c], **h)**[a] & **i)**[b] R= $(CH_3)_2CH$; **j)**[c], **k)**[d] & **l)**[d] R= Ph-CH_2;

m)[c], **n)**[d] & **o)**[d] R= CH_2=CH-CH_2; **p)**[c] R= $CH_3(CH_2)CH_2$; **q)**[c] R= $CH_2COOC_2H_5$; **r)**[c] R= $(CH_3)_2CH$-CH_2

[a]*l*-Isomer, [b]*d*-Isomer, [c]*dl*-Isomer, [d]Epimeric mixtures of **51j** and **51m**

Scheme 23:

(Scheme **21**). The **45** was afforded as per the reported procedure [47] The **46** were evaluated for cytotoxic activity [47] against various human tumor cell lines, some of which showed relatively high cytotoxicity.

Rezaei *et al.* [48] reported the $FeCl_3$.THF solution catalyzed highly efficient preparation of α-aminophosphonates **47** *via* a three-component system composing of aldehydes, amines and diethylphosphite (Scheme **22**). This protocol was also applied to the one-pot preparation of bis(α-aminophosphonates) **48** (Scheme **22**). The advantage of this method is eco-friendly mild reaction conditions and to form α-aminophosphonates in high yields. Some were found to have cytotoxic activity on the cell lines RAJI, JURKAT and MCF-7. An indole derived bis(α-aminophosphonates) showed maximum cytotoxic effect [48] comparable to doxorubicin.

A new series of vinblastine (VLB) alkaloid aminophosphonates (**51a-r)** was synthesized by Lavielle and co-workers [49] (Scheme **23**), and tested *in vitro* and *in vivo* for antitumor activity. They (**51a-r**) were prepared by coupling O^4-deacetyl-VLB azide (**49**) to appropriate α-aminophosphonates **50**. The procedure for the preparation of the azide **49** from VLB was based on that of Barnett *et al.* [50] and Rao *et al.* [51] All the compounds (**51a-r**) were capable of inhibiting tubulin polymerization *in vitro*. In these compounds, the antitumor activity strongly depended on the stereochemistry of the phosphonate. The phosphonate (1*S*)-[1-[[[O^4-deacetyl-3-de(methoxy-carbonyl)vincaleukoblastin-3-yl]carbonyl]amino]-2-methylpropyl] phosphonic acid diethyl ester (**51i**) exhibited a remarkable activity [49, 52] against cancer cell lines.

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