

Facile formation of phosphono-acridanes *via* chloroacridines

Venu Srinivas and K. C. Kumara Swamy*

School of Chemistry, University of Hyderabad, Hyderabad-500046, A. P., India

E-mail: kckssc@yahoo.com, kckssc@uohyd.ernet.in

Abstract

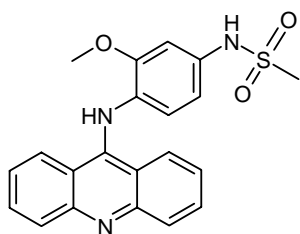
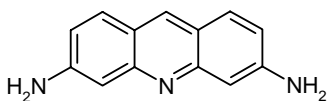
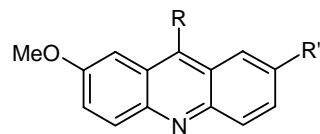
Novel bis-phosphonates bearing an acridane moiety are readily synthesized by the simple reaction of appropriate 9-chloroacridines with phosphites of the type $(RO)_2P(O)H$. The by-product acridones could be converted back to the chloroacridines by treating them with thionyl chloride, and thus the effective yield is high. The structures of three bis-phosphonates are confirmed by X-Ray crystallography.

Keywords: Bis-phosphonates, acridine, acridones, phosphorylation, X-ray structure

Introduction

Acridine derivatives have numerous applications¹ that include biological fluorescent/chemiluminiscent probes^{2,3} as well as anti-tumor,⁴ anti-bacterial,⁵ anti-HIV,⁶ antimalarial,⁷ and DNA-binding agents.⁸ Amsacrine [*N*-(4-(acridin-9-ylamino)-3-methoxyphenyl)-methanesulfonamide, **1**] is a drug used in acute *lymphoblastic leukemia*. Proflavine (3,6-acridinediamine, **2**), used effectively during World War II for deep wound dressing, has been studied extensively as a novel RNA-targeted antiviral drug and as an intercalator in cancer treatments. It has been the CAS molecule of the week (September 2005). Recently, some mono-, bis-, and tetra-acridines have also shown *in vitro* anti-parasitic activity against *Leishmania infantum* (e.g., **3**).⁹

We have been interested in organophosphonates,¹⁰ and in this context wanted to prepare phosphono-substituted acridines for possible future drug-related applications. As precursors, we chose 9-chloroacridines. Since the addition of P-H bond to aryl halides is an important reaction for the preparation of organophosphorus compounds,¹¹ and bis-phosphonates are clinically the most important class of anti-resorptive agents available to treat diseases characterized by osteoclast-mediated bone resorption such as osteoporosis, Paget's disease, and tumor-associated bone diseases,¹² we became more interested in this aspect. The results of our studies are reported herein.

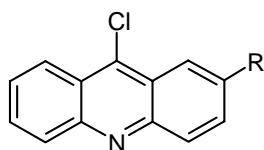
**1** (Amsacrine)**2** (Proflavine)**3** (Antiproliferative)

Results and Discussion

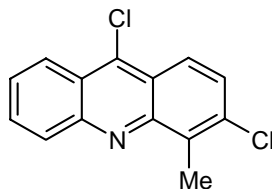
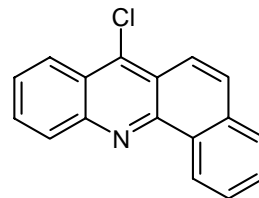
Treatment of anthranilic acids with phosphorus oxychloride (POCl_3) at $130\text{ }^\circ\text{C}$ for 2-4 h¹³ afforded the corresponding substituted 9-chloroacridines **4–7**. Compounds **8**, **9** were also synthesized in a similar manner. Among these, **6–9** are new. When these 9-chloroacridines **4–9** were treated with the cyclic phosphite **10** under neat conditions at $90\text{ }^\circ\text{C}$ for 2-4 h, the bis-phosphonates **11–16** were formed along with the corresponding acridones (Scheme 1). Although the yield of the compounds is only moderate (reaction mixture, single phosphonate product, yield in the reaction mixtures 50–60%; isolated yield of pure compounds 15–30%) the formation of these compounds represents a new type of phosphonylation and is thus unprecedented.

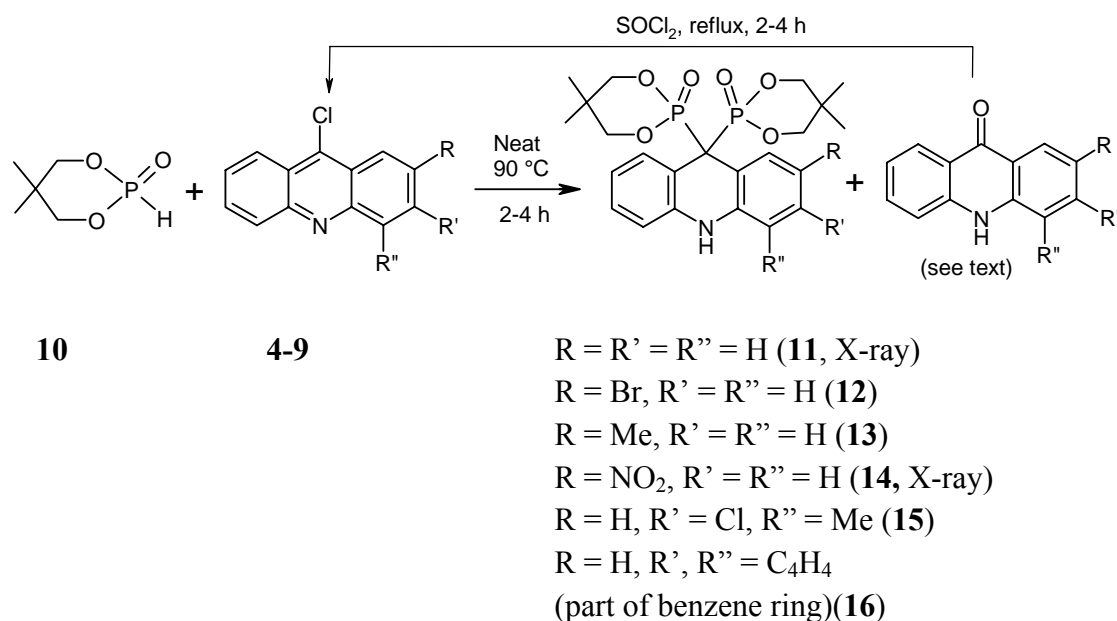
We have made an attempt to increase the yield by changing the reaction conditions; however, we always ended up in having acridone (30–40%) by-product, probably because of a competing $-\text{OH}$ to $-\text{Cl}$ exchange between chloro-acridine and phosphite. However, this problem could be circumvented since the acridones formed were readily converted back to the chloroacridines by simple treatment with thionyl chloride.¹⁴ Isolation of **11–16** is also fairly straightforward.

An analogous reaction of **4** with diethyl phosphite afforded the corresponding bis-phosphonate **17**.¹⁵ Only one phosphonate product is generally formed. Considering that the by-product acridone could be converted quantitatively into the corresponding chloroacridines, the effective yield is very good. Use of different solvents (THF and toluene) did not alter the yield significantly. Employing more than two mole equivalents of phosphite **10** did not significantly alter the yields, and even the use of less than one mole equivalent of **10** led mostly to the bis-phosphonate as the only solid phosphorus product (^{31}P NMR). However, by using a lower stoichiometry of phosphite **10** in its reaction with chloro-acridine **5**, the mono-phosphonate **18** could be isolated.

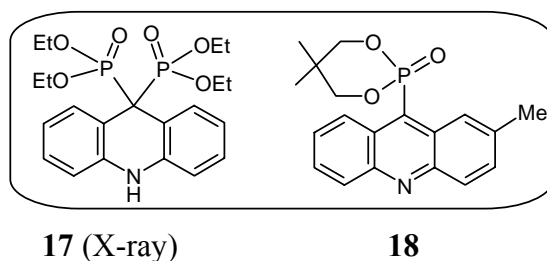


R = H (**4**), Me (**5**),
Br (**6**), NO_2 (**7**)

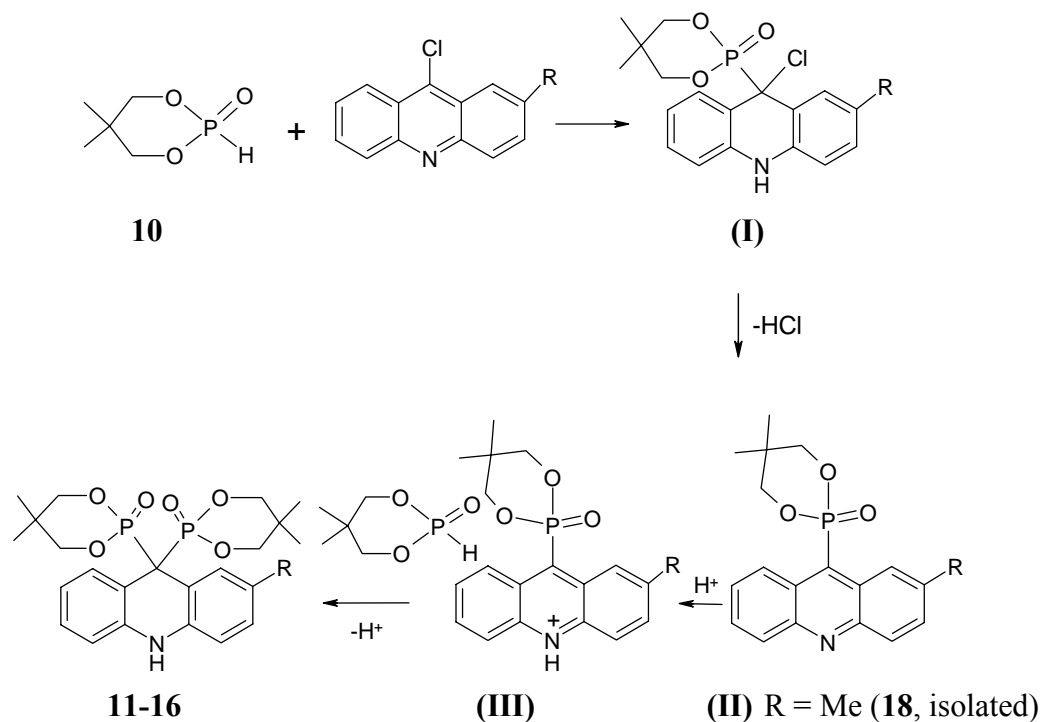
**8****9**



Scheme 1



A possible pathway for the formation is shown in Scheme 2. The monophosphonate of type **I** could undergo elimination of a molecule of HCl to afford the 9-phosphono-acridine **II**. Since the nitrogen site is basic, it can take up the available proton from the acid to lead to a species like **III**, in which the double bond attached to the phosphonate group is activated to accept a second phosphonate entity to lead to the bis-phosphonates **11-16**. It is also possible that species **I** can simply reorganize to the amine salt **III** with chloride as the counter-ion, prior to the addition of the second molecule of **10**. Evidence for the involvement of **II** comes from the fact that we could isolate the mono-phosphonate **18**, albeit in modest yields. These reactions differ from the nucleophilic substitution reactions of these chloroacridines that lead to monosubstituted products.¹⁶



Scheme 2. Plausible reaction mechanism for the formation of bis-phosphonate.

A brief discussion of the X-ray structures of **11**.CH₃CN, **14**.OC₄H₈ and **17**

The ORTEP drawings of **11**.CH₃CN, **14**.OC₄H₈ and **17** are shown in Figure 1. The P–C distances are in the expected range for P–C single bonds^{10a-c,17} although marginal variations are found in the three structures (**11**, **14** and **17**). There is clear-cut hydrogen-bonding interaction between the NH of the acridane residue and one of the P=O groups of the phosphonate group in all the three compounds. This is exhibited by the formation of dimeric units in **11**.CH₃CN and **14**.OC₄H₈. However, in the ethyl compound **17** the preference is in favor of a hydrogen-bonded chain rather than dimer formation. Interestingly, compound **11**.CH₃CN crystallizes in the trigonal space group R-3 which appears to be a manifestation of additional C–H...O hydrogen bonding interactions between the three protons of the solvent acetonitrile and an oxygen atom of 1,3,2-dioxaphosphorinane of the ring as shown in Figure 2. We have observed before the involvement of acetonitrile hydrogen atoms in C–H...O interactions.¹⁸

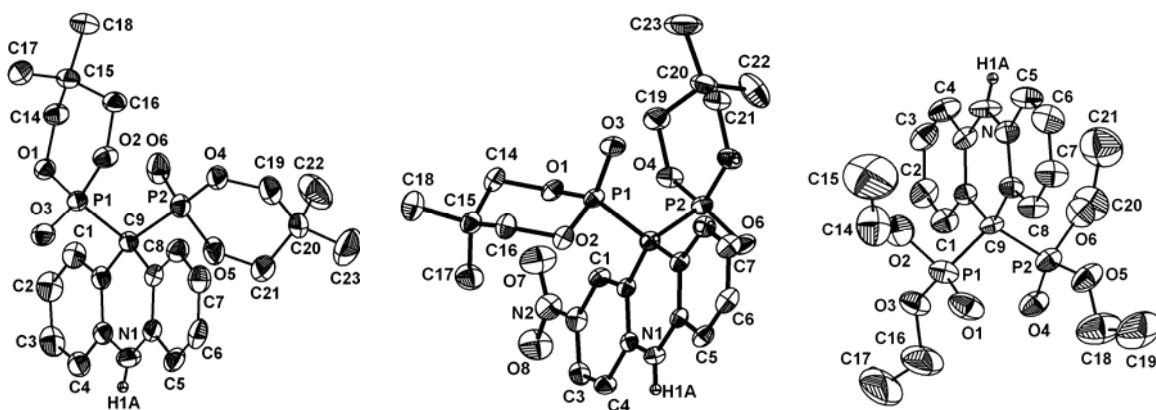


Figure 1. ORTEP diagrams of compounds **11**. CH₃CN (left, solvent molecule not shown), **14**.OC₄H₈ (middle, solvent molecule not shown) and **17** (right). Selected P-C distances (Å): Compound **11**. CH₃CN: P(1)-C(9) 1.851(5), P(2)-C(9) 1.853(5). Compound **14**. OC₄H₈: P(1)-C(9) 1.829(5), P(2)-C(9) 1.848(5). Compound **17**: P(1)-C(9) 1.864(5), P(2)-C(9) 1.849(5).

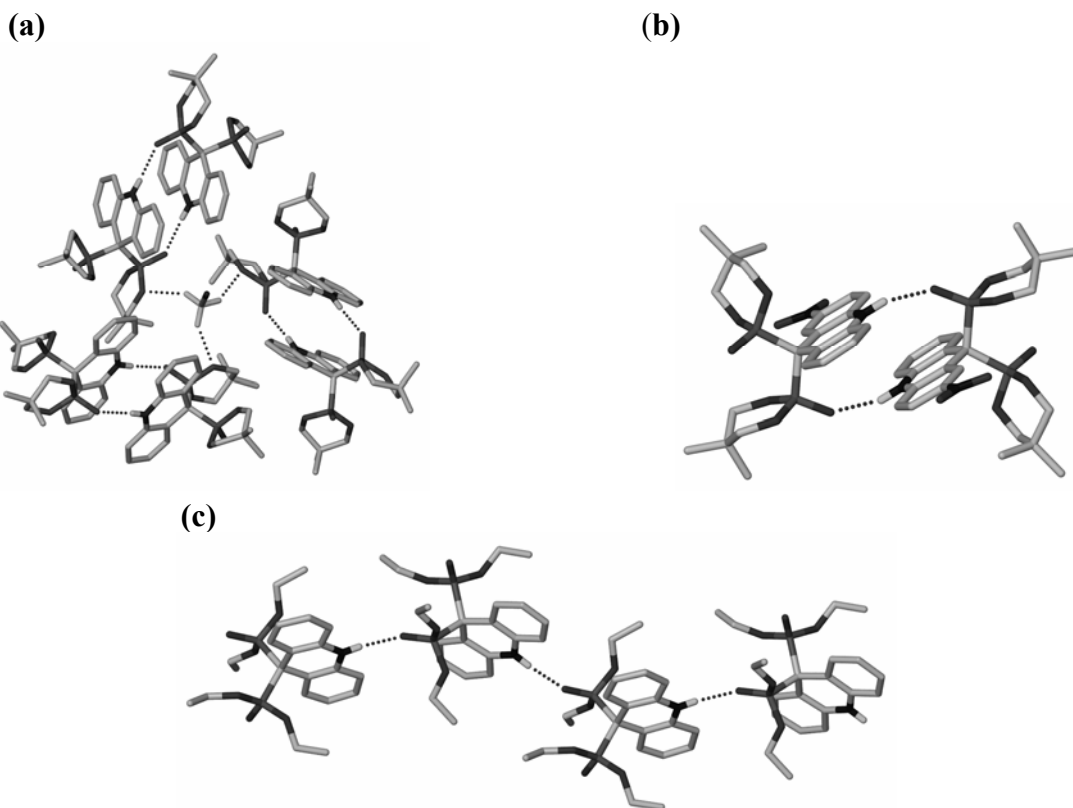


Figure 2. Drawings showing hydrogen- bonding interactions in (a) **11**.CH₃CN, (b) **14**.OC₄H₈, and (c) **17**. Hydrogen- bonding interactions: Compound **11**.CH₃CN (Å, °): N(1)-H(1A)...O(3') 0.77(4), 2.18(4), 2.952(7), 176(4); C(25)-H(25A)...O(2) 1.07(7), 2.41(8), 3.361(8), 147(6). Symm. Equiv.: 5/3-x, 4/3-y, 1/3-z. Compound **14**.OC₄H₈ N(1)-H(1A)...O(6') 0.86, 1.99, 2.820(6), 162.5. Symm. Equiv.: 2-x, 1-y, -z. Compound **17** N-H(1A)...O(4') 0.78(5), 2.18(5), 2.910(6), 155(5). Symm. Equiv.: 2-x, 0.5+y, -z.

The cytotoxicity (IC_{50} in μM) for compound **13** with cell lines Hep G2 and HeLa was found to be 150 and 79, respectively.¹⁹ These data suggest that our compounds are fairly active, and efforts are under way to obtain the corresponding diphosphonic acids and check their activity.

Conclusions

A novel and very simple synthesis of bis-phosphonate bearing an acridane component, *via* the reaction of chloro-acridines with phosphites of the type $(RO)_2P(O)H$, has been discovered. Since the by-product acridones can be converted back readily to the chloroacridines the overall yield is quite good. The preliminary cytotoxicity data for **13** appears to be encouraging.

Experimental Section

General. Chemicals were procured from Aldrich or local manufacturers and were purified when required.²⁰ 1H -, ^{13}C - and ^{31}P - NMR spectra (1H -400 MHz, ^{13}C -100 MHz and ^{31}P -162 MHz, respectively) were recorded using a BRUKER 400 MHz spectrometer in $CDCl_3$ (unless stated otherwise) with shifts referenced to $SiMe_4$ ($\delta = 0$) or 85 % H_3PO_4 ($\delta = 0$). IR spectra were recorded on a JASCO FT-IR 5300 spectrophotometer. Melting points were determined by using a local hot-stage melting point apparatus and are uncorrected. Elemental analyses were carried out on a Perkin-Elmer 240C CHN analyzer. Mass spectra were recorded using GCMS-QP2010 and LCMS-2010A instruments. *N*-phenylanthranilic acid derivatives were prepared according to a reported procedure.²¹ The cyclic phosphite **10** was prepared by a method previously reported from our laboratory.²²

(a) Synthesis of the substituted 9-chloroacridines 4–9

The appropriate anthranilic acid (6.7 mmol) was dissolved in $POCl_3$ (10 mL) and heated under reflux for 4 h. After cooling to room temperature, excess of $POCl_3$ was distilled off, and the mixture was added very carefully with vigorous stirring to a mixture containing crushed ice, aq. ammonia (10 mL) and chloroform (30 mL), making sure that the solution was always basic. The aqueous layer was extracted with chloroform (2 x 30 mL) and combined with the original organic layer, dried over anhyd. $CaCl_2$. The solvent was removed to yield the crude product. Analytically pure samples were obtained after flash-chromatography. Compounds **4–5** are known. Data for the new compounds **6–9** are given below.

9-Chloro-2-bromo-acridine (6). Yield: 1.38 g, 71%; mp 160-162 °C; brown solid; IR (KBr) 3123, 3088, 2980, 1636, 1595, 1524, 1466, 1346, 754 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.92 (t, 1 H, $J \sim 7.8$ Hz, Ar-*H*), 8.14-8.18 (m, 2 H, Ar-*H*), 8.60 (d, 1 H, $J = 8.8$ Hz, Ar-*H*), 8.76 (d, 1 H, $J = 1.5$ Hz, Ar-*H*), 8.93 (d, 1 H, $J \sim 9.0$ Hz, Ar-*H*), 8.98 (d, 1 H, $J \sim 9.0$ Hz, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.6, 124.5, 124.7, 125.0, 126.6, 127.7, 129.6, 131.1, 131.2, 134.5, 146.8, 148.6; LC-MS $m/z = 294$ $[M+1]^+$. Anal. Calcd for $C_{13}H_7BrClN$: C, 53.37; H, 2.41; N, 4.79. Found: C, 53.41; H, 2.41; N, 4.74%.

9-Chloro-2-nitro-acridine (7). Yield: 0.87 g, 50%; mp 172-174 °C; yellow solid; IR (KBr,) 3088, 2919, 2847, 1935, 1634, 1520, 1354, 764 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.63 (td, 1 H, *J* ~ 8.0 Hz, *J* ~ 2.0 Hz, Ar-*H*), 7.75 (~t, 1 H, *J* ~ 8.0 Hz, Ar-*H*), 8.25 (d, 1 H, *J* ~ 8.8 Hz, Ar-*H*), 8.33 (d, 1 H, *J* = 9.5 Hz, Ar-*H*), 8.47 (d, 1 H, *J* = 8.8 Hz, Ar-*H*), 8.48-8.52 (m, 1 H, Ar-*H*), 9.41 (d, 1 H, *J* = 2.0 Hz, Ar-*H*); ¹³C NMR (100 MHz, CDCl₃) δ 122.8, 123.7, 125.1, 128.5, 130.0, 131.9, 133.1, 145.1, 145.7, 149.2, 150.7; LC-MS *m/z* = 259 [M+1]⁺. Anal. Calcd for C₁₃H₇ClN₂O₂: C, 60.36; H, 2.73; N, 10.83. Found: C, 60.48; H, 2.69; N, 10.96%.

3,9-Dichloro-4-methylacridine (8). Yield: 1.30 g, 75%; mp 150-152 °C; light yellow solid; IR (KBr, cm⁻¹) 2966, 1601, 1549, 1520, 1454, 1395, 1314, 1009, 752; ¹H NMR (400 MHz, CDCl₃) δ 2.98 (s, 3 H, CH₃), 7.53 (d, 1 H, *J* = 9.3 Hz, Ar-*H*), 7.62 (~t, 1 H, *J* ~ 7.6 Hz, Ar-*H*), 7.78 (~t, 1 H, *J* ~ 7.6 Hz, Ar-*H*), 8.18 (d, 1 H, *J* = 9.3 Hz, Ar-*H*), 8.22 (d, 1 H, *J* = 8.8 Hz, Ar-*H*), 8.36 (d, 1 H, *J* = 8.8 Hz, Ar-*H*); ¹³C NMR (100 MHz, CDCl₃) δ 15.0, 122.7, 123.0, 123.8, 124.5, 127.1, 128.5, 130.4, 130.5, 134.9, 135.5, 144.2, 148.3, 148.5. Anal. Calcd for C₁₄H₉Cl₂N: C, 64.15; H, 3.46; N, 5.34. Found: C, 64.22; H, 3.47; N, 5.24%.

7-Chloro-benzo[*c*]acridine (9). Yield: 1.17 g, 60%; mp 144-146 °C; light yellow solid; IR (KBr, cm⁻¹) 3036, 1624, 1557, 1493, 1470, 1393, 1304, 1238, 742; ¹H NMR (400 MHz, CDCl₃) δ 7.70 (~t, 1 H, *J* ~ 8.0 Hz, Ar-*H*), 7.75-7.82 (m, 3 H, Ar-*H*), 7.85-7.90 (m, 2 H, Ar-*H*), 8.21 (d, 1 H, *J* = 9.3 Hz, Ar-*H*), 8.40 (d, 1 H, *J* = 8.6 Hz, Ar-*H*), 8.46 (d, 1 H, *J* = 8.6 Hz, Ar-*H*), 9.50 (d, 1 H, *J* = 7.9 Hz, Ar-*H*); ¹³C NMR (100 MHz, CDCl₃) δ 121.8, 122.7, 124.5, 124.9, 125.7, 127.0, 127.7, 128.0, 129.1, 129.5, 130.1, 130.2, 131.4, 133.6, 140.1, 147.6, 147.9; LC-MS *m/z* = 264 [M+1]⁺. Anal. Calcd for C₁₇H₁₀ClN: C, 77.42; H, 3.82; N, 5.31. Found: C, 77.41; H, 3.84; N, 5.53%.

(b) Preparation of the 9,9-diphosphono-10-hydroacridanes (11–17) using 9-chloroacridines: Representative procedure for 11

In a 25 mL round bottom flask, 9-chloroacridine (1.07 g, 5 mmol) and the phosphite **10** (1.50 g, 10 mmol) were heated at 90 °C under nitrogen for 4 h. At this stage, only one phosphorus signal due to the product was observed. When there was no 9-chloroacridine left (TLC), ethyl acetate (20 mL) was added to the reaction mixture followed by saturated sodium bicarbonate solution. The organic layer was separated and aqueous layer extracted thrice (3 x 10 mL) with ethyl acetate. The combined organic part was washed with water (5 x 20 mL), brine solution, dried over anhyd. Na₂SO₄ and concentrated to yield brown colored gummy solid. Pure 9,9-bis-(5,5-dimethyl-2-oxo-2λ⁵-[1,3,2]dioxaphosphinan-2-yl)-9,10-dihydro-acridine (**11**) was isolated by column chromatography (ethyl acetate: hexane 4:1) as a white solid. Other compounds **12–17** were prepared similarly. The reaction mixture showed a single phosphonate product in most cases, in *ca* 50-60% yield (¹H NMR). We could also recover the corresponding acridone formed as a byproduct, and convert it back to chloroacridine in nearly quantitative yields by treatment with thionyl chloride.

9,9-Bis-(5,5-Dimethyl-2-oxo-2λ⁵-[1,3,2]dioxaphosphinan-2-yl) 9,10-dihydro-acridine (11). Yield (by NMR; isolated) 55%, 0.50 g (20%); mp 248-250 °C; white solid; IR (KBr) 3266, 2965, 1613, 1530, 1491, 1344, 1250, 1064 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.71 (s, 6 H, 2 CH₃), 1.22 (s, 6 H, 2 CH₃), 3.91–3.97 (m, 4 H, 2 OCH₂), 4.15–4.17 (m, 4 H, 2 OCH₂), 6.03 (d, 2 H, *J* = 7.6 Hz, Ar-*H*), 6.64 (~t, 2 H, *J* ~ 7.6 Hz, Ar-*H*), 6.71 (~t, 2 H, *J* ~ 7.6 Hz, Ar-*H*), 7.80 (d, 2 H, *J* = 7.6 Hz,

Ar-*H*), 7.96 (s, 1 H, NH); ^{13}C NMR (100 MHz, CDCl_3) δ 20.7, 22.5, 32.4 and 32.5 (2 d, $J_{(\text{P-C})} \sim 4.4$ Hz, CMe_2), 51.8 (t, $J_{(\text{P-C})} = 132.1$ Hz, P-C-P), 78.3, 110.0 and 110.1 (2 d, $J_{(\text{P-C})} \sim 7.2$ Hz), 115.0, 118.4, 129.4, 131.7, 139.0 and 139.2 (2 d, $J_{(\text{P-C})} \sim 5.5$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ 8.0 (s); LC-MS $m/z = 478$ $[\text{M}+1]^+$; Anal. Calcd for $\text{C}_{23}\text{H}_{29}\text{NO}_6\text{P}_2$: C, 57.86; H, 6.12; N, 2.93. Found: C, 58.04; H, 6.10; N, 2.84%. This compound was crystallized from acetonitrile (2 mL). An X-ray structure analysis was performed on this compound (left diagram in Figure 1).

2-Bromo-9,9-bis-(5,5-dimethyl-2-oxo-2 λ^5 -[1,3,2]dioxaphosphinan-2-yl) 9,10-dihydro-acridine (12). Yield [by NMR; isolated] 58%, 0.72 g (26%); mp 268-270 $^\circ\text{C}$; white solid; IR (KBr, cm^{-1}) 3254, 3177, 2967, 1615, 1489, 1244, 1069, 1028; ^1H NMR (400 MHz, CDCl_3) δ 0.75 (s, 6 H, 2 CH_3), 1.26 (s, 6 H, 2 CH_3), 4.01 (not resolved, 4 H, 2x OCH_2), 4.22 and 4.24 (\sim 2 d, 4 H, $J_{(\text{H-H})} \sim J_{(\text{P-H})} \sim 7.1$ Hz, 2 OCH_2), 5.92-5.98 (m, 2 H, Ar-*H*), 6.68-6.77 (m, 3 H, Ar-*H*), 7.78 (d, 1 H, $J = 6.6$ Hz, Ar-*H*), 7.86 (s, 1 H), 8.39 (s, 1 H). ^{13}C NMR (100 MHz, CDCl_3) δ 20.6, 22.4, 32.4 and 32.5 (2 d, $J_{(\text{P-C})} \sim 4.0$ Hz, CMe_2), 51.6 (t, $J_{(\text{P-C})} = 131.0$ Hz, P-C-P), 78.5 and 78.6 (2 d, $J_{(\text{P-C})} \sim 11.0$ Hz, OCH_2), 109.5 and 109.6 (2 d, $J_{(\text{P-C})} \sim 8.0$ Hz), 109.9, 111.9, 115.2, 116.3, 118.8, 129.6, 131.5, 132.1, 134.0, 138.6, 138.8; ^{31}P NMR (162 MHz, CDCl_3) δ 7.3 (s); LC-MS $m/z = 556$ $[\text{M}]^+$. Anal. Calcd for $\text{C}_{23}\text{H}_{28}\text{BrNO}_6\text{P}_2$: C, 49.66; H, 5.07; N, 2.52. Found: C, 49.61; H, 5.12; N, 2.70%.

9,9-Bis-(5,5-dimethyl-2-oxo-2 λ^5 -[1,3,2]dioxaphosphinan-2-yl)-2-methyl-9,10-dihydro-acridine (13). Yield [by NMR; isolated] 52%, 0.74 g (30%); mp 262-264 $^\circ\text{C}$; white solid; IR (KBr, cm^{-1}) 3272, 2963, 2926, 1615, 1495, 1343, 1256, 1066. ^1H NMR (400 MHz, CDCl_3) δ 0.71 (s, 6 H, 2 CH_3), 1.22 (s, 6 H, 2 CH_3), 2.25 (s, 3 H, CH_3), 3.92-3.98 (m, 4 H, 2 OCH_2), 4.13-4.16 (m, 4 H, 2 OCH_2), 6.00 (d, 1 H, $J = 7.6$ Hz, Ar-*H*), 6.05 (d, 1 H, $J = 7.9$ Hz, Ar-*H*), 6.53 (d, 1 H, $J = 7.9$ Hz, Ar-*H*), 6.64 (\sim t, 1 H, $J \sim 7.6$ Hz, Ar-*H*), 6.72 (\sim t, 1 H, $J \sim 7.6$ Hz, Ar-*H*), 7.61 (s, 1 H), 7.82 (d, 1 H, $J = 7.6$ Hz, Ar-*H*), 7.86 (s, 1 H). ^{13}C NMR (100 MHz, CDCl_3) δ 20.7, 21.1, 22.4, 32.4 and 32.5 (2 d, $J_{(\text{P-C})} \sim 4.2$ Hz, CMe_2), 51.8 (t, $J_{(\text{P-C})} = 132.4$ Hz, P-C-P), 78.2, 109.7 and 109.8 (2 d, $J_{(\text{P-C})} \sim 9.2$ Hz), 114.7 and 114.8 (2 d, $J_{(\text{P-C})} \sim 7.9$ Hz), 118.2, 127.3, 129.2, 130.1, 131.9 (t, $J_{(\text{P-C})} = 3.6$ Hz), 136.7, 139.4; ^{31}P NMR (162 MHz, CDCl_3) δ 8.1 (s); LC-MS $m/z = 492$ $[\text{M}+1]^+$. Anal. Calcd for $\text{C}_{24}\text{H}_{31}\text{NO}_6\text{P}_2$: C, 58.65; H, 6.36; N, 2.85. Found: C, 58.64; H, 6.36; N, 2.86%.

9,9-Bis-(5,5-dimethyl-2-oxo-2 λ^5 -[1,3,2]dioxaphosphinan-2-yl)-2-nitro-9,10-dihydro-acridine (14). Yield [by NMR; isolated] 50%, 0.39 g (15%); mp 272-274 $^\circ\text{C}$; yellow solid; IR (KBr, cm^{-1}) 2963, 2924, 2855, 1624, 1491, 1262, 1092, 1020, 800; ^1H NMR (400 MHz, CDCl_3) δ 0.76 (s, 6 H, 2 CH_3), 1.28 (s, 6 H, 2 CH_3), 4.04-4.13 (m, 4 H, 2 OCH_2), 4.24-4.28 (not resolved, 4 H, 2 OCH_2), 5.98 and 6.00 (2 closely spaced d, 2 H, Ar-*H*), 6.71 (\sim t, 1 H, $J \sim 7.8$ Hz, Ar-*H*), 6.82 (\sim t, 1 H, $J \sim 7.8$ Hz, Ar-*H*), 7.47 (d, 1 H, $J = 8.8$ Hz, Ar-*H*), 7.83 (d, 1 H, $J = 7.8$ Hz, Ar-*H*), 8.76 (d, 1 H, $J = 1.9$ Hz, Ar-*H*), 9.27 (s, 1 H, NH); ^{13}C NMR (100 MHz, CDCl_3) δ 20.6, 22.2, 32.6 and 32.7 (2 d, $J_{(\text{P-C})} \sim 4.2$ Hz, CMe_2), 52.1 (t, $J_{(\text{P-C})} \sim 132.2$ Hz, P-C-P), 78.6, 110.0 and 110.7 (2 d, $J_{(\text{P-C})} \sim 8.0$ Hz), 114.1, 115.7, 121.0, 125.3, 129.2, 129.8, 131.6, 137.2 (d, $J_{(\text{P-C})} \sim 5.3$ Hz), 139.0, 144.8 (d, $J_{(\text{P-C})} \sim 4.3$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ 7.1 (s); LC-MS $m/z = 522$ $[\text{M}]^+$. Anal. Calcd for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_8\text{P}_2$: C, 52.88; H, 5.40; N, 5.36. Found: C, 52.79; H, 5.45; N, 5.45%. This compound was crystallized from dichloromethane (3 mL) containing traces of THF. X-Ray structural analysis was performed on this sample (middle diagram in Figure 1).

3-Chloro-9,9-bis-(5,5-dimethyl-2-oxo-2 λ^5 -[1,3,2]dioxaphosphinan-2-yl)-4-methyl-9,10-dihydro-acridine (15). Yield [by NMR; isolated] 54%, 0.52 g (20%); mp 280-282 °C; yellow solid; IR (KBr, cm⁻¹) 3285, 2965, 1611, 1470, 1258, 1061; ¹H NMR (400 MHz, CDCl₃) δ 0.73 (s, 6 H, 2 CH₃), 1.17 (s, 6 H, 2 CH₃), 1.90 (s, 3 H, CH₃), 3.98-4.02 (s, not resolved, 4 H, 2 OCH₂), 4.08-4.11 (m, 4 H, 2 OCH₂), 6.53 (d, 1 H, *J* = 7.8 Hz, Ar-*H*), 6.72-6.83 (m, 3 H, Ar-*H*), 6.93 (s, 1 H, NH), 7.74 (d, 1 H, *J* = 8.7 Hz, Ar-*H*), 7.85 (d, 1 H, *J* = 7.8 Hz, Ar-*H*); ¹³C NMR (100 MHz, CDCl₃) δ 13.5, 20.8, 22.3, 32.4 and 32.5 (2 d, *J*_(P-C) ~ 3.1 Hz, CMe₂), 52.0 (t, *J*_(P-C) = 132.0 Hz, P-C-P), 77.9 and 78.0 (2 d, *J*_(P-C) ~ 4.0 Hz, OCH₂), 109.4 and 110.3 (2 d, *J*_(P-C) ~ 7.0 Hz), 115.5, 119.4, 119.8, 120.0, 129.4, 130.5, 132.0, 135.2, 138.2, 138.4; ³¹P NMR (162 MHz, CDCl₃) δ 8.0 (s); LC-MS *m/z* = 525 [M-1]⁺. Anal. Calcd for C₂₄H₃₀ClNO₆P₂: C, 54.81; H, 5.75; N, 2.66. Found: C, 54.88; H, 5.71; N, 2.69%.

7,7-Bis-(5,5-dimethyl-2-oxo-2 λ^5 -[1,3,2]dioxaphosphinan-2-yl)-7,12-dihydro-benzo-[c]-acridine (16). Yield [by NMR; isolated] 52%, 0.26 g (15%); mp 298-300 °C; yellow solid; IR (KBr, cm⁻¹) 3295, 3061, 2963, 1607, 1535, 1495, 1414, 1262, 1061, 745; ¹H NMR (400 MHz, CDCl₃) δ 0.66 (s, 6 H, 2 CH₃), 1.21 (s, 6 H, 2 CH₃), 3.91-3.99 (m, 4 H, 2 OCH₂), 4.13 (not resolved, 4 H, 2 OCH₂), 6.40-6.43 (m, 1 H, Ar-*H*), 6.53 (~t, 2 H, *J* ~ 7.2 Hz, Ar-*H*), 7.09-7.15 (m, 2 H, Ar-*H*), 7.24-7.27 (m, 1 H, Ar-*H*), 7.45 (d, 1 H, *J* = 7.8 Hz, Ar-*H*), 7.73-7.79 (m, 2 H, Ar-*H*), 7.92 (d, 1 H, *J* = 8.8 Hz, Ar-*H*), 8.02 (s, 1 H, NH); ¹³C NMR (100 MHz, CDCl₃) δ 20.8, 22.5, 32.5 and 32.6 (2 d, *J*_(P-C) ~ 4.4 Hz, CMe₂), 52.7 (t, *J*_(P-C) = 136.2 Hz, P-C-P), 78.1, 115.5, 118.6, 119.8, 121.2, 122.0, 125.1, 126.0, 127.5, 128.8, 129.0, 131.0, 132.6, 134.8, 138.6; ³¹P NMR (162 MHz, CDCl₃) δ 8.0 (s). Anal. Calcd for C₂₇H₃₁NO₆P₂: C, 61.48; H, 5.92; N, 2.66. Found: C, 61.42; H, 5.96; N, 2.73%.

[9-(Diethoxy-phosphoryl)-9,10-dihydro-acridin-9-yl]-phosphonic acid diethyl ester (17). Yield [by NMR; isolated] 60%, 0.60 g (25%); mp 214-216 °C; white solid; IR (KBr, cm⁻¹) 3266, 2963, 2894, 1613, 1530, 1491, 1344, 1250, 743; ¹H NMR (400 MHz, CDCl₃) δ 1.16 (t, 12 H, *J* = 7.2 Hz, -OCH₂CH₃), 4.00-4.10 (m, 8 H, -OCH₂CH₃), 6.12 (s, 1 H, -NH), 6.47 (d, 2 H, *J* = 7.6 Hz, Ar-*H*), 6.78 (~t, 2 H, *J* = 7.6 Hz, Ar-*H*), 7.07 (~t, 2 H, *J* ~ 7.6 Hz, Ar-*H*), 8.16 (d, 2 H, *J* = 7.6, Ar-*H*); ¹³C NMR (100 MHz, CDCl₃) δ 16.2 and 16.3 (2 d, *J*_(P-C) ~ 2.7 Hz, OCH₂CH₃), 50.5 (t, *J*_(P-C) = 132.5 Hz, P-C-P), 63.8 and 63.9 (2 d, *J*_(P-C) ~ 3.5 Hz, OCH₂CH₃), 112.0 (t, *J*_(P-C) = 8.2 Hz), 114.0, 118.8, 129.0, 133.3, 138.7 (t, *J*_(P-C) = 5.5 Hz); ³¹P NMR (162 MHz, CDCl₃) δ 15.9 (s); LC-MS *m/z* = 453 [M]⁺. Anal. Calcd for C₂₁H₂₉NO₆P₂: C, 55.63; H, 6.45; N, 3.09. Found: C, 55.71; H, 6.41; N, 3.12%. This compound was crystallized from EtOAc-hexane (4 + 1 mL). X-Ray structural analysis was performed on this sample (right diagram in Figure 1). This compound has been mentioned in the literature before.¹⁵

(c) Synthesis of 9-(5,5-dimethyl-2-oxo-2 λ^5 -[1,3,2]dioxaphosphinan-2-yl)-acridine (18)

A mixture of 9-chloro-2-methyl-acridine (1.14 g, 5 mmol) and the phosphite **10** (0.60 g, 4 mmol) were heated at 90 °C under nitrogen for 4 h. Ethyl acetate (20 mL) was added to the reaction mixture followed by saturated sodium bicarbonate solution. The organic layer was separated and the aqueous layer extracted thrice (3 x 10 mL) with ethyl acetate. The combined organic layer was washed with water (5 x 20 mL), brine solution, dried over anhyd. Na₂SO₄, and concentrated to yield a brown gummy solid. Pure 9-(5,5-dimethyl-2-oxo-2 λ^5 -[1,3,2]dioxaphosphinan-2-yl)-acridine (**18**)

was isolated by column chromatography (ethyl acetate: hexane, 2:3) as a pale yellow solid. Yield [by NMR; isolated] 20%, 0.17 g (10%); mp 182-184 °C; IR (KBr, cm^{-1}) 2974, 2924, 1634, 1474, 1262, 1051, 1009; ^1H NMR (400 MHz, CDCl_3) δ 0.67 and 1.44 (2 s, 6 H, 2 CH_3), 2.63 (s, 3 H, CH_3), 3.59-3.63 (m, 2 H, OCH_2), 3.99-4.07 (m, 2 H, OCH_2), 7.63-7.83 (m, 3 H, Ar-*H*), 8.22 (d, 1 H, J = 8.8 Hz, Ar-*H*), 8.30 (d, 1 H, J = 7.6 Hz, Ar-*H*), 8.57 (s, 1 H, Ar-*H*); 8.80 (d, 1 H, J = 8.8 Hz, Ar-*H*); ^{13}C NMR (100 MHz, CDCl_3) δ 20.4, 22.2, 22.5, 32.1 (d, $J_{\text{P-C}}$ = 6.0 Hz, CMe_2), 76.8, 76.9, 124.3 (d, $J_{\text{P-C}}$ = 5.8 Hz), 126.0 (d, $J_{\text{P-C}}$ = 5.7 Hz), 126.8, 127.1, 127.2, 127.8, 129.5, 130.2, 130.6, 133.0, 138.2 [the doublet due to $^1J_{\text{P-C}}$ was not clear]; ^{31}P NMR (162 MHz, CDCl_3) δ 10.6 (s); LC-MS m/z = 342 $[\text{M}+1]^+$. Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_3\text{P}$: C, 66.85; H, 5.91; N, 4.10. Found: C, 66.81; H, 5.86; N, 4.18%.

X-ray crystallography

X-Ray data were collected on a Bruker AXS SMART diffractometer using Mo- $\text{K}\alpha$ (λ = 0.71073 Å) radiation. The structures were solved and refined by standard methods.²³ All non-hydrogen atoms were refined anisotropically. Crystal data have been deposited in the Cambridge database.

Crystal data for compounds (11) CH_3CN , (14) OC_4H_8 and (17)

(11) CH_3CN : $\text{C}_{71}\text{H}_{90}\text{N}_4\text{O}_{18}\text{P}_6$, M = 1473.29, Trigonal, Space group R-3, a = 21.029(3), b = 21.029(3), c = 28.896(7) Å, α = β = 90.0°, γ = 120.0°, V = 11067 (3) Å³, Z = 6, μ = 0.217 mm^{-1} , data/restraints/parameters: 4237/0/311, R indices ($I > 2\sigma(I)$): R_1 = 0.0785, wR_2 (all data) = 0.1638. Max./min. residual electron density ($\text{e}\text{\AA}^{-3}$) 0.628 / -0.243. CCDC No. 727444.

(14) $\text{C}_4\text{H}_8\text{O}$: $\text{C}_{27}\text{H}_{36}\text{ON}_2\text{O}_9\text{P}_2$, M = 594.52, Monoclinic, Space group P2(1)/c, a = 15.240(5), b = 10.453(3), c = 21.548(7) Å, β = 100.909(5)°, V = 3370.6(19) Å³, Z = 4, μ = 0.176 mm^{-1} , data/restraints/parameters: 5928/0/410, R indices ($I > 2\sigma(I)$): R_1 = 0.1013, wR_2 (all data) = 0.2839. Max./min. residual electron density ($\text{e}\text{\AA}^{-3}$) 0.918 / -0.417. CCDC No. 727445.

17: $\text{C}_{21}\text{H}_{29}\text{NO}_6\text{P}_2$, M = 453.39, Monoclinic, Space group P2(1), a = 8.096(6), b = 15.300(11), c = 19.538(7) Å, β = 96.211(13)°, V = 1174.5(15) Å³, Z = 2, μ = 0.220 mm^{-1} , Flack parameter - 0.01(14), data/restraints/parameters: 4011/1/279, R indices ($I > 2\sigma(I)$): R_1 = 0.0681, wR_2 (all data) = 0.1252. Max./min. residual electron density ($\text{e}\text{\AA}^{-3}$) 0.242 / -0.204. CCDC No. 727446.

Acknowledgements

We acknowledge financial and equipment support from the Department of Science and Technology (DST), Council of Scientific and Industrial Research (CSIR), and University Grants Commission (UGC) [all in New Delhi]. V.S. thanks the CSIR for a fellowship.

References

1. Review pertaining to acridine chemistry: Chiron, J.; Galy, J.-P. *Synthesis* **2004**, 313.

2. (a) Kuruvilla, E.; Andaman, P. C.; Schuster, G. B.; Ramaiah, D. *Org. Lett.* **2008**, *10*, 4295. (b) Benniston, A. C.; Rewinska, D. B. *Org. Biomol. Chem.* **2006**, *4*, 3886. (c) Mizuki, K.; Sakakibara, Y.; Ueyama, H.; Nojima, T.; Waki, M.; Takenaka, S. *Org. Biomol. Chem.* **2005**, *3*, 578.
3. Motoyoshiya, J.; Ikeda, T.; Tsuboi, S.; Kusaura, T.; Takeuchi, Y.; Hayashi, S.; Yoshioka, S.; Takaguchi, Y.; Aoyama, H. *J. Org. Chem.* **2003**, *68*, 5950.
4. (a) Cheng, M.-K.; Modi, C.; Cookson, J. C.; Hutchinson, I.; Heald, R. A.; McCarroll, A. J.; Missailidis, S.; Tanious, F.; Wilson, W. D.; Mergny, J.-L.; Laughton, C. A.; Stevens, M. F. G. *J. Med. Chem.* **2008**, *51*, 963. (b) Sánchez, I.; Reches, R.; Caignard, D. H.; Renard, P.; Pujol, M. D. *Eur. J. Med. Chem.* **2006**, *41*, 340. (c) Bacherikov, V. A.; Chang, J.-Y.; Lin, Y.-W.; Chen, C.-H.; Pan, W.-Y.; Dong, H.; Lee, R.-Z.; Chou, T.-C.; Su, T.-L. *Bioorg. Med. Chem.* **2005**, *13*, 6513.
5. Wainwright, M. J. *Antimicrob. Chemother.* **2001**, *47*, 1.
6. Hamy, F.; Brondani, V.; Flörsheimer, A.; Stark, W.; Blommers, M. J. J.; Limkait, T. *Biochemistry* **1998**, *37*, 5086.
7. (a) Jones, M.; Mercer, A. E.; Stocks, P. A.; Pensée, L. J. I. L.; Cosstick, R.; Park, B. K.; Kennedy, M. E.; Piantanida, I.; Ward, S. A.; Davies, J.; Bray, P. G.; Rawe, S. L.; Baird, J.; Charidza, T.; Janneh, O.; O'Neill, P. M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2033. (b) Zsila, F.; Visy, J.; Mady, G.; Fitos, I. *Bioorg. Med. Chem.* **2008**, *16*, 3759.
8. (a) Kuzuya, A.; Mizoguchi, R.; Sasayama, T.; Zhou, J.-M.; Komiyama, M. *J. Am. Chem. Soc.* **2004**, *126*, 1430. (b) Joseph, J.; Eldho, N. V.; Ramaiah, D. *Chem. Eur. J.* **2003**, *9*, 5926 (c) Antonini, I.; Polucci, P.; Magnano, A.; Martelli, S. *J. Med. Chem.* **2001**, *44*, 3329.
9. (a) Giorgio, C. D.; Shimi, K.; Boyer, G.; Delmas, F.; Galy, J.-P. *Eur. J. Med. Chem.* **2007**, *42*, 1277. (b) Carole, D. G.; Michel, D. M.; Julien, C.; Florence, D.; Anna, N.; Severine, J.; Gerard, D.; Pierrea, T. -D.; Galy, J.-P. *Bioorg. Med. Chem.* **2005**, *13*, 5560. (c) Giorgio, C. D.; Delmas, F.; Filloux, N.; Robin, M.; Seferian, L.; Azas, N.; Gasquet, M.; Costa, M.; David, P. T.; Galy, J.-P. *Antimicrob. Agents Chemother.* **2003**, *47*, 174.
10. (a) Praveen Kumar, K.; Muthiah, C.; Kumaraswamy, S.; Kumara Swamy, K. C. *Tetrahedron Lett.* **2001**, *42*, 3219. (b) Senthil Kumar, K.; Kumara Swamy, K. C. *J. Organomet. Chem.* **2001**, *637*, 616. (c) Muthiah, C.; Senthil Kumar, K.; Vittal, J. J.; Kumara Swamy, K. C. *Synlett* **2002**, *11*, 1787. (d) Chakravarty, M.; Srinivas, B.; Muthiah, C.; Kumara Swamy, K. C. *Synthesis* **2003**, 2368. (e) Kumara Swamy, K. C.; Balaraman, E.; Satish Kumar, N. *Tetrahedron* **2006**, *62*, 10152. (f) Chakravarty, M.; Kumara Swamy, K. C. *J. Org. Chem.* **2006**, *71*, 9128. (g) Kumara Swamy, K. C.; Srinivas, V.; Pavan Kumar, K. V. P.; Praveen Kumar, K. *Synthesis* **2007**, 893.
11. (a) Baillie, C.; Xiao, J. *Curr. Org. Chem.* **2003**, *7*, 477. (b) Tanaka, M. *Top. Curr. Chem.* **2004**, *232*, 25. (c) Montchamp, J.-L. *J. Organomet. Chem.* **2005**, *690*, 2388. (d) Troev, K. D. *Chemistry and Application of H-Phosphonates*, Elsevier: Amsterdam, 2006.
12. Russel, R. G. G.; Rogers, M. J. *Bone* **1999**, *25*, 97.
13. Rouband, G.; Faure, R.; Galy, J.-P. *Magn. Reson. Chem.* **2003**, *41*, 549.
14. Feng, S.; Panetta, C. A.; Graves, D. E. *J. Org. Chem.* **2001**, *66*, 612.

15. Also see: (a) Kosolapoff, G. M. *J. Am. Chem. Soc.* **1947**, *69*, 1002. (b) Redmore, D. *J. Org. Chem.* **1969**, *34*, 1420.
16. (a) Chen, Y.-L.; Chen, I.-L.; Lu, C.-M.; Tzeng, C.-C.; Tsao, L.-T.; Wang, J.-P. *Bioorg. Med. Chem.* **2003**, *11*, 3921.
17. Chakravarty, M.; Bhuvan Kumar, N. N.; Sajna, K. V.; Kumara Swamy, K. C. *Eur. J. Org. Chem.* **2008**, 4500.
18. Kumara Swamy, K. C.; Kumaraswamy, S.; Kommana, P. *J. Am. Chem. Soc.* **2001**, *123*, 12642.
19. Roy, K. R.; Arunasree, K. M.; Reddy, N. P.; Dheeraj, B.; Reddy, G. V.; Reddanna, P. *Biotechnol. Appl. Biochem.* **2007**, *47*, 159.
20. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon: Oxford, UK, 1986.
21. Wolf, C.; Liu, S.; Mei, X.; August, A. T.; Casimir, M. D. *J. Org. Chem.* **2006**, *71*, 3270.
22. Muthiah, C.; Praveen Kumar, K.; Aruna Mani, C.; Kumara Swamy, K. C. *J. Org. Chem.* **2000**, *65*, 3733.
23. (a) Sheldrick, G. M. *SHELX-97- A Program for Crystal Structure Solution and Refinement*, University of Göttingen, 1997. (b) Sheldrick, G. M. *SADABS, Siemens Area Detector Absorption Correction*, University of Göttingen, Germany, 1996. (c) Sheldrick, G. M. *SHELXTLNT Crystal Structure Analysis Package, Bruker AXS, Analytical X-ray System*, WI, USA, 1999, Version 5.10.