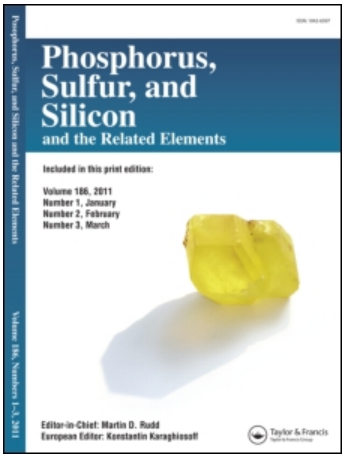

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Synthesis and Biological Evaluation of a Novel Series of (Hydroxyphenyl)-Aminophosphonates

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Synthesis and Biological Evaluation of a Novel Series of (Hydroxyphenyl)-Aminophosphonates

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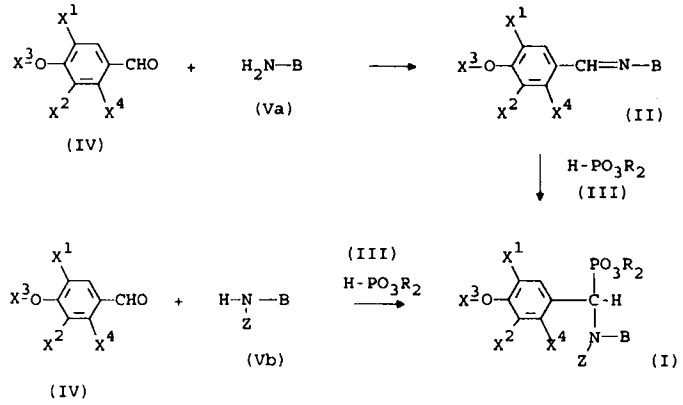
Elevated plasma cholesterol is now well established as a major risk factor for cardiovascular diseases. It has also been shown that the oxidation of low density lipoproteins leads to the formation of foam cells which contribute to the deposition of cholesterol in arteries.

We have synthesized and screened a series of new (hydroxyphenyl) aminophosphonates (I) for cholesterol lowering and antioxidant activities. Aldimines (II) obtained by condensation of an aldehyde (IV) and a primary amine (Va) reacted readily with dialkyl phosphite (III) to give the aminophosphonate (I). An alternative method consisted in refluxing a mixture of aldehyde (IV), amine (Vb, Z is alkyl but not H) and phosphite (III) in toluene with simultaneous elimination of water. Various structural modifications were carried out on the groups X^1- X^4,B , Z and R.

Pharmacological evaluation of aminophosphonate compounds (I) in the mouse has identified several derivatives with potent cholesterol lowering and antioxidant properties:$X^1 = X^2 = tBu$, $X^3 = X^4 = H$, B = Ph-$(CH_2)_n$ or Py-$(CH_2)_n$, n = 0-4, Z = H or Ac, R = Me, Et, iPr [1]. The best analogs were then tested in the dog as the secondary screening model where the pyridyl-substituted aminophosphonates (B = 3-Py or 4-CH_2-Py, Z =H, R = Et) were observed to potently lower cholesterol (-45% to -60%) at 25mg/kg/day.



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[1] Symphar SA, U.S. Patent 5'424'303 (1995); H.T. Phan. L.M. Nguyen, E. Niesor, Y. Guyon-Gellin and C.L. Bentzen.