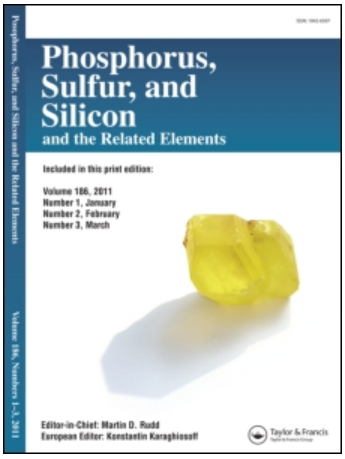

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Forlani, Giuseppe , Kafarski, Pawel , Lejczak, Barbara , Boduszek, Bogdan , Gancarz, Roman , Torreilles, Christophe , Soloducho, Jadwiga , Wojtasek, Hubert , Hafner, Joanna , Korf, Joanna and Wieczorek, Piotr(1996) 'Herbicidally Active Derivatives of Aminomethylenebis-Phosphonic Acid-Mode of Action and Structure - Activity Relationship', Phosphorus, Sulfur, and Silicon and the Related Elements, 109: 1, 353 — 356
To link to this Article: DOI: 10.1080/10426509608545163
URL: http://dx.doi.org/10.1080/10426509608545163

Phosphorus, Sulfur, and Silicon, 1996, Vols. 109–110, pp. 353–356
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HERBICIDALLY ACTIVE DERIVATIVES OF AMINOMETHYLENEBIS-PHOSPHONIC ACID - MODE OF ACTION AND STRUCTURE - ACTIVITY RELATIONSHIP

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Abstract: (N-pyridylamino)methylenebisphosphonates exhibit strong herbicidal activity which may be reversed by supplementation of the growth media with aromatic amino acids.They appeare to be the inhibitors of aromatic amino acids biosynthesis acting as inhibitors of DAHP synthase the first enzyme of shikimate pathway. Over 40 analogues of these acids were synthesized in order to determine the structure-activity relationship.

INTRODUCTION

The disclosure of glyphosate (N-phosphonomethylglycine), in 1971, instituted a milestone in a rational design of herbicides and pointed out an aromatic amino acids biosynthesis pathway as a particularly attractive target of such an approach.[1] This discovery initiated also the extensive research concerned with the design, synthesis and evaluation of physiological properties of hundreds, or perhaps thousands of glyphosate derivatives, homologues and analogues. Obviously, it is difficult to improve on a

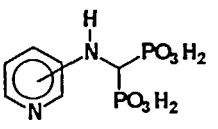
Using bacterial (*Escherichia coli*, *Micrococcus luteus*, *Sarcina lutea* and *Bacillus cereus*) and plant models (cell cultures of *Nicotiana plumbaginifolia*, and whole *Lepidium sativum* plants) we have found the reversal of the toxic action of the bisphosphonates by the combination of phenylalanine, tyrosine and tryptophan. Since nearly identical effects were observed in the case of N-phosphonomethylglycine (used as positive control) the shikimate pathway should be considered as a site of action of (N-pyridylamino)methylenebisphosphonic acids. Further studies indicated that these acids did not inhibit EPSP synthase, the target enzyme for glyphosate. They appeared, however, to be the strong inhibitors of DAHP (3-deoxy-*D*-arabinoheptulosonate-7-phosphate) synthase partially purified from *Nicotiana plumbaginifolia* suspension cultured cells. DAHP synthase is the first enzyme of the shikimate pathway. At milimolar concentrations Co^{2+}-dependent, cytosol localized enzyme form was inhibited by the tested compounds. This inhibition was nearly completely relieved by the increase of cobalt ion concentration. This suggests that the inhibition could be due to the chelating properties of these phosphonates. They also significantly reduced the activity of the other isoform of DAHP synthase - plastidal Mn^{+2}-stimulated. A kinetic analysis showed that compoud 2 was an uncompetitive with respect to phosphoenolpyruvate, but competitive with respect to other substrate - erythrose-4-phosphate. The studies also ruled out the possibility that an inhibition simply bases upon metal chelation.

In order to determine structural features of aminomethylenebisphosphonates responsible for their herbicidal action over 40 derivatives of aminomethylene-bisphosphonic acids were synthesized and screened for their herbicidal activity on *Lepidium sativum* and *Cucumis sativus*. The structural changes introduced were as follows: (1) modification or substitution of pyridyl moiety, (2) replacement of pyridyl fragment of herbicide by aromatic or another heteroaromatic one, (3) replacement of N-pyridyl by aliphatic or heteroaliphatic moiety, (4) replacement of aminomethylene-bisphosphonate fragment of the molecule by iminodi(methylphosphonate). Although some of the synthesized compouds (for example, compounds **3**, **4**, **5**, **6**, **7**, **8** and **9**) exerted strong herbicidal activity, being equipotent or even stronger than the parent compounds **1**, it is not possible to draw any meaningful relations on structure-activity relationship for them.

compound that is as simple as glyphosate and exhibits such a powerful activity. Indeed most of the analogues are less active than the herbicide itself. However, these efforts were not totally unsuccessful and resulted in discoveries of numerous highly active compounds. These include, at least, herbicidal phosphinothricin, introduced simultaneously in Germany and Japan,[2] N-pyridyl derivatives of aminomethylenebisphosphonic acid being developed in Japan,[3] as well as phosphonic acid analogues of morphactins first synthesized in our laboratories.[4] Among these compounds (N-pyridylamino)methylenebisphosphonic acids (compounds 1) are of special interest since the structure of aminomethylenebisphosphonic acid, which posses two strongly acidic groups and positively charged amino group, closely resembles N-phosphonomethylglycine. Glyphosate has long been postulated to act as transition state analogue for the putative tetrahedral intermediate formed transiently during reaction catalyzed by EPSP (5-enoylpyruvylshikimate-3-phosphate) synthase, the sixth enzyme of shikimate pathway.[5] One may thus speculate that pyridyl fragment of compounds 1 resembles nearly flat cyclic part of this intermediate while aminomethylene-bisphosphonic moiety, similarly as glyphosate, mimics the tetrahedral fragment of the intermediate. In order to check this speculation we undertook the studies on the mode of herbicidal action of these compounds.

RESULTS AND DISCUSSION

(N-pyridylamino)methylenebisphosphonates strongly inhibited the growth of five plant species (*Fagopyrum esculentum* Munch., *Lepidium sativum* L., *Cucumis sativus* L., *Triticum aestivum* L. and *Zea mays* L.) being equipotent or even stronger than glyphosate. These effects were additionally supported by studies on the influence of aminomethylenebisphosphonates 1 on the growth characteristics of plant cell suspension cultures of *Nicotiana plumbaginifolia, Daucus carrota, Zea mays* and *Oryza sativa.*



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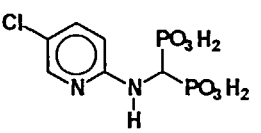

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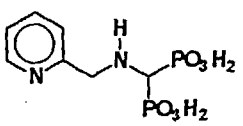
Powerful inhibition of the *Fagopyrum esculentum* anthocyanin production by all the compounds 1 indicate that aromatic acids biosynthesis pathway may be the site of action of these compounds.



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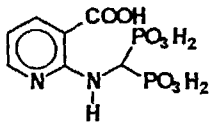

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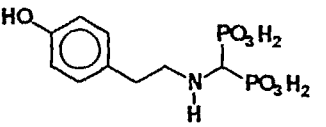

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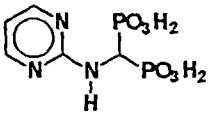

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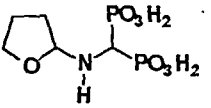

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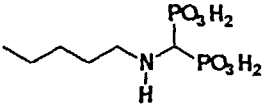

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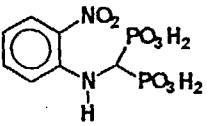

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ACKNOWLEDGEMNET

This work was supported by Komitet Badań Naukowych.

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