

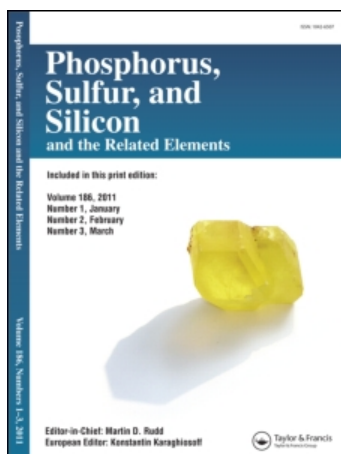
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Hydrolytic Pathway of Isophosphoramidate Mustard (IPM), the Cytotoxic Metabolite of the Anticancer Drug Ifosfamide

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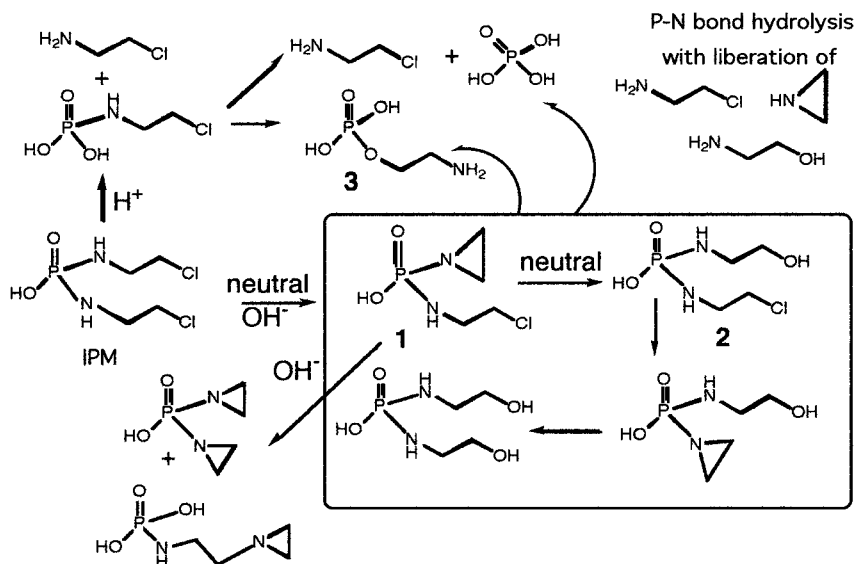
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HYDROLYTIC PATHWAY OF ISOPHOSPHORAMIDE MUSTARD (IPM), THE CYTOTOXIC METABOLITE OF THE ANTICANCER DRUG IFOSFAMIDE

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IPM is the alkylating metabolite of the anticancer oxazaphosphorine drug ifosfamide (Holoxan). The alkylation chemistry of IPM by nucleophiles was extensively studied, but the concurrent P–N bond hydrolysis pathway is not well documented. We used NMR spectroscopy



SCHEME 1

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(^{31}P , ^1H , ^{13}C) to determine the products of IPM degradation in buffered solutions at pH ranging from 1 to 13. The complex hydrolytic scheme (Scheme 1) was established.

^{31}P NMR analysis of the urinary excretion in rats treated with ifosfamide showed that the three IPM degradation products **1**, **2**, and **3** represented 60–80% of excreted IPM.