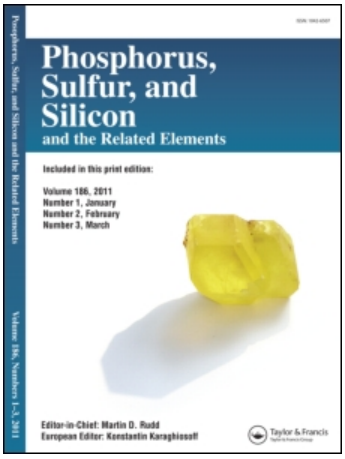

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Arylbenzylphosphonates - A New Class of Irreversible Penicillin Acylase Inhibitors

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ARYLBENZYLPHOSPHONATES - A NEW CLASS OF IRREVERSIBLE PENICILLIN ACYLASE INHIBITORS

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Abstract Anionic phosphonates are shown to inactivate penicillin acylase via phosphonilation of active site with simultaneous release of appropriate phenol.

Phosphorus-containing inhibitors are valuable tools for understanding the properties and physiological role of hydrolytic enzymes. Previously derivatives of benzylphosphonic acid have been investigated as reversible inhibitors of penicillin acylase from *E. coli* (EC 3.5.1.11). On the contrary, compounds with general structure (I) have quite different mode of action and are irreversible competitive inhibitors of enzyme:

$$\underset{\text{(Ia-d)}}{C_6H_5CH_2P(O)(O^-)\text{-}O\text{-}C_6H_4\text{-}R} + E(Ser)OH \longrightarrow E(Ser)OP(O)(O^-)\text{-}O\text{-}CH_2C_6H_5 + R\text{-}C_6H_4OH$$

where R=CO_2H, CO_2CH_3, $CO_2CH_2C_6H_5$, NO_2 for the compounds (Ia-d) respectively. Now only β-lactamase is known to have such types of inhibitors. Inactivation process involves formation of an intermediate before the chemical stage. Second order rate constants have been determined (k_2=1,78x10^3 $M^{-1}min^{-1}$, 40x10^3 $M^{-1}min^{-1}$, 200x10^3 $M^{-1}min^{-1}$, 1220x10^3 $M^{-1}min^{-1}$ for compounds Ia-d, respectively). The effectiveness of these compounds varies in a very broad range and depends on the nature of R-group. There is strong correlation between inactivation activity and phenolic fragment properties as a good leaving group. It indicates general mechanism of enzyme interaction with anionic arylbenzylphosphonates: the greater acidity of phenol is accompanied with greater inhibitors effect. The enzyme's inactivation by compound (Ia-d) is accompanied by stoichiometric release of appropriate phenol even when large excess of inhibitor is used. The reactivation of the inactivated enzyme has not been observed both in water solution and in presence of 6-aminopenicillanic acid. Apart from kinetic stability of the inactivated enzyme, the most striking feature of these inhibitors is the high rate phosphonylation itself. Based on obtained results we suggest that catalytic activity loss take place due to phosphonilation of active site serine hydroxyl with simultaneous release of appropriate phenol.

Thus, the phosphonates include in their mode of action an admixture of transition-state analogue and mechanism based inhibitor characteristics. They are thought to be used as convenient active site titrants, as sources of fresh insight into the chemical properties of enzyme active site.