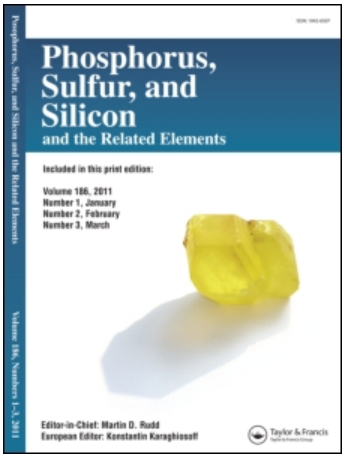

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Non-hydrolysable Phosphinic Analogues of Dipeptides

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Non-hydrolysable Phosphinic Analogues of Dipeptides

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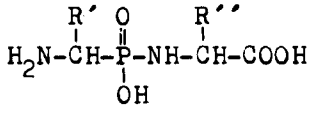
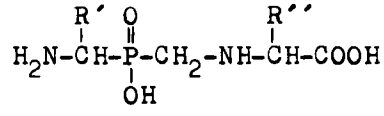
Peptide analogues 1 in which the phosphonamide group replaces the amide function are thought to mimic the tetrahedral intermediates and transition states in peptide hydrolysis. While peptides 1 are potent inhibitors of some peptidases, their unsefulness is limited by rapid hydrolysis of P-N bond in aqueous media. To circumvent the instability problem we designed peptide analogues 2 with a CH_2 group inserted between the phosphorus and nitrogen atoms. Such structures are resistant to hydrolysis but it was interesting to see if they are similar enough to peptides to retain any affinity to enzyme active sites.



1



2

2a: R′= H, R′′= CH_3; 2b: R′= H, R′′= $CH_2C_6H_5$

2c: R′= H, R′′= CH_2CH_2COOH

We have accomplished the synthesis of 2a - 2c by hydrogenation of aldimines prepared in situ from corresponding carbonyl compounds and bis(aminomethyl)phosphinic acid. The N-carbobenzoxy derivative of 2b is a moderate inhibitor of carboxypeptidase A from bovine pancreas with K_i/K_m= 0.1 .