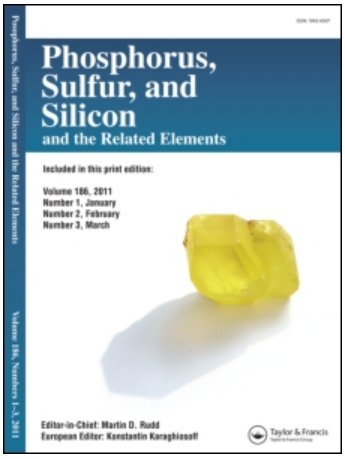

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PHOSPHONIC ANALOGUES OF PHENYLALANINE AND HISTIDINE AS STRONG INHIBITORS OF PHENYLALANINE AND HISTIDINE AMMONIA-LYASES

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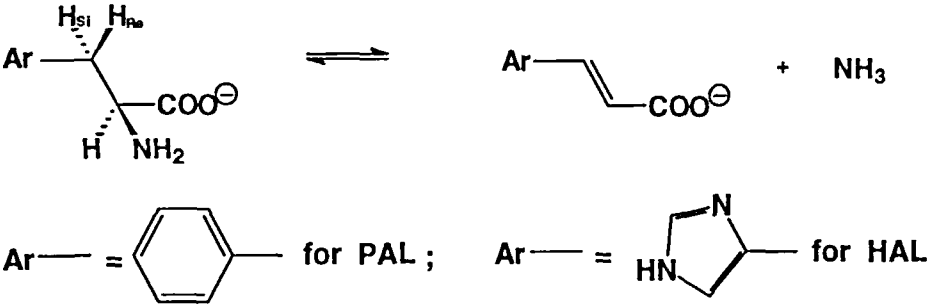
Abstract Syntheses of phosphonic analogues of phenylalanine (**5**) and histidine (**7**) as well as their biological activities as phenylalanine and histidine ammonia-lyases inhibitors have been discussed.

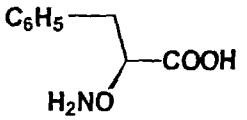
Both phenylalanine ammonia-lyase (PAL) (the common enzyme in plants) and histidine ammonia-lyase (HAL) (the enzyme occurs in bacteria) catalyze the anti-elimination of ammonia to give (E)-cinnamic acid and (E)-urocanoic acid, respectively.



It was pointed out a similarity of both enzymes based on the common carbanion intermediates [1-2], the presence of dehydroalanine in the active sites [3-5] and amino acids homology [6, 7].

We would like to present the synthesis of 2-aminoindan-2-phosphonic acid (**5**) [8] and racemic 1-amino-2-imidazol-4'-ylethylphosphonic acid (**7**) [9], as well as to discuss their biological activities as PAL [8,10] or HAL [11] inhibitors.

Inspired by the strong inhibition of PAL by (S)-2-aminooxy-3-phenylpropanoic acid (**1**) [12,13], we have synthesized (±)-2-aminomethyl-3-phenylpropanoic acid (**2**) and (E)-2-aminomethyl-3-phenylpropenoic acid (**3**) as potential PAL inhibitors [14].



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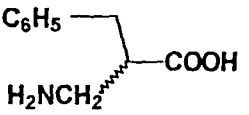

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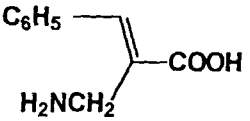
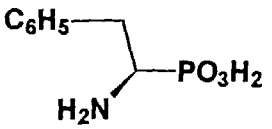


3

The analogue 3 is much better inhibitor than 2, and inhibits PAL less strongly by two orders of magnitude than 1 [14]. We have assumed that some active conformation of aminooxy acid 1 better fits into PAL's active site than that of amino acid 3. The compound 3 very weakly inhibits *in vivo* PAL activity although does not inhibit *in vitro* phenylalanine transamination activity as well as phenylalanine hydroxylase [14]. We have concluded that the analogue 3 is not delivered to the active site of PAL due to factors such as poor uptake and transport. Then, we have turned our attention to the phosphonic analogues of phenylalanine. Inhibitory activity of (R)-1-amino-2-phenylethylphoshonic acid (4) has already been known [15,16]. On the other hand, we considered the cyclic analogues of phenylalanine as a very interesting models to study, due to their fixed conformation. In this context we undertook the synthesis of 2-aminoindan-2-phosphonic acid (5) [8].



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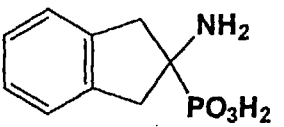
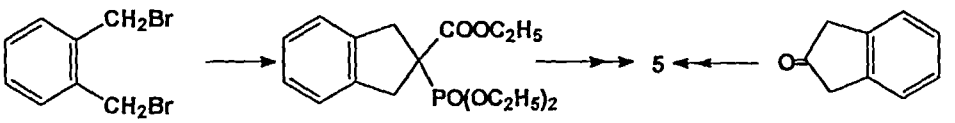


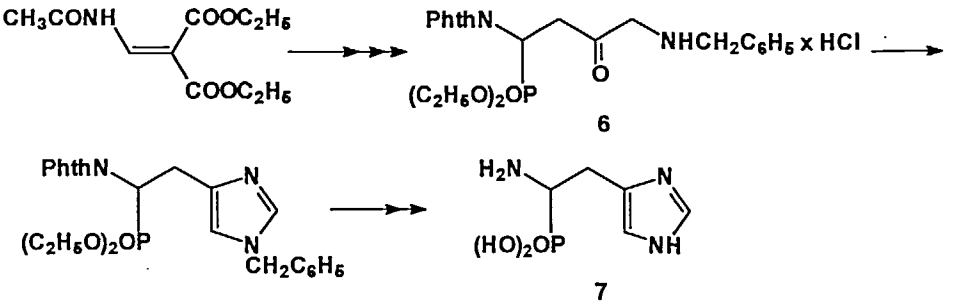
5

2-Aminoindan-2-phosphonic acid (5) was obtained by two independent synthetic routes from 1,2-bis(bromomethyl)benzene and triethyl phosphonoacetate or 2-indanon [8].

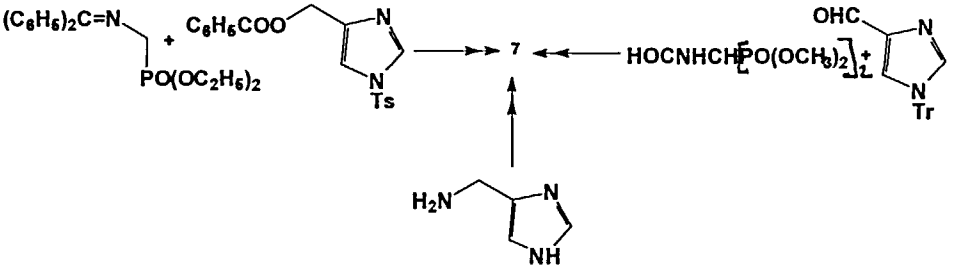


Synthesis and evaluation of a few compounds related to 5 provided evidence that both the amino group and the phosphonic group as well as the benzene moiety of the indan backbone are required for the effective inhibition of PAL [8]. 2-Aminoindan-2-carboxylic acid is poorer substrate for PAL than (±)-2-amino-3,4-dihydronaphthalene-2-carboxylic acid [10]. We assume that the fixed conformation of 5 [17] is between a flexible one for 1 and completely flat one for cinnamic acid. We think that this allows the better understanding what is the active conformation of (1).

The idea of similarity of histidine ammonia-lyase and phenylalanine ammonia-lyase has encouraged us to evaluate (±)-1-amino-2-imidazol-4'-ylethylphosphonic acid (7) as a HAL's inhibitor [11]. Merrett et al. [9] have reported synthesis of phosphonic analogue of histidine from diethyl acetamidomethylenemalonate. They introduced the imidazole ring using compound (6) as the appropiate precursor.

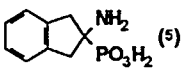


Then, other methods for the synthesis of (±)-1-amino-2-imidazol-4'-ylethyl-phosphonic acid using imidazole containing precursor have been worked out [18-20].



Phosphonic cyclic analogue of phenylalanine (**5**) is strong inhibitor of PAL [8] and phosphonic analogue of histidine (7) is strong inhibitor of HAL [11]. In contrary, racemic 3-phosphonoalanine, the phosphonic analogue of aspartic acid, is weak inhibitor (Ki/K_m = 0.2) of aspartate ammonia lyase [21]. Inhibitory activities of some selected compounds are presented in Table I.

TABLE I Inhibitory activities of phosphonic and some other analogues [8, 11, 13, 15 and 22].

PAL's inhibitors	K_i/K_m	HAL's inhibitors	K_i/K_m
(S)-$C_6H_5CH_2CH(ONH_2)COOH$ (1)	0.0003		
 (5)	0.002		
(R)-$C_6H_5CH_2CH(NH_2)PO_3H_2$ (4)	0.03		
(±)-$C_6H_5CH_2CH(NH_2)PO_3H_2$	0.06	(±)-$C_3H_3N_2CH_2CH(NH_2)PO_3H_2$ (7)	0.002
(±)-$C_6H_5CH_2CH(NHNH_2)COOH$	0.06	(±)-$C_3H_3N_2CH_2CH(NHNH_2)COOH$	0.02

It is worthy of mention that *in vivo* inhibition of PAL by the compound **5** is superior to that of either 1 and 4 [8]. We think that the mechanism of the strong PAL and HAL inhibition by the both phosphonic analogues involves ionic and hydrogen bond interaction between the phosphonic groups with the guanidine group of the enzyme arginine.

The strongest inhibition *in vivo* of phenylalanine ammonia-lyase by 2-amino-indan-2-phosphonic acid (**5**) among inhibitors, was used to some studies on different aspects of phenylpropanoid compounds biosynthesis in plants [23-30].

Futher study of a inhibitor with more or less fixed conformation as well as of an inhibitor containing an additional photoreactive group are in progress.

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