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Inhibitors of phenylalanine ammonia-lyase: Substituted derivatives of 2-aminoindane-2-phosphonic acid and 1-aminobenzylphosphonic acid

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Abstract

Six derivatives of 2-aminoindane-2-phosphonic acid and 1-aminobenzylphosphonic acid were synthesized. The compounds were tested both as inhibitors of buckwheat phenylalanine ammonia-lyase (in vitro) and as inhibitors of anthocyanin biosynthesis (in vivo). (±)-2-Amino-4-bromoindane-2-phosphonic acid was found to be the strongest inhibitor from investigated compounds. The results obtained are a basis for design of phenylalanine ammonia-lyase inhibitors useful in the enzyme structure studies in photo labelling experiments.
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Keywords: Phenylalanine ammonia-lyase; Inhibitor; 2-Aminoindane-2-phosphonic acid; 2-Amino-4-bromoindane-2-phosphonic acid; (+)-1-Amino-3′,4′-dichlorobenzylphosphonic acid

1. Introduction

Phenylalanine ammonia-lyase (PAL, *EC* 4.1.3.5) is a plant enzyme which catalysis elimination of ammonia from (*S*)-phenylalanine (Poppe and Rétey, 2005; Pilbak et al., 2006). The enzyme plays an important role in secondary metabolite pathways (Croteau et al., 2000). In spite of much recent work on the structure and catalytic mechanism of PAL, the precise binding site of phenylalanine in the enzyme is not known (Poppe and Rétey, 2005; Pilbak et al., 2006). Inhibitors of PAL containing a photoaffinity group may therefore be useful tools in studies of PAL structure and function.

2-Aminoindane-2-phosphonic acid (AIP) and (+)-1-amino-3′,4′-dichlorobenzylphosphonic acid have been found to be potent inhibitors of phenylalanine ammonia-lyase (Zoń and Amrhein, 1992; Appert et al., 2003; Zoń et al., 2004, 2002). Recently, 5-substituted derivatives of 2-aminoindane-2-phosphonic acid have been synthesized and tested (Zoń et al., 2005). Here, we describe the synthesis of new derivatives of AIP (**1**–**4**, Fig. 1) as well as derivatives of 1-aminobenzylphosphonic acid (**5** and **6**, Fig. 1). The obtained compounds were evaluated as inhibitors of buckwheat PAL as well as inhibitors of anthocyanin biosynthesis in buckwheat hypocotyls (Zoń and Amrhein, 1992; Zoń et al., 2002, 2005).

2. Results and discussion

The derivatives of 2-aminoindane-2-phosphonic acid (**1**–**4**, Fig. 1) were synthesized from derivatives of 1,2-bis(bromomethyl)benzene (**7**–**9** and **19**, Scheme 1) by known methods (Zoń, 1979). First, 4-substituted derivatives of ethyl 2-(diethoxyphosphoryl)indane-2-carboxylates

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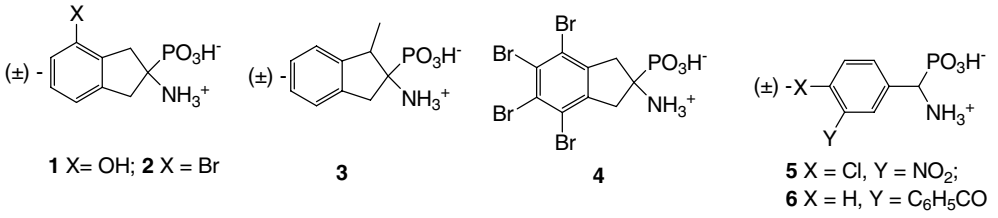
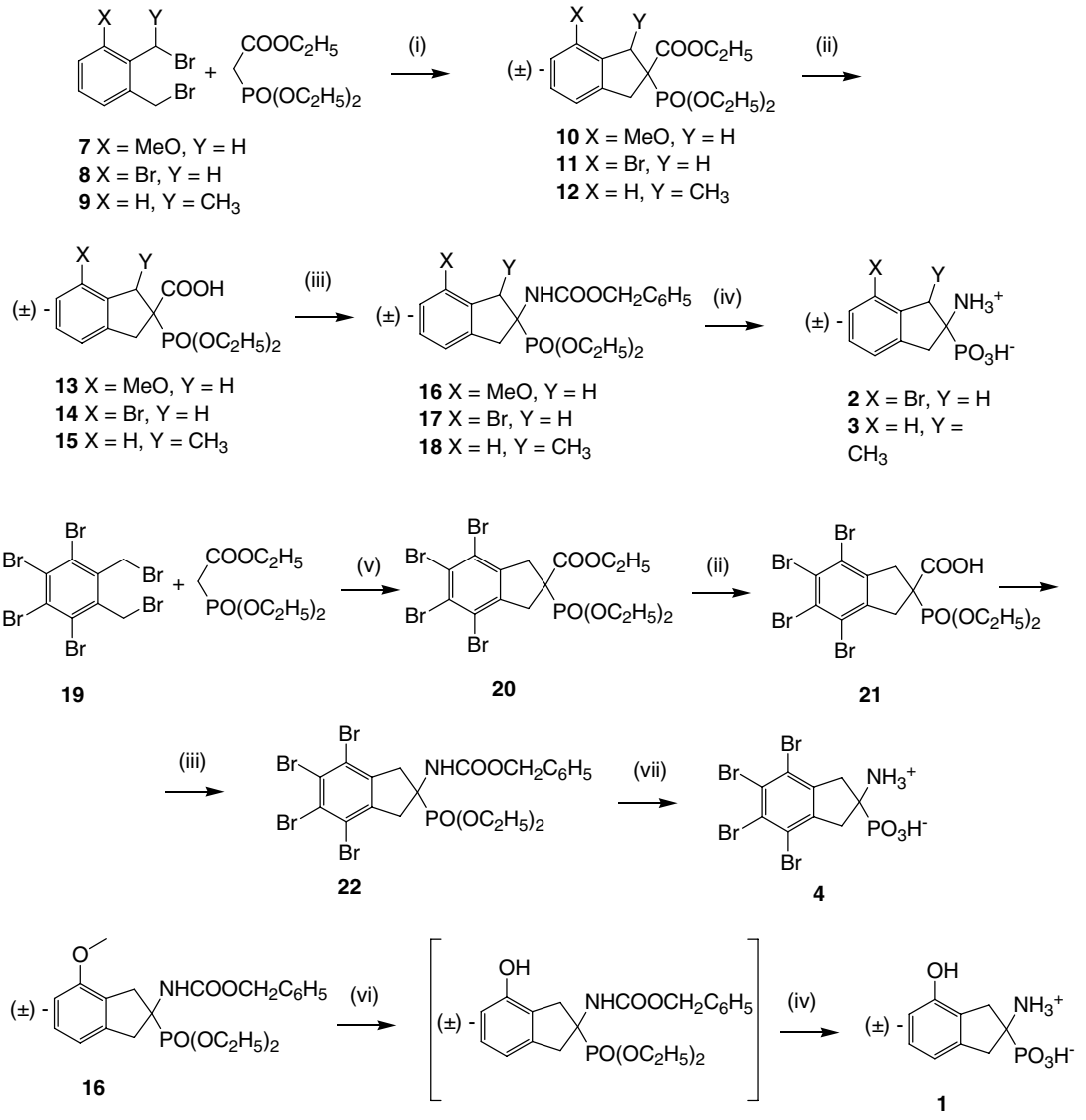


Fig. 1. The structures of synthesized and evaluated compounds in this work.



Scheme 1. *Reagents and conditions*: (i) NaOH, $C_6H_5CH_3$, $(C_4H_9)_4NBr$, 14° → RT; (ii) NaOH, H_2O, reflux; (iii) $C_6H_5CH_3$, $(C_6H_5)_2P(O)N_3$, $C_6H_5CH_2OH$, reflux; (iv) conc. HCl, H_2O, reflux, 20 h; (v) THF, NaH, RT and then heated to reflux; (vi) CH_2Cl_2, BBr_3, O °C → RT; (vii) 40% HBr in water–CH_3COOH, reflux, 10 h.

(**10**–**11** and **20**, Scheme 1) were synthesized. These compounds (**10**–**12** and **20**) were obtained with lower yields than the corresponding 5-substituted ethyl 2-(diethoxyphosphoryl)indane-2-carboxylates (Zoń et al., 2005). Ethyl 2-(diethoxyphosphoryl)-1-methylindane-2-carboxylate (**12**) was obtained in medium yield as a single diastereoisomer, as determined by ^{31}P NMR. In the second step, the ethyl carboxylates (**10**–**12** and **20**, Scheme 1) were hydrolysed with high yield to the corresponding carboxylic acids (**13**–**15** and **21**, Scheme 1). Next, after the *Curtius* degradation of the carboxylic acids, the urethane-phosphosphonates (**16**–**18** and **22**, Scheme 1) were formed. Finally, the complete deprotection of the functionality gave the derivatives of 2-aminoindane-2-phosphonic acids (**1**–**4**, Scheme 1).

The derivatives of substituted 1-aminobenzylphosphonic acid (**5**–**6**, Fig. 1) were obtained in a modified Green's et al. hydrophosphonylation procedure using diphenylmethylamine (benzhydrylamine) as a source of the amino group (Green et al., 1994). Pure diethyl 1-(diphenylmethylamino)benzylphosphonates (**27** and **28**, Scheme 2) were completely deprotected in a simple acidic hydrolysis to yield the corresponding aminophosphonic acids **5** and **6** (Scheme 2).

The six new derivatives of 2-aminoindane-2-phosphonic acid and 1-aminobenzylphosphonic acid (**1**–**6**, Fig. 1) were evaluated as inhibitors of buckwheat phenylalanine ammonia-lyase and as well as inhibitors of anthocyanin biosynthesis in buckwheat hypocotyls (Zoń and Amrhein, 1992; Zoń et al., 2002, 2005). The results are presented in Table 1.

2-Amino-4-bromoindane-2-phosphonic acid (**2**) was the strongest inhibitor both in PAL and anthocyanin tests. In general 4-substituted derivatives of AIP are stronger inhibitors of PAL than corresponding 5-substituted compounds, however IC_{50} is not changed. For example the inhibition constant of 2-amino-4-bromoindane-2-phosphonic acid (**2**, $K_i = 0.09$ μM, $IC_{50} = 33.88$ μM, Table 1) is one order of magnitude lower than that for 2-amino-5-bromoindane-2-phosphonic acid ($K_i = 0.57$ μM and $IC_{50} = 39.8$ μM) (Zoń et al., 2005). A similar tendency was observed for hydroxy substituted derivatives of 2-aminoindane-2-phosphonic acid based on comparison of corresponding data for 2-amino-4-hydroxyindane-2-phosphonic acid (**1**, Table 1) with 2-amino-5-hydroxyindane-2-phosphonic acid from the reference (Zoń et al., 2005).

1-Amino-4′-chloro-3′-nitrobenzylphosphonic acid (**5**) is a weaker inhibitor of PAL compared to compound **2** by two orders of magnitude. The lower inhibitory activities for compounds **4** and **6** can be explained by the presence of too bulky substituents at the benzene ring, as our earlier studies indicated that the PAL hydrophobic pocket is of limited space (Zoń et al., 2002).

Table 1
In vitro (K_i) and in vivo (IC_{50}) inhibitory activity of obtained aminophosphonic acids (**1**–**6**)

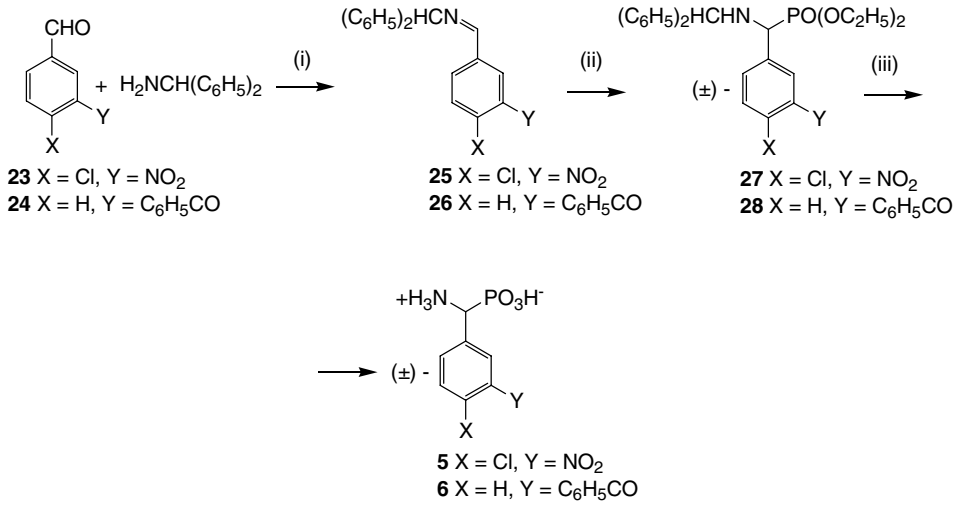
Compound	K_i, buckwheat PAL[a] (μM)	IC_{50} anthocyanin[b] (μM)
1	1.95	60.26
2	0.09	33.88
3	8.64	851.14
4	n.d.[c]	n.d.[d]
5	7.27	19.95
6	n.d.[c]	n.d.[c]
AIP	0.08[e]	1.5[e]

[a] Standard deviations for K_i values were in the range of 5–8%.
[b] Standard deviations for IC_{50} values were in the range of 10–15%.
[c] Inhibition about 90% for the 1 mM inhibitor concentration.
[d] Inhibition about 70% for the 1 mM inhibitor concentration.
[e] AIP is the strongest in vivo PAL inhibitor and was used in this studies as standard. The data were taken from the literature (Zoń and Amrhein, 1992).

A ratio of inhibition constants for enantiomers of any 4-substituted derivatives of 2-aminoindane-2-phosphonic acid (K_i^S/K_i^R) are expected to be different by one order of magnitude since for conformationally labile enantiomers of 1-amino-2-phenylethylphosphonic acid we have found it to be at that range (Laber et al., 1986; $K_i^S = 11.6$ μM; $K_i^R = 1.5$ μM; $K_i^S/K_i^R \approx 8$).

3. Conclusions

The results suggest that 4-substituted are promising derivatives of 2-aminoindane-2-phosphonic acid containing a photoreactive group may lead to phenylalanine ammonia-lyase inhibitors suitable for photoaffinity labelling of the enzyme and they are more promising than corresponding 5-substituted derivatives. In the line of derivatives of 1-aminobenzylphosphonic acid we cannot yet formulate similar conclusion as the above.



Scheme 2. *Reagents and conditions*: (i) CH_2Cl_2, K_2CO_3, RT, 3 h; (ii) $(C_2H_5O)_2P(O)H$, 100 °C, 2 h; (iii) conc. HCl, H_2O, reflux, 20 h.

4. Experimental

^{1}H NMR spectra were recorded at 300 MHz; ^{31}P NMR at 121 MHz; ^{13}C NMR at 75 MHz on Bruker instruments. For samples dissolved in $CDCl_3$ the reference signal was $CHCl_3$: whereas for measurements in D_2O–DCl it was the external H_2O. Melting points were determined using a Boëtius apparatus and are uncorrected. Elemental analyses were performed by the Laboratory of Elemental Analysis of the Institute Organic Chemistry, Biochemistry and Biotechnology, Wrocław. TLC was carried out on commercially available pre-coated plates (Fluka silica gel on TLC-PET foils with or without fluorescent indicator 254 nm).

The inhibition constants (K_i) for buckwheat PAL and the concentrations of the compounds inhibiting anthocyanin production in illuminated buckwheat hypocotyls by 50% (IC_{50}values) were determined as described previously (Zoń and Amrhein, 1992; Zoń et al., 2002, 2005; Laber et al., 1986).

4.1. 1,2-Bis(bromomethyl)-3-methoxybenzene (7)

1,2-Bis(bromomethyl)-3-methoxybenzene (**7**) was obtained from commercially available 2,3-dimethylphenol. To a solution of 2,3-dimethylphenol (100 g, 0.818 mol), dimethyl sulfate (155 ml, 1.636 mol) and tetrabutylammonium hydrogensulfate (22.79 g, 0.0818 mol) in acetone (500 ml) and solid K_2CO_3 (339.2 g, 2.454 mol) was added gradually while stirring. After initial exothermic reaction stirring under reflux was continued for 24 h. The acetone solution was filtered off and the precipitate washed with acetone (3×350 ml). Acetone from the washings was evaporated to yield an oily residue, which was dissolved in $CHCl_3$ (150 ml) and consecutively washed with 1 M NaOH (50 ml and 30 ml), water (2×50 ml), and brine (2×50 ml) and then dried over $MgSO_4$. The dry $CHCl_3$ solution was evaporated and the residue was distilled under reduced pressure to give 2,3-dimethylanisole: 81.8 g, 74%, bp 86–88 °C (42 mm Hg). Then 3-methoxyphthalic acid was obtained from 2,3-dimethylanisole by permanganate oxidation according to a modified literature procedure (Wentzel et al., 2000). To a suspension of 2,3-dimethylanisole (10.0 g, 0.073 mol), *t*-BuOH (120 ml), water (295 ml) and solid $KMnO_4$ (73.89 g, 0.467 mol) was added. The suspension was refluxed for 2 h. The precipitate of MnO_2 was filtered off and washed with hot water (2×40 ml). The combined filtrates were acidified to pH ~ 1 with concentrated HCl and a precipitate of 3-methoxyphthalic acid was filtered off and washed with $CHCl_3$ to give product: 5.80 g, 40%, mp 156–159 °C (Beard and Hauser, 1960; mp 169.5–170.5 °C). To reduce 3-methoxyphthalic acid with the borane-methyl sulfide complex (Fujita and Mori, 2001) a solution of 3-methoxyphthalic acid (8.40 g, 0.0428 mol) in dry tetrahydrofuran (140 ml) was added at −6 °C to a solution of the borane-methyl sulfide complex (12.2 ml, 0.13 mol) in dry tetrahydrofuran (12 ml) dropwise during 20 min under a nitrogen atmosphere. Cooling and stirring were continued for another 10 min. Then the cooling bath was removed and the reaction mixture was gradually warmed to 55 °C and kept at 55 °C during 13 h while stirring. After cooling down to 20 °C, 1 M NaOH (360 ml) was added and the solution was stirred during the next 1 h. Finally the solution was concentrated to 1/3 of its starting volume on a vacuum evaporator. The residue was extracted with ethyl acetate (3×60 ml). The combined extracts were washed with brine (60 ml) and dried with $MgSO_4$. The solution was evaporated to obtain 1,2-bis(hydroxymethyl)-3-methoxybenzene. The crude product was crystallized from $CHCl_3$ to give the pure diol: 1.41 g, 20%, mp 94–95 °C (lit. Brewster and Jones, 1969; mp 92–93 °C). Then 3-methoxy-1,2-bis(bromomethyl)benzene (**7**) was obtained from 3-methoxy-1,2-bis(hydroxymethyl)-benzene by modified literature procedures (Tolbert and Haubrich, 1994; Oshakawa et al., 1997). To a solution of 3-methoxy-1,2-bis(hydroxymethyl)benzene (1.50 g, 8.92 mmol) in dry diethyl ether (55 ml) at 4–8 °C, PBr_3 (3.0 ml, 0.0312 mol) in dry diethyl ether (7 ml) was added dropwise during 20 min. The mixture was heated at reflux for 9 h and then poured into crushed ice (100 ml). The ether layer was separated and the aqueous layer was additionally extracted with diethyl ether (3×15 ml). The combined ether extracts were washed with brine (25 ml) and dried with Na_2SO_4. The ether was evaporated to give 1,2-bis(bromomethyl)-3-methoxybenzene (**7**): 2.23 g, 85%, mp 80–81 °C ((Oshakawa et al., 1997) mp 78–79 °C).

4.2. 3-Bromo-1,2-bis(bromomethyl)benzene (8)

3-Bromo-1,2-bis(bromomethyl)benzene (**8**) was obtained according to a modified literature procedure (Kreher and Herd, 1988). A suspension of 3-bromo-o-xylene (5.0 g, 0.027 mol), *N*-bromosuccinimide (9.62 g, 0.054 mol) and azoisobutyronitrile (0.126 g, 0.77 mmol) in dry CCl_4 (26 ml) was gradually warmed to boiling point and kept under reflux for 0.5 h. The precipitate of succinimide was filtered off and the solution was evaporated to dryness to give **8**: 8.15 g, 88%, mp 44–48 °C.

4.3. 1-(1′-Bromoethyl)-2-bromomethylbenzene (9)

1-(1′-Bromoethyl)-2-bromomethylbenzene (**9**) was obtained from 2-acetylbenzoic acid (Cannone et al., 1988; Berner, 1982). To a suspension of $LiAlH_4$ (3.3226 g, 0.088 mol) in dry (135 ml), cooled to −1 °C, was added during 80 min a solution of 2-acetylbenzoic acid (9.06 g, 0.055 mol) in THF (20 ml). The mixture was stirred during 10 min then warmed to room temperature and left overnight. The resulting suspension was cooled to 0 °C and a saturated solution of NH_4Cl (120 ml) was added. Additional diethyl ether (240 ml) was added. Layers of the mixture were separated and the water layer was washed with diethyl ether (50 ml). All organic layers were combined, washed with brine (3×100 ml) and dried with $MgSO_4$.

The solvent was evaporated to dryness and the residue was crystallized from *t*-BuOMe to give 1-(1′-hydroxyethyl)-2-hydroxymethylbenzene: 2.40 g, 30%, mp 66–67 °C ((Berner, 1982) mp 71 °C); ^{1}H NMR spectral data (300 MHz, $CDCl_3$): δ 1.47 (3H, *d*, $^3J_{HH} = 6.5$ Hz, CH_3); 3.32 (2H, *bs*, OH); 4.50 (1H, *d*, $^3J_{HH} = 12.1$ Hz, CH_2O); 4.66 (1H, *d*, $^3J_{HH} = 12.1$ Hz, CH_2O); 5.03 (1H, *q*, $^3J_{HH} = 6.5$ Hz, CHO); 7.18–7.28 (3H, *m*, C_6H_4); 7.38 (1H, *d*, $^3J_{HH} = 7.5$ Hz, C_6H_4).

Using a similar procedure as for the synthesis of 1,2-bis(bromomethyl)-3-methoxybenzene (**7**), 1-(1′-bromoethyl)-2-bromomethylbenzene (**9**) was obtained from 1-(1′-hydroxyethyl)-2-hydroxymethylbenzene (2.40 g, 0.0162 mol): 3.66 g, 81%. ^{1}H NMR spectral data (300 MHz, $CDCl_3$): δ 2.04 (3H, *d*, $^3J_{HH} = 6.8$ Hz, CH_3); 4.44 (1H, *d*, $^2J_{HH} = 9.5$ Hz, CH_2Br); 4.73 (1H, *d*, $^2J_{HH} = 10.6$ Hz, CH_2Br); 5.55 (1H, *q*, $^3J_{HH} = 6.8$ Hz; CH(Br)C); 7.20–7.33 (3H, *m*, C_6H_4); 7.57 (1H, *d*, $^3J_{HH} = 7.7$ Hz, C_6H_4).

4.4. General procedure for the synthesis of substituted ethyl 2-(diethoxyphosphoryl)indane-2-carboxylate (**10–12**) (Zoń et al., 2005)

A solution of derivatives of 1,2-bis(bromomethyl)benzene (0.02 mol), triethyl phosphonoacetate (5.2 ml, 0.026 mol) and tetrabutylammonium bromide (1.290 g, 0.004 mol) in toluene (20 ml) was stirred and cooled to 14 °C. Powdered sodium hydroxide (2.4 g, 0.06 mol) was added in about 25 portions during 5 h at a temperature of 14–18 °C. The solution was stirred additionally for 50 min at the same temperature. The reaction mixture was filtered off to remove NaBr precipitate and the filtrate was washed with water (3×5 ml; to pH $\sim$ 7) and brine (2×5 ml). The toluene layer was dried with $MgSO_4$. The toluene was then evaporated and the residue was purified by silica gel chromatography.

Data of ***10***: 0.91 g; 13%; $R_f = 0.34$ (ethyl acetate); ^{1}H NMR spectral data (300 MHz, $CDCl_3$): δ 1.21–1.28 (9H, *m*, CH_3C); 3.42–3.74 (4H, *m*, CH_2CCH_2); 3.78 (3H, *s*, CH_3O); 4.02–4.23 (6H, *m*, CH_2O); 6.63 (1H, *d*, $^3J_{HH} = 8.1$ Hz, C_6H_3); 6.77 (1H, *d*, $^3J_{HH} = 7.5$ Hz, C_6H_3); 7.11 (1H, *dd*, $^3J_{HH} = 7.8$ Hz, $^3J_{HH} = 7.8$ Hz, C_6H_3); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, $CDCl_3$): δ 27.45 (*s*).

Data of ***11***: 1.12 g; 14%; $R_f = 0.39$ (ethyl acetate); ^{1}H NMR spectral data (300 MHz, $CDCl_3$): δ 1.23–1.28 (9H, *m*, CH_3C); 3.49–3.82 (4H, *m*, CH_2CCH_2); 4.02–4.23 (6H, *m*, CH_2O); 7.00 (1H, *dd*, $^3J_{HH} = 7.6$ Hz, $^3J_{HH} = 7.6$ Hz, C_6H_3); 7.09 (1H, *d*, $^3J_{HH} = 7.1$ Hz, C_6H_3); 7.28 (1H, *dd*, $^3J_{HH} = 7.7$ Hz, $^4J_{HH} = 0.5$ Hz, C_6H_3); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, $CDCl_3$): δ 26.74 (*s*).

Data of ***12***: 2.25 g; 33%; $R_f = 0.31$ (ethyl acetate); ^{1}H NMR spectral data (300 MHz, $CDCl_3$): δ 1.17 (3H, *dxt*, $^3J_{HH} = 7.1$ Hz, $^4J_{HP} = 0.4$ Hz, CH_3C); 1.24 (3H, *dxt*, $^3J_{HH} = 6.4$ Hz, $^4J_{HP} = 0.3$ Hz, CH_3C); 1.28 (3H, *t*, $^3J_{HH} = 7.2$ Hz, CH_3C); 1.32 (3H, *d*, $^3J_{HH} = 7.1$ Hz, CH_3C); 3.44 (1H, *dd*, $^2J_{HH} = 16.3$ Hz, $^3J_{HP} = 16.4$ Hz, CCH_2); 3.67 (1H, *dd*, $^2J_{HH} = 16.3$ Hz, $^3J_{HP} = 16.1$ Hz, CCH_2); 3.78– 4.15 (5H, *m*, CH_2OP and CHC); 4.25 (2H, *q*, $^3J_{HH} = 8.3$ Hz, CH_2O); 7.12–7.28 (4H, *m*, C_6H_4); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, $CDCl_3$): δ 28.34 (*s*).

4.5. General procedure for the synthesis of substituted 2-(diethoxyphosphoryl)indane-2-carboxylic acid (**13–15**)

A solution of ethyl 2-(diethoxyphosphoryl)indane-2-carboxylates (**10–12**, 0.01 mol), sodium hydroxide (0.50 g, 0.0125 mol) in water (0.78 ml) and 95% ethanol (7.6 ml) was heated at reflux for about 18 h. The ethanol was evaporated to dryness under reduced pressure. Water (21 ml) was added to the residue and extracted with diethyl ether (3×10 ml), which was discarded. The aqueous layer was acidified with concentrated hydrochloric acid to pH $\sim$ 1 and extracted with CH_2Cl_2 (3×18 ml). The combined CH_2Cl_2 layers were washed with water (2×18 ml), and brine (18 ml), then dried with $MgSO_4$, before evaporation of the CH_2Cl_2.

Data of ***13***: 1.97 g; 60%; ^{1}H NMR spectral data (300 MHz, $CDCl_3$): δ 1.22 (6H, *2xt*, $^3J_{HH} = 6.7$ Hz; CH_3); 3.37–3.55 (2H, *m*, CH_2O); 3.62–3.71 (2H, *m*, CH_2O); 3.77 (3H, *s*, CH_3O); 4.06–4.19 (4H, *m*, CH_2CCH_2); 6.63 (1H, *d*, $^3J_{HH} = 8.1$ Hz, C_6H_3); 6.76 (1H, *d*, $^3J_{HH} = 7.4$ Hz, C_6H_3); 7.10 (1H, *dd*, $^3J_{HH} = 7.8$ Hz, $^3J_{HH} = 7.8$ Hz, C_6H_3); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, $CDCl_3$): δ 28.59 (*s*).

Data of ***14***: 2.79 g; 74%; ^{1}H NMR spectral data (300 MHz, $CDCl_3$): δ 1.21–1.28 (6H, *m*, CH_3); 3.45–3.82 (4H, *m*, CH_2CCH_2); 4.08–4.25 (4H, *m*, CH_2O); 6.97–7.30 (3H, *m*, C_6H_3); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, $CDCl_3$): δ 27.70 (*s*).

Data of ***15***: 2.50 g; 80%; mp 127–130 °C; ^{1}H NMR spectral data (300 MHz, $CDCl_3$): δ 1.12 (6H, *t*, $^3J_{HH} = 7.0$ Hz, CH_3); 1.31 (3H, *d*, $^3J_{HH} = 7.1$ Hz, CH_3); 3.26 (1H, *m*, CH_2O); 3.65–3.76 (1H, *m*, CH_2O); 3.79–3.92 (1H, *m*, CH_2O); 3.94–4.02 (3H, *m*, CH_2CCH_2); 4.04–4.17 (1H, *m*, CH_2O); 7.04–7.14 (4H, *m*, C_6H_4); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, $CDCl_3$): δ 29.96 (*s*).

4.6. General procedure for the synthesis of substituted of diethyl 2-(benzyloxycarbonylamino)indane-2-phosphonate (**16–18**)

A solution of the substituted derivative of 2-(diethoxyphosphoryl)indane-2-carboxylic acids (**13-15**, 0.01 mol), triethylamine (1.8 ml, 0.013 mol), diphenylphosphoryl azide (DPPA, 2.8 ml, 0.013 mol), benzyl alcohol (1.3 ml, 0.013 mol) in dry toluene (6.7 ml) was refluxed for 8 h under protection from moisture. CH_2Cl_2 (75 ml) was added to the solution and washed with water (2×30 ml), then with a saturated aqueous solution of $NaHCO_3$ (2×38 ml), and finally with brine (2×38 ml). The organic layer was then dried with $MgSO_4$ and evaporated to dryness under reduced pressure to give the crude product, which was purified by chromatography on silica gel.

Data of ***16***: 2.51 g; 58%; $R_f = 0.33$ (ethyl acetate); ^{1}H NMR spectral data (300 MHz, $CDCl_3$): δ 1.19–1.26 (6H,

m, CH_3); 3.36–3.64 (4H, *m*, CH_2CCH_2); 3.78 (3H, *s*, CH_3O); 4.02–4.13 (4H, *m*, CH_2O); 5.01 (2H, *s*, $ArCH_2O$); 5.05 (1H, *bs*, NH); 6.66 (1H, *d*, $^3J_{HH} = 7.4$ Hz, C_6H_3); 6.78 (1H, *d*, $^3J_{HH} = 7.4$ Hz, C_6H_3); 7.13 (1H, *dd*, $^3J_{HH} = 7.8$ Hz, $^3J_{HH} = 7.8$ Hz, C_6H_3); 7.25–7.34 (5H, *m*, C_6H_5); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, $CDCl_3$): δ 28.12 (*s*).

Data of ***17***: 1.64 g; 34%; $R_f = 0.44$ (ethyl acetate); ^1H NMR spectral data (300 MHz, $CDCl_3$): δ 1.20–1.28 (6H, *m*, CH_3); 3.46–3.76 (4H, *m*, CH_2CCH_2); 4.02–4.14 (4H, *m*, CH_2O); 5.02 (2H, *s*, $ArCH_2O$); 5.16 (1H, *d*, $^3J_{PH} = 4.1$ Hz, NH); 6.99–7.10 (2H, *m*, $C_6H_3$and C_6H_5); 7.24–7.36 (6H, *m*, C_6H_3 and C_6H_5); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, $CDCl_3$): δ 27.56 (*s*).

Data of ***18***: 1.16 g; 28%; $R_f = 0.44$ (ethyl acetate); mp 114–115 °C (ethyl acetate); ^1H NMR spectral data (300 MHz, $CDCl_3$): δ 1.18–1.29 (6H, *m*, CH_3); 1.36 (3H; *d*, $^3J_{HH} = 7.1$ Hz, CH_3C); 3.42–3.52 (1H, *m*, $CHCCH_2$); 3.73–3.82 (1H, *m*, $CHCCH_2$); 4.04–4.15 (5H, *m*, $CHCCH_2$ and CH_2OP); 4.92 (1H, *d*, $^2J_{HH} = 12.2$ Hz, $ArCH_2$); 4.99 (1H, *d*, $^3J_{PH} = 2.7$ Hz, NH); 5.04 (1H, *d*, $^3J_{HH} = 12.2$ Hz, $ArCH_2$); 7.09–7.13 (1H, *m*, C_6H_4); 7.15–7.18 (3H, *m*, C_6H_4 and C_6H_5); 7.26–7.33 (5H, *m*, C_6H_4 and C_6H_5); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, $CDCl_3$): δ 28.14 (*s*).

4.7. (±)-2-Amino-4-hydroxyindane-2-phosphonic acid (*1*)

2-Amino-4-hydroxyindane-2-phosphonic acid (**1**) was obtained by a two-step deprotecting procedure from diethyl 2-(benzyloxycarbonylamino)-4-methoxyindane-2-phosphonate (**16**). To a stirred solution of compound **16** (0.778 g, 1.795 mmol) in dry CH_2Cl_2 (1.8 ml), cooled in an ice-NaCl bath for 30 min under an N_2 atmosphere, a solution ~1 M of BBr_3 (0.69 ml, 7,8 mmol) in CH_2Cl_2 (7.2 ml) was added over the course of 5 min. The solution was stirred until the ice had melted, and was then left overnight. The reaction mixture was cooled to 0 °C and water (15 ml) was added dropwise. The mixture was warmed to room temperature and evaporated to dryness. The residue was dissolved in water (16 ml) and again evaporated. Water (21 ml) and concentrated hydrochloric acid (21 ml) were added to the residue, and the mixture was refluxed for 20 h. The solution was washed with diethyl ether (2 × 22 ml) and evaporated to dryness. The water layer was treated with charcoal and then evaporated to dryness. The residue was dissolved in 0.05 M HCl and purified by ion exchange chromatography on Dowex 50W (eluent: 0.05 M HCl). Fractions containing 2-amino-4-hydroxyindane-2-phosphonic acid were identified based on TLC ($R_f = 0.36$, silicagel; butanol–acetic acid–water=3:1:1 v/v/v, ninhydrin). The selected fractions were combined and evaporated yielding 2-amino-4-hydroxyindane-2-phosphonic acid (**1**) as hydrochloride: 0.086 g; 18%; mp 320–330 °C (decomposition); ^1H NMR spectral data (300 MHz, D_2O–DCl): δ 3.02–3.22 (2H, *m*, CH_2CCH_2); 3.41–3.62 (2H, *m*, CH_2CCH_2); 6.74 (1H, *d*, $^3J_{HH} = 8.0$ Hz, C_6H_3); 6.88 (1H, *d*, $^3J_{HH} = 7.5$ Hz, C_6H_3); 7.15 (1H, *dd*, $^3J_{HH} = 7.6$ Hz, $^3J_{HH} = 7.6$ Hz, C_6H_3); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, D_2O–DCl): δ 17.06 (*s*); ^{13}C NMR spectral data (75 MHz, D_2O–DCl): δ 37.10, 40.42, 61.02 (*d*, $^1J_{PC} = 152.9$ Hz, NCP), 114.09, 117.27, 124.85 (*d*, $J_{PC} = 9.0$ Hz), 129.55, 141.23 (*d*, $J_{PC} = 9.2$ Hz), 152.26.

4.8. Procedure for the synthesis of substituted 2-aminoindane-2-phosphonic acids (*2*–*3*)

A solution of the substituted derivative of diethyl 2-(benzyloxycarbonylamino)indane-2-phosphonate (**17** and **18**, 0.01 mol), concentrated hydrochloric acid (30 ml) and water (30 ml) was refluxed for 20 h. The solution was extracted with diethyl ether (3 × 60 ml). The water layer was boiled with activated charcoal and evaporated to dryness. The residue was dissolved twice in methanol (80 ml and 40 ml) and twice evaporated to dryness. Propylene oxide was added (0.6 ml). The resulting precipitate was isolated by filtration and was used in the biological tests.

Data of ***2*** *as hydrochloride*: 1.74 g; 53%; mp 238–240 °C; ^1H NMR spectral data (300 MHz, D_2O–DCl): δ 2.54 (1H, *dd*, $^2J_{HH} = 24.0$ Hz, $^3J_{HP} = 5.6$ Hz, CH_2CCH_2); 2.61 (1H, *dd*, $^2J_{HH} = 21.0$ Hz, $^3J_{HP} = 5.9$ Hz, CH_2CCH_2); 2.88 (1H, *dd*, $^2J_{HH} = 32.1$ Hz, $^3J_{HP} = 12.6$ Hz, CH_2CCH_2); 2.93 (1H, *dd*, $^2J_{HH} = 31.9$ Hz, $^3J_{HP} = 13.7$ Hz, CH_2CCH_2); 6.42 (1H, *t*, $^3J_{HH} = 7.7$ Hz, C_6H_3); 6.53 (1H, *d*, $^3J_{HH} = 7.4$ Hz, C_6H_3); 6.69 (1H, *d*, $^3J_{HH} = 7.8$ Hz, C_6H_3); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, D_2O–DCl): δ 18.64 (*s*); ^{13}C NMR spectral data (75 MHz,D_2O–DCl): δ 39.45; 39.96, 57.93 (*d*, $^1J_{PC} = 160.8$ Hz, NCP), 118.04, 123.04, 128.79, 129.66, 137.22 (*d*, $^3J_{PC} = 9.3$ Hz), 138.58 (*d*, $^3J_{PC} = 8.6$ Hz).

Data of ***3*** *as hydrochloride*: 0.11 g; 45%; mp 231–231 °C; ^1H NMR spectral data (300 MHz, D_2O–DCl): δ 1.06 (3H, *d*, $^3J_{HH} = 7.3$ Hz, CH_3); 2.75–2.81 (1H, *d*, $^3J_{HH} = 17.2$ Hz, CH_2CCH); 3.10–3.24 (1H, *m*, CH_2CCH); 3.38–3.46 (1H, *m*, CH_2CCH); 6.87–6.92 (4H, *m*, C_6H_4); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, $CDCl_3$): δ 19.44 (*s*); ^{13}C NMR spectral data (75 MHz, D_2O–DCl): δ 11.68, 39.15, 43.04, 64.0 (*d*, $^1J_{PC} = 158.7$ Hz, NCP), 123.69, 124.67, 127.75, 127.77, 136.66 (*d*, $^3J_{PC} = 10.9$ Hz), 142.60 (*d*, $^3J_{PC} = 11.6$ Hz).

4.9. 1,2,3,4-Tetrabromo-5,6-bis(bromomethyl)benzene (*19*)

1,2,3,4-Tetrabromo-5,6-bis(bromomethyl)benzene was obtained according to a modified literature procedure (Kreher and Herd, 1988). A solution of 3,4,5,6-tetrabromo-o-xylene (16.6 g, 0.0393 mol), *N*-bromosuccinimide (14.34 g, 0.0806 mol) and azobisisobutyronitrile (0.20 g, 1.2 mmol) in dry CCl_4 (26 ml) was gradually warmed to boiling point and kept under reflux for 2.5 h. The precipitate of succinimide was filtered off from the hot solution and filtrate was cooled to room temperature. 1,2,3,4-Tetrabromo-5,6-bis(bromomethyl)benzene (**19**) was filtered off: 16.9 g; 74%; mp 165–167 °C (Kreher and Herd, 1988; mp 158–160 °C).

4.10. Ethyl 2-(diethoxyphosphoryl)-4,5,6,7-tetrabromoindane-2-carboxylate (**20**)

To a suspension of NaH (80% suspension in mineral oil, 19 mmol) in dry THF (30 ml), under N_2, a solution of 1,2,3,4-tetrabromo-5,6-bis(bromomethyl)benzene (**19**, 5.0 g, 0.0086 mol) and triethyl phosphonoacetate (1.93 g, 0.0086 mol) in dry THF (45 ml) was added dropwise. The mixture was stirred for 30 min at room temperature, then refluxed for 4 h and finally was evaporated to dryness. The residue was taken up in CH_2Cl_2 (60 ml), and the solution extracted: water (50 ml), 2 M HCl (25 ml), saturated solution of $NaHCO_3$ (25 ml), brine (2×25) and dried with $MgSO_4$. The solvent was evaporated to dryness and the residue extracted with diethyl ether. The ether extract was concentrated and the product left to crystallise. Yield **20**: 1.50 g; 27%; mp 116–118 °C; ^{1}H NMR spectral data (300 MHz, $CDCl_3$): δ 1.21–1.31 (9H, *m*, CH_3C); 3.59–3.86 (4H, *m*, CH_2CCH_2); 4.08–4.26 (6H, *m*, CH_2O); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, $CDCl_3$): δ 25.55 (*s*).

4.11. 2-(Diethoxyphosphoryl)-4,5,6,7-tetrabromoindane-2-carboxylic acid (**21**)

A solution of ethyl 2-(diethoxyphosphoryl)-4,5,6,7-tetrabromoindane-2-carboxylate (**20**, 1.12 g, 1.74 mmol), sodium hydroxide (0.084 g, 3.09 mmol) solution in water (0.14 ml) and 95% ethanol (1.4 ml) was refluxed for about 20 h. The solvents were evaporated under reduced pressure. Then water (3.5 ml) was added to the residue and the resulting suspension acidified with concentrated hydrochloric acid to pH $\sim$ 1. The precipitate was filtered off to give **21**: 1.04 g; 97%; mp 235–236 °C; ^{1}H NMR spectral data (300 MHz, $CDCl_3$–DMSO): δ 0.83 (6H, *t*, $^3J_{HH} = 7.0$ Hz, CH_3); 3.07–3.19 (2H, *m*, CH_2O); 3.30–3.39 (2H, *m*, CH_2O); 3.64–3.73 (4H, *m*, CH_2CCH_2); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, $CDCl_3$): δ 30.74 (*s*).

4.12. Diethyl 2-(benzyloxycarbonylamino)-4,5,6,7-tetrabromoindane-2-phosphonate (**22**)

A solution of the 2-(diethoxyphosphoryl)-4,5,6,7-tetrabromoindane-2-carboxylic acid (**21**, 1.0 g, 1.63 mmol), diphenylphosphoryl azide (DPPA, 0.46 ml, 2.2 mmol), triethylamine (0.3 ml, 2.2 mmol), benzyl alcohol (0.2 ml, 2.2 mol) in dry toluene (2.2 ml) was refluxed for 6 h under protection from moisture. CH_2Cl_2 (12 ml) was then added to the solution, which was then washed with: water (2×5 ml), a saturated aqueous solution of $NaHCO_3$ (2×5 ml), brine (2×5 ml). The organic layer was dried with $MgSO_4$ and then evaporated to dryness under reduced pressure to give the crude product, which was treated with ethyl acetate (2 ml) and the solution obtained discarded. The residue was crystallized from ethanol to yield **22**: 0.45 g; 38%; mp 200–201 °C; ^{1}H NMR spectral data (300 MHz, $CDCl_3$): δ 1.27 (6H, *t*, $^3J_{HH} = 7.0$ Hz, CH_3); 3.64–3.69 (4H, *m*, CH_2CCH_2); 4.04–4.22 (4H, *m*, CH_2O); 5.01 (2H, *s*, $ArCH_2O$); 5.36 (1H, *d*, $^3J_{PH} = 6.3$ Hz, NH); 7.25–7.35 (5H, *m*, C_6H_5); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, $CDCl_3$): δ 26.86 (*s*).

4.13. 2-Amino-4,5,6,7-tetrabromoindane-2-phosphonic acid (**4**)

A suspension of diethyl 2-(benzyloxycarbonylamino)-4,5,6,7-tetrabromoindane-2-phosphonate (**22**, 0.20 g, 0.28 mmol) in glacial acetic acid (3 ml) and a solution of 40% HBr in water (6 ml) were refluxed for 10 h. The solution was evaporated to dryness. To the residue water was added (5 ml) and evaporated to dryness. This was done again to give 2-amino-4,5,6,7-tetrabromoindane-2-phosphonic acids (**4**) as hydrobromide: 0.13 g; 77%; mp 228–229 °C; ^{1}H NMR spectral data (300 MHz, DMSO–DCl): δ 3.26–3.35 (2H, *m*, CH_2CCH_2); 3.52–3.69 (2H, *m*, CH_2CCH_2); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, DMSO–DCl): δ 17.65 (*s*); ^{13}C NMR spectral data (75 MHz, DMSO–DCl): δ 44.84, 56.50 (*d*, $^1J_{PC} = 154.4$ Hz, NCP), 121.91, 126.82, 142.44 (*d*, $^3J_{PC} = 7.5$ Hz).

4.14. 3-Benzoylbenzaldehyde (**24**)

3-Benzoylbenzaldehyde was obtained from 3-(bromomethyl)benzophenone according to a modified literature procedure (Meerpoel et al., 1991). The latter was obtained by bromination of 3-methylbenzophenone according to the literature procedure (Stephenson, 1963).

A solution of Na (0.097 g, 4.2 mmol) and 2-nitropropane (0.36 ml, 4.0 mmol) in absolute MeOH (60 ml) under N_2 was stirred for 40 min. 3-(Bromomethyl)benzophenone was added and the solution left for 24 h. The mixture was poured into 10% aqueous solution of NH_4Cl (110 ml), stirred for 25 min and washed with CH_2Cl_2 (3×50 ml). The combined organic layer was dried with $MgSO_4$. The solvent was evaporated to dryness and the residue was crystallized from hexane to yield **24**: 0.46 g; 61%; mp 91–99 °C; ^{1}H NMR spectral data (300 MHz, $CDCl_3$): δ 7.45–8.48 (9H, *m*, C_6H_5 and C_6H_4), 10.00 (1H, *s*, CHO).

4.15. Derivatives of benzylidenebenzhydrylamine (**25**, **26**)

A solution of aldehyde (**23** or **24**, 0.027 mol) and benzhydrylamine (4.65 ml, 0.027 mol), CH_2Cl_2 (14 ml) was stirred at room temperature for 3 h. K_2CO_3 (7.1 g, 0.051 mol) was added and the mixture left overnight. The K_2CO_3 was filtered off and the solution evaporated to dryness under reduced pressure:

Data of **25**: 6.94 g; 73%; mp 81–82 °C (ethanol).

Data of **26**: the residue was washed with hexane; 5.27 g; 52%; mp 62–69 °C; ^{1}H NMR spectral data (300 MHz, $CDCl_3$): δ 5.20 (1H, *s*, CH $(Ar)_2$, *Z*-isomer); 5.61 (1H, *s*, $CH(Ar)_2$, *E*-isomer); 7.24–7.80 (19H, *m*, C_6H_5 and C_6H_4); 7.81 (1H, *s*, CHN, *Z*-isomer); 7,81 (1H, *s*, CHN, *E*-isomer).

4.16. Derivatives of diethyl 1-benzhyrylaminebenzylphosphonate (27, 28)

Benzylidenebenzhydryloamine (**25** or **26**, 0.0168 mol) and diethyl phosphite (2.6 ml, 0.02 mol) were heated for 2 h in ~100 °C.

Data of ***27***: This was crystallized from cyclohexane: 4.66 g; 58%; mp 98–99 °C; ^{1}H NMR spectral data (300 MHz, $CDCl_3$): δ 1.14 (3H, *t*, $^3J_{HH} = 7.1$ Hz, CH_3); 1.27 (3H, *t*, $^3J_{HH} = 7.1$ Hz, CH_3); 2.35 (1H, *bs*, NH); 3.88–4.00 (5H, *m*, CH_2O and CHN); 4.63 (1H, *s*, $CHAr_2$); 7.14–7.31 (10H, *m*, $2 \times C_6H_5$); 7.47 (2H, *m*, C_6H_3); 7.79 (1H, *s*, C_6H_3); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, $CDCl_3$): δ 23.36 (*s*).

Data of ***28***: This was purified by chromatography on silica gel; 1.60 g; 18%; $R_f = 0.27$ (ethyl acetate); ^{1}H NMR spectral data (300 MHz, $CDCl_3$): δ 1.11 (3H, *t*, $^3J_{HH} = 7.2$ Hz, CH_3); 1.32 (3H, *t*, $^3J_{HH} = 7.1$ Hz, CH_3), 1.63 (1H, *bs*, NH); 3.99 (1H, *d*, $^3J_{HP} = 19.0$ Hz, PCHN); 3.92–4.03 (2H, *m*, CH_2O); 4.12–4.22 (2H, *m*, CH_2O); 4.69 (1H, *s*, $CHAr_2$); 7.17–7.31 (10H, *m*, $2 \times C_6H_5$); 7.40–7.59 (5H, *m*, C_6H_5); 7.70–7.71 (1H, *m*, C_6H_3); 7.76–7.80 (3H, *m*, C_6H_4); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, $CDCl_3$): δ 24.75 (*s*).

4.17. Substituted 1-aminobenzylphosphonic acids (5, 6)

A solution of substituted derivatives of 1-aminobenzylphosphonic acid (**27** or **28**, 0.01 mol) in water (30 ml) and concentrated hydrochloric acid (30 ml) was refluxed for 20 h. The solution was washed with diethyl ether (3×60 ml), boiled with activated charcoal and evaporated to dryness. The residue was dissolved in methanol (80 ml) and evaporated to dryness. The residue was again dissolved in methanol (40 ml) and propylene oxide added (0.6 ml). The resulting precipitate was isolated by filtration.

Data of ***5***: 1.70 g; 64%; mp 240–241 °C; ^{1}H NMR spectral data (300 MHz, D$_2$O–DCl): δ 3.90 (1H, *d*, $^3J_{HP} = 17.3$ Hz, PCH); 6.78 (2H, *m*, C_6H_3); 7.22 (1H, *s*, C_6H_3); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, D$_2$O–DCl): δ 11.97 (*s*); ^{13}C NMR spectral data (75 MHz, D$_2$O–DCl): δ 50.58 (*d*, $^1J_{PC}$ =145.0 Hz, NCP), 124.92, 127.16, 130.71, 132.27, 132.64, 146.45.

Data of ***6***: 2.25 g; 77%; mp 255–257 °C; ^{1}H NMR spectral data (300 MHz, D$_2$O–DCl): δ 3.47 (1H, *d*, $^1J_{HP} = 17.3$ Hz, PCH); 6.07–6.12 (2H, *m*, C_6H_3 and C_6H_5); 6.19–6.33 (5H, *m*, C_6H_3 and C_6H_5); 6.40–6.44 (2H, *m*, C_6H_3 and C_6H_5); $^{31}P\{^1H\}$ NMR spectral data (121 MHz, D$_2$O–DCl): δ 13.25 (*s*); ^{13}C NMR spectral data (75 MHz, DMSO–D$_2$O–DCl): δ 50.88 (*d*, $^1J_{PC} = 147.3$ Hz, NCP), 127.50, 128.47, 129.23, 129.67 (*d*, $^3J_{PC} = 4.7$ Hz), 130.19, 131.30, 131.36, 132.72, 134.91, 136.34, 198.62.

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