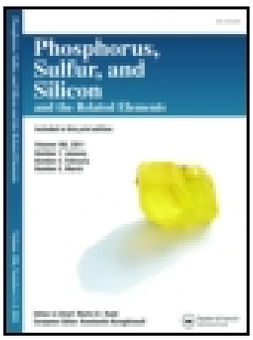

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Synthesis and *in vitro* antioxidant evaluation of new bis(α-aminoalkyl)phosphinic acid derivatives

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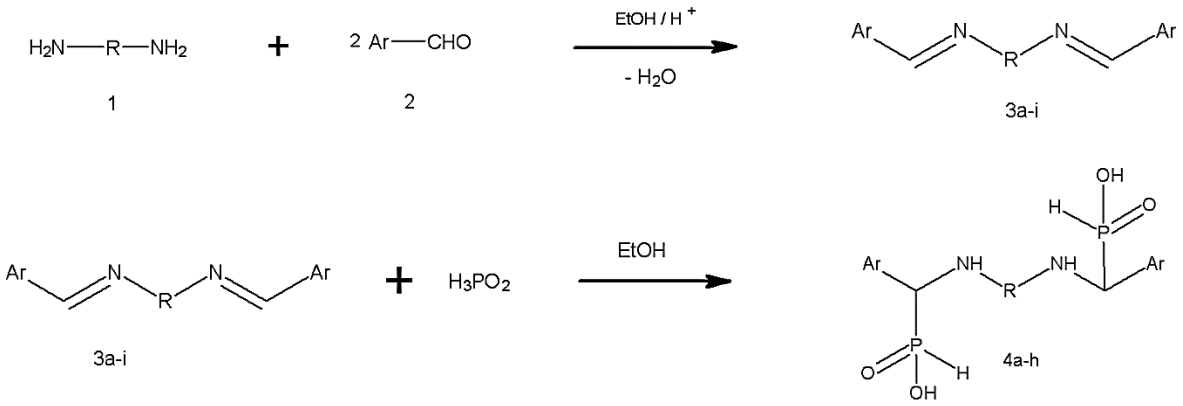
Abstract

Diamines were added to arylaldehydes in ethanol, which resulted in corresponding diimines. Novel bis-1-aminophosphinic acid compounds were synthesized through the interaction of diimines and hypophosphorous acid. The new compounds were characterized by elemental analyses, FT-IR and ^{1}H, ^{13}C and ^{31}P NMR techniques. The in vitro *antioxidant activity of the newly synthesized compounds were measured and found to exhibit significantly higher antioxidant activity than the standard.*



Keywords

Aldehydes; Amines; 1-Aminophosphinic acids; Antioxidant activity

INTRODUCTION

It is well known that amino acids are the main components of various proteins and that they generally play an important physiological role in life process. 1-aminophosphinic acids are phosphorus analogues of natural amino acids and are selective inhibitors of various proteolytic enzymes, particularly metallo-proteases.[1--3] For this reason, aminophosphinic acids have been researched and developed as potential antibacterial, antitumor and antivirotic materials in recent years.[4--6] Much consideration has been given to aminophosphinic acid ligands and their complexes because of their novel structures and properties.[7--13] Aminophosphonic acids are also found as constituents of natural products.[14] In contrast to the widely studied 1-aminophosphonic acid derivatives,[15--18] relatively few papers have reported the chemistry of α-aminophosphinic acid derivatives.

Reactive oxygen species (ROS) such as O_2^-, H_2O_2 and $^{\bullet}OH$ are generated in cells through aerobic metabolic processes or as a result of interaction with exogenous agents. Low ROS levels are essential for proper cell function, but excess levels lead to ‘oxidative stress’, which has been linked to the progression of ageing and many human diseases, e.g. neurogenerative, cardiovascular and cancer. Superoxide dismutases (SODs), catalase (CAT) and glutathione peroxidase (GPx) are enzymes which act as a primary cellular defence system against oxidative damage in living organisms. Organophosphorus compounds and P-heterocycles, in particular, have been recognized as antioxidant drugs.[19,20] Their mechanism and structure activity relationships (SAR) have been extensively studied.[21] Depending on their structure and scavenging properties, phosphites and phosphonates may act as both primary and secondary

antioxidants. In general, phosphites are considered to be hydroperoxide decomposing (secondary antioxidants), but certain aryl phosphites should also be capable of acting as radical chain-terminating (primary antioxidants) by trapping peroxyl radicals to produce aroxyl radicals. Recent studies have elucidated reaction modes and the relationship between structure, reaction mechanism and antioxidant activity.[20,21]

Over the past several years, our laboratories have reported the synthesis of 1-amino-*H*-phosphinic acids.[22,23] We have reported the synthesis and *in vitro* antimicrobial activity of novel aminophosphinic acids containing cyclobutane and 1.3-thiazole. Building on previous studies, we have prepared a series of derivatives of new α-aminophosphinic acids (Figure 1). In view of the importance of phosphinic acid derivatives, this study's goal was to find new biologically active molecules. Here we report a new series of bis-1-amino-*H*-phosphinic acids and a preliminary biological study of their antioxidative activity.

RESULTS AND DISCUSSION

Chemistry

Diimines are good precursors for synthesizing numerous organic compounds, especially heterocyclic compounds.[24,25] These easily accessible precursors can be produced by reacting aromatic aldehydes in ammonia.

Schiff bases **3a--i** were prepared following the published procedure[22,23] by condensing the corresponding diamines **(1)** with arylaldehyde **(2)** in ethanol at room temperature. The corresponding imines were obtained in quantitative yields. The preparation of bis-

aminophosphinic acids **4a--h** was performed following Baylis *et al*.[26] Reactions were carried out in boiling ethanol for 24 h, after which mixtures were left overnight to stir at room temperature (Figure 1).

Because two stereogenic carbons bonded to a phosphorus atom, and due to the prototopic transfer of the acidic proton between the phosphoryl (P = O) and acidic (P--OH) sites, these compounds exist as two diastereomeric forms: one meso-compound (R*, S*-4) and one racemic pair (S*, S* or R*, R*-4), as shown in Figure 2.

The structures of **4a--h** were determined by spectroscopy (^{1}H, ^{13}C and ^{31}P NMR and FT-IR) and by comparison to data in the literature of similar compounds.[26--28]

The ^{1}H NMR spectra of **4a--h** showed characteristic doublets at δ 6.5--7.0 ppm with J_{P-H}≈520 Hz constants, responsible for the P-H coupling. The ^{31}P NMR spectrum exhibited two major peaks at δ 28.6 and 24.4 due to the **4g** diastereoisomers. In the infrared (IR) spectrum, the most characteristic absorptions were at 3461--3533 cm^{-1} (OH), 3270--3309 cm^{-1} (NH), 1163--1182 cm^{-1} (P = O), 1010--1080 cm^{-1} (P-O) and 2307--2390 cm^{-1} (P-H).

The proposed mechanism of formation of **4a-h** is illustrated in Figure 3. The addition of hypophosphorous acid to the azomethine bond of Schiff bases **3a--i** led to the formation of meso-compounds and racemic pairs.

Antioxidant Activity

All phosphinic acid derivatives **4a--h** and standards were prepared at a range of concentrations from 50 to 500 µg/mL. Table S 1 (Supplemental Materials) shows the results of

antioxidant activity. Various methods were used to compare the antioxidant activity of the new compounds against the standards. Experimental details are given in the supplemental materials available online.

Hydroxyl radical (•OH) scavenging activity.

All compounds, BHT and ascorbic acid standards showed similar hydroxyl radical scavenging activity. Nonetheless, compounds **4c** and **4f** exhibited the highest values. The hydroxyl radical (•OH) scavenging activity of test compounds were in the following order: ascorbic acid > BHT > 4c > 4f > 4h > 4g > 4d > 4a > 4e > 4b (Table 1).

Superoxide radical scavenging activity

Superoxide anions are oxygen-centred radicals and indicators of active free radicals with the potential of reacting with biological macromolecules and thus causing tissue damage.[29] All compounds showed nearly equal activity levels. Compounds **4c, 4e** and **4f** exhibited the greatest values, which were higher than α-tocopherol. Compound **4b** exhibited the lowest activity. The superoxide radical scavenging activity of the standards and test compounds were in the following order: BHT > ascorbic acid > 4c > 4e > 4f > α-tocopherol > 4d > 4a > 4h > 4g > 4b (Table 1).

Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity

The power of an antioxidant to transfer one electron to reduce a compound may be a significant indicator of potential antioxidant activity.[30] The ability to scavenge stable DPPH radicals is a widely preferred and important method of evaluating antioxidant activity.[31] In this study, scavenging DPPH radicals was variable. Compound **4a** exhibited the lowest activity,

while compounds **4e** and **4g** had the greatest values. Scavenging efficiency on DPPH radicals was in following order: ascorbic acid > 4e > 4g > 4h > 4b > BHT > 4c > 4f > 4d > 4a (Table 1).

Metal chelating activity

Chelating reactives are useful as secondary antioxidants as they reduce redox potential and thus stabilize a metal ion's oxidized form. Ferrozine can form complexes with Fe^{2+}. This process is obstructed when chelating agents are present, which decreases the red colour of the complex. Thus, measuring the reduction of colour makes it possible to calculate chelating activity.[32] The production of these radicals may cause lipid peroxidation, protein modification and DNA damage. Chelating agents may not trigger metal ions and possibly prevent metal-dependent processes.[33] In this study, **4c** demonstrated the most activity while other compounds showed a low ion chelating activity. In terms of chelating activity, they were in the following order: α-tocopherol > 4c > BHT > 4f > 4d > 4h > 4g > 4a > 4b > 4e (Table S 1).

Hydrogen peroxide scavenging activity

Hydrogen peroxide exhibits powerful oxidizing effects and can be generated *in vivo* by various oxidizing enzymes, including superoxide dismutase. The activity of hydrogen peroxide scavenging was in the following order: ascorbic acid > 4f > 4c > BHT > 4h > 4g > 4d > 4e > 4a > 4b. Compound **4f** (*IC*50: 60.07µg/ml) and **4c** (*IC*50: 60.87µg/ml) scavenged hydrogen peroxide much more than other compounds and the BHT standard. It appears that levels of hydrogen peroxide at or below around 20--50 mg have restricted cytotoxicity for many cell types. Hence the elimination of hydrogen peroxide is crucial for the protection of pharmaceutical and food systems (Table S 1).[34]

EXPERIMENTS

All solvents and reagents were purchased from commercial sources and used without further purification. Melting points were determined on an Electrothermal 9100 melting point apparatus and uncorrected, but checked with a differential scanning calorimeter (DSC). The IR spectra were measured with a Perkin--Emler Spectrum One FT-IR spectrophotometer. The ^{1}H, ^{13}C and ^{31}P spectra were taken on a Bruker AC-400 NMR spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 162 MHz for ^{31}P. Compounds were dissolved in $NaOD/D_2O$ and chemical shifts were referenced to TMS (^{1}H and ^{13}C NMR) and 85% H_3PO_4 (^{31}P NMR). Elemental analyses were performed on a LECO-CHNS-938. The Supplemental Material contains ^{1}H, ^{13}C and ^{31}P NMR spectra for compounds **4a--h** (Figures S 1 -- S 21)

General procedure for the synthesis of 3a--h

A solution of diamine (20 mmol) in absolute ethanol (30 mL) was slowly added to a solution of aldehyde (40 mmol) in absolute ethanol (20 mL). The stirred reaction mixture was refluxed for 4 h. After cooling, a precipitate was formed which was collected by filtration, washed with cold ethanol and recrystallized from a 9:1 mixture of ethanol and water.

General procedure for the synthesis of 4a--h

Hypophosphorous acid (50%, 2 mol equivalent) in ethanol was added to the imine in ethanol (50 ml for 20 mmol). The mixture was refluxed for 24 h and then cooled. The solid product was filtered off and washed with a solvent mixture of ethanol and water and air dried at room temperature.

(Ethane-1,2-diylbis{imino[(2-hydroxyphenyl)methanediyl]})bis(phosphinic acid) (4a)($C_{16}H_{22}N_2O_6P_2$)

White solid, yield 60%, m.p. 250-252°C. IR (KBr, υ, cm^{-1}): 3400 (─OH), 3215 (─NH), 3041 (─Ar-H), 2825-2971 (─C-H), 2384 (─PH), 1597 (─C = C), 1182 (─P = O), 1017-1042 (─P-O) cm^{-1}. ^{1}H-NMR (400 MHz, NaOD/D_2O, δ, ppm): 6.92 (m, 4H, Ar-H), 6.60 (d, 2H, *J* = 514.8 Hz, PH), 6.40 (m, 4H, Ar-H), 3.99 (m, 2H, PCH), 2.71 (m, 4H, N-CH_2). ^{13}C-NMR (100 MHz, NaOD/D_2O, δ, ppm): 163.3, 128.2, 127.7, 124.4, 118.6, 113.6, 55.9 46.1. Elem. Anal.: Calculated: C, 48.01; H, 5.54; N, 7.00. Found: C, 48.50; H, 5.20; N, 6.85.

(Ethane-1,2-diylbis{imino[(4-methoxyphenyl)methanediyl]})bis(phosphinic acid) (4b)($C_{18}H_{26}N_2O_6P_2$)

White solid, yield 55%, m.p. 200-203°C. IR (KBr, υ, cm^{-1}): 3411 (─OH), 3266 (─NH), 3078 (─Ar-H), 2836-2997 (─C-H), 2324 (─PH), 1612 (─C = C), 1165 (─P = O), 1046-1069 (─P-O) cm^{-1}. ^{1}H-NMR (400 MHz, NaOD/D_2O, δ, ppm): 6.88 (m, 4H, Ar-H), 6.57 (d, 2H, *J* = 516.4 Hz PH), 6.28 (m, 4H, Ar-H), 3.01 (m, 2H, PCH), 2.87 (s, 6H, O-CH_3), 2.02 (m, 4H, N-CH_2). ^{13}C-NMR (100 MHz, NaOD/D_2O, δ, ppm): 158.1, 129.6, 127.9, 114.0, 63.1, 62.3, 55.3, 44.8. Elem. Anal.: Calculated: C, 50.47; H, 6.12; N, 6.54. Found: C, 50.05; H, 6.50; N, 6.93.

{Ethane-1,2-diylbis[imino(thiophen-2-ylmethanediyl)]}bis(phosphinic acid) (4c)($C_{12}H_{18}N_2O_4P_2S_2$)

White solid, yield 43%, m.p. 220-222°C. IR (KBr, υ, cm^{-1}): 3437 (─OH), 3241 (─NH), 3082-3095 (─Ar-H), 2940-2963 (─C-H), 2318 (─PH), 1617 (─C = C), 1180 (─P = O), 1066

(─P-O) cm^{-1}. ^{1}H-NMR (400 MHz, NaOD/D_2O, δ, ppm): 7.10 (s, 2H, Ar-H), 6.75 (s, 2H, Ar-H), 6.71(d, 2H, *J* = 518.4 Hz PH), 6.68 (s, 2H, Ar-H), 3.67 (m, 2H, PCH), 2.22 (m, 4H, N-CH_2). ^{13}C-NMR (100 MHz, NaOD/D_2O, δ, ppm):138.5, 126.7, 125.5, 59.2, 58.2, 45.4, 42.5, 39.2. Elem. Anal.: Calculated: C, 37.89; H, 4.77; N, 7.36. Found: C, 37.50; H, 4.85; N, 7.08.

(Propane-1,3-diylbis{imino[(2-hydroxyphenyl)methanediyl]})bis(phosphinic acid) (4d)($C_{17}H_{24}N_2O_6P_2$)

White solid, yield 47%, m.p. 217-219°C. IR (KBr, υ, cm^{-1}): 3403 (─OH), 3258 (─NH), 3050 (─Ar-H), 2935-2997 (─C-H), 2335 (─PH), 1605 (─C = C), 1179 (─P = O), 1049 (─P-O) cm^{-1}. ^{1}H-NMR (400 MHz, NaOD/D_2O, δ, ppm): 6.84 (m, 4H, Ar-H), 6.62 (d, 2H, *J* = 514.4 Hz, PH), 6.40 (m, 4H, Ar-H), 3.94 (d, 2H, *J* = 12.8 Hz, PCH), 2.07 (m, 4H, N-CH_2), 1.23 (s, 2H, N-CH_2-$\underline{CH_2}$). ^{13}C-NMR (100 MHz, NaOD/D_2O, δ, ppm): 165.2, 128.1, 127.6, 124.3, 118.6, 113.5, 55.5, 44.6, 28.2. Elem. Anal.: Calculated: C, 49.28; H, 5.84; N, 6.76. Found: C, 49.04; H, 5.64; N, 7.28.

(Propane-1,3-diylbis{imino[(4-methoxyphenyl)methanediyl]})bis(phosphinic acid) (4e)($C_{19}H_{28}N_2O_6P_2$)

White solid, yield 45%, m.p. 256-258°C. IR (KBr, υ, cm^{-1}): 3414 (─OH), 3252 (─NH), 3043 (─Ar-H), 2912-2997 (─C-H), 2315 (─PH), 1613 (─C = C), 1181 (─P = O), 1070 (─P-O) cm^{-1}. ^{1}H-NMR (400 MHz, NaOD/D_2O, δ, ppm): 7.30 (m, 4H, Ar-H), 7.05 (m, 4H, Ar-H), 6.95 (d, 2H, *J* = 520 Hz, PH), 3.77 (s, 6H, O-CH_3), 3.70 (m, 2H, PCH), 2.15 (m, 4H, N-CH_2), 1.24 (m, 2H, N-CH_2-$\underline{CH_2}$). ^{13}C-NMR (100 MHz, NaOD/D_2O, δ, ppm): 158.1, 129.6, 127.9, 114.0,

63.1, 62.3, 55.3, 44.8, 27.7. Elem. Anal.: Calculated: C, 51.59; H, 6.38; N, 6.33. Found: C, 51.24; H, 6.45; N, 6.83.

{Propane-1,3-diylbis[imino(thiophen-2-ylmethanediyl)]}bis(phosphinic acid) (4f)($C_{13}H_{20}N_2O_4P_2S_2$)

White solid, yield 45%, m.p. 243-245°C. IR (KBr, υ, cm^{-1}): 3400 (─OH), 3224 (─NH), 3072 (─Ar-H), 2914-2971 (─C-H), 2328 (─PH), 1613 (─C = C), 1198 (─P = O), 1054 (─P-O) cm^{-1}. ^{1}H-NMR (400 MHz, NaOD/D_2O, δ, ppm): 7.55 (d, 2H, Ar-H), 7.21 (t, 2H, Ar-H), 7.13 (s, 2H, Ar-H), 6.99 (d, 2H, *J* = 524.4 Hz, PH), 4.06 (m, 2H, PCH), 2.39 (m, 4H, N-CH_2), 1.65 (m, 2H, N-CH_2-$\underline{CH_2}$). ^{13}C-NMR (100 MHz, NaOD/D_2O, δ, ppm): 138.6, 127.2, 127.0, 125.7, 59.5, 58.6, 45.0, 27.7. Elem. anal.: Calculated: C, 39.59; H, 5.11; N, 7.10. Found: C, 39.09; H, 5.45; N, 7.43.

(2,2-dimethylpropane-1,3-diylbis[imino(4-methoxyphenyl)methanediyl)]bis(phosphinic acid) (4g)($C_{21}H_{32}N_2O_6P_2$)

White solid, yield 55%, m.p. 244-246°C. IR (KBr, υ, cm^{-1}): 3417 (─OH), 3221 (─NH), 3041 (─Ar-H), 2933-2992 (─C-H), 2307 (─PH), 1609 (─C = C), 1163 (─P = O), 1054 (─P-O) cm^{-1}. ^{1}H-NMR (400 MHz, NaOD/D_2O, δ, ppm): 7.50 (m, 4H, Ar-H), 7.25 (m, 4H, Ar-H), 6.53 (d, 2H, *J* = 517.6 Hz, PH), 3.42 (s, 6H, O-CH_3), 3.19 (d, 2H, *J* = 12.4 Hz, PCH), 1.66 (s, 4H, N-CH_2), 0.38 (m, 6H, CH_2-C-$\underline{CH_3}$). ^{13}C-NMR (100 MHz, NaOD/D_2O, δ, ppm): 157.7, 129.2, 128.1, 113.7, 64.5, 63.5, 57.4, 55.0, 33.7, 22.8. ^{31}P-NMR (162 MHz, NaOD/D_2O, δ, ppm): 28.6, 24.4. Elem. Anal.: Calculated: C, 53.62; H, 6.86; N, 5.95. Found: C, 53.41; H, 6.41; N, 5.64.

{(2,2-dimethylpropane-1,3-diyl)bis[imino(thiophen-2-ylmethanediyl)]}bis(phosphinic acid)(4h)($C_{15}H_{24}N_2O_4P_2S_2$)

White solid, yield 49%, m.p. 217-219°C. IR (KBr, υ, cm^{-1}): 3400 (─OH), 3215 (─NH), 3074 (─Ar-H), 2928-2973 (─C-H), 2351 (─PH), 1697 (─C = C), 1197 (─P = O), 1054 (─P-O) cm^{-1}. ^{1}H-NMR (400 MHz, NaOD/D_2O, δ, ppm): 7.01 (m, 2H, Ar-H), 6.60 (m, 4H, Ar-H), 6.54 (d, 2H, *J* = 525.2 Hz, PH), 3.50 (d, 2H, *J* = 15.2 Hz, PCH), 1.76 (m, 4H, N-CH_2), 0.40 (m, 6H, CH_2-C-$\underline{CH_3}$). ^{13}C-NMR (100 MHz, NaOD/D_2O, δ, ppm): 139.59, 127.0, 126.3, 125.2, 61.1, 60.2, 57.6, 33.7, 23.4, 22.8. ^{31}P-NMR (162 MHz, NaOD/D_2O, δ, ppm): 27.6, 24.3.Elem. Anal.: Calculated: C, 48.43; H, 6.32; N, 6.27. Found: C, 48.61; H, 6.51; N, 6.04.

CONCLUSION

In this study, we synthesized a new series of bis-1-amino-*H*-phosphinic acid derivatives and used different methods to compare their antioxidative activity. The novel phosphonous acids were obtained in moderate yields varying from 40--60%, which was more than expected, since several authors [40--42] reported much lower conversion rates for additions to two azomethine groups. Among various bis-1-amino-*H*-phosphinic acids derivatives, compounds **4c** and **4f** showed higher antioxidant activity than the other derivatives and the standard BHT compound. The lowest activity values were generally from compounds **4a** and **4b**.

STATISTICAL EVALUATION

Data analyses were done using SPSS 22.0 (IBM Corp., Armonk, NY, USA). Linear regression was conducted to provide mathematical models of determinism between dependency (concentration) and independency (inhibition percentage). *IC*50 values were calculated with both

linear and cubical models. Data were evaluated at 95% confidence intervals.

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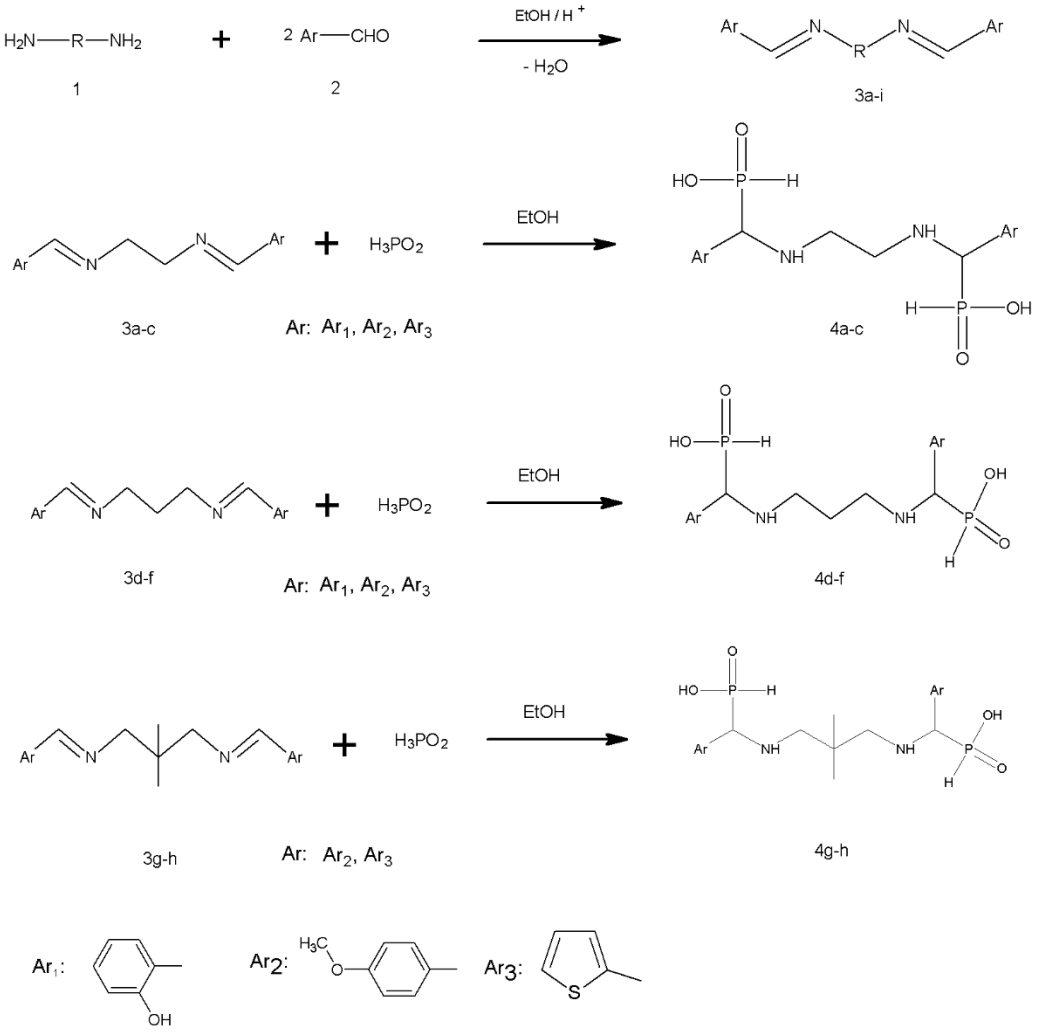

Figure 1. Synthesis of compound **4a–h**.

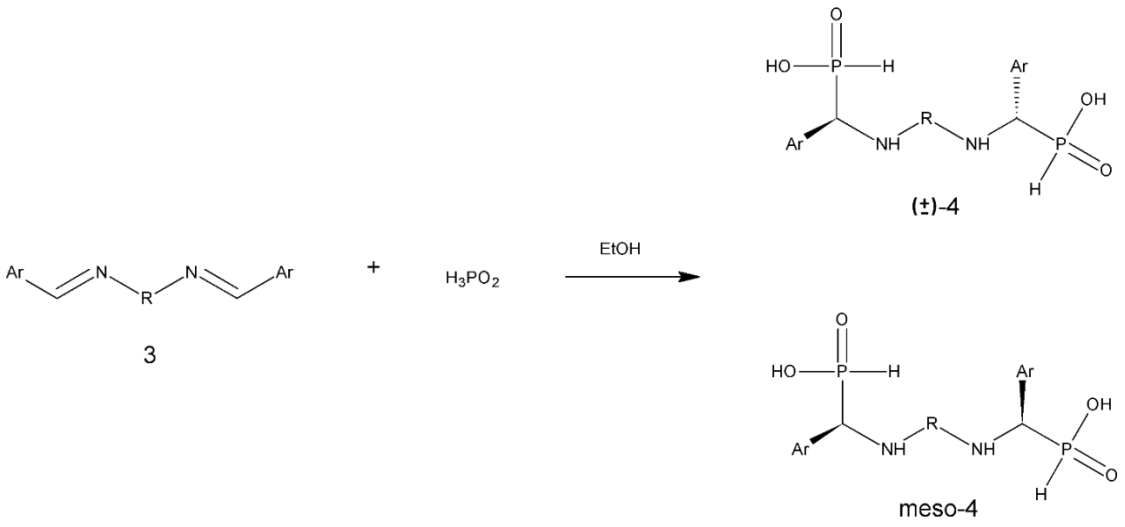

Figure 2. Preparation of racemic and meso **4a–h**.

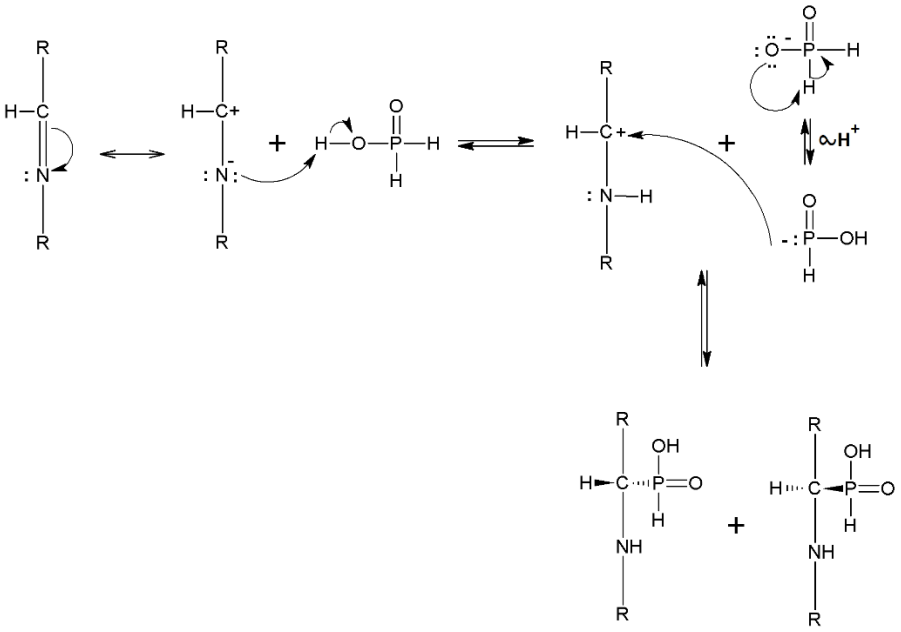

Figure 3. Mechanism of formation of **4a–h.**