Comparisons of pKa and Log P Values of Some Carboxylic and Phosphonic Acids: Synthesis and Measurement*

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ABSTRACT The changes in the physiochemical properties accompanying the substitution of a phosphonic acid group for a carboxylic acid group on various heterocyclic platforms was determined. A series of low molecular weight heterocyclic carboxylic and phosphonic acids was prepared, and the acid dissociation content (pKa) and log P values were measured potentiometrically. These values were compared to those of substituted benzene phosphonic acids, carboxylic acids, sulfonamides, and tetrazoles. The carboxylic acids included 3 pyrazoles, an imidazole, a triazole, 2 pyrimidines, and 6 aryl compounds. The phosphonic acids included a triazole, 2 pyrazoles, 4 pyrimidines, a thiophene, and 6 aryl compounds. Most of the compounds synthesized had adequate water solubility, although a simple methyl substituent in 2 series had a great effect, completely changing the properties. Log P values for the synthesized carboxylic and phosphonic acid compounds were below 2, and pK₁ values for the heterocyclic phosphonic acids were generally 2 to 3 log units lower than for the heterocyclic carboxylic acids.

Key Words: log P, pKa, Heterocyclic Phosphonic Acids, Heterocyclic Carboxylic Acids

INTRODUCTION

Acid dissociative content (pKa) and log P values are important parameters to be considered in the design of pharmaceuticals. In some therapeutic classes, a phosphonic acid is a bioisostere for a carboxylic acid.

In the World Drug Index there are many compounds, primarily aliphatic, which contain a phosphonic acid group. While there are phosphates and many diphosphonic acid compounds used as chelators, there are numerous compounds with a single phosphonic acid group, and often of low molecular weight. There are a few aromatic or heteroaromatic examples.

Activities investigated include γ -aminobutyric acid (GABA), *N*-Methyl-D-aspartic acid (NMDA), (R,S)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA), Substance P and glutamic acid receptor activity; antiseptic activity; antiviral activity; and inhibition of osteoclast-mediated bone resorption. It is clear that phosphonic acid functionality has been used in drug design, and it may be possible to incorporate phosphonic acids to impart desirable physiochemical properties or selectivity into other classes of drug candidates. In an investigation of metabotropic glutamic acid receptors (mGlu), investigators observed that the dicarboxylic acid analogue ([S]- α -aminoadipic acid) activates the mGlu₂ and mGlu₆ receptor subtypes without interacting detectably with other mGlu receptors, whereas (S)-2-amino-5-phosphonovaleric acid selectively blocks (S)-Glu activation of mGlu₂ (1). Baclofen, a GABA_B agonist, contains a carboxylic acid group, while phaclofen, which substitutes a phosphonic acid for the carboxylic acid, is an antagonist (2). In compounds that have a phosphonic acid group attached directly to a heterocyclic ring, HAB 439, an isoxazoline derivative, is an immunostimulator (3) and L-758298 (4), a triazole derivative with the phosphonic acid attached to a nitrogen of the ring, is a prodrug of L-754030 and is in clinical trials as a substance P-antagonist. An AMPA receptor antagonist, S-17625, which is an oxoquinoline-3-phosphonic acid, has also been developed (5).

In the therapeutic area of Angiotensin II Receptor antagonists, there are numerous papers that explore the substitution of a carboxylic acid group for other groups such as tetrazoles, sulfonic acids, acyl sulfonamides, and acyl sulfamides (6,7,8). The replacement of a carboxylic acid group by a phosphonic acid group is less common. The compounds synthesized herein and those selected from the literature seek to explore the differences in the physicochemical properties that result

from the substitution of a phosphonic acid for a carboxylic acid in a series of small ring polynitrogen heterocycles, specifically the pKa and log P values. The polynitrogen heterocycles were chosen because polynitrogen molecules are common in medicinals. The heterocyclic carboxylic acids synthesized are shown in Figure 1, and the heterocyclic phosphonic acids are shown in Figure 2.

MATERIALS AND METHODS

The synthesis of 1-methyl-1*H*-imidazole-2-carboxylic acid **1** was by electrophilic substitution by carbobenzoxy chloride on *N*-methylimidazole, followed by hydrogenation. 1-Methyl-1*H*-pyrazole-4-carboxylic acid **2** was prepared by a Vilsmeier reaction on *N*-methylpyrazole to give pyrazole-4-carboxaldehyde, followed by oxidation to give the acid (**9**). The synthesis of 1-methyl-1*H*-1,2,3-triazole-4-carboxylic acid **3** was by the method of Pederson (**10**). 1-Methyl-3-trifluoromethyl-1*H*-pyrazole-4-carboxylic acid **4** was prepared by the method of Huppertz (**11**). The acidic rearrangement (**12**) of 5-acetyluracil provided 1,3-dimethyl-1*H*-pyrazole-4-carboxylic acid **5**, and this structure was confirmed by nuclear Overhauser effects (NOE) experiments. The 2-amino-5-pyrimidine carboxylic acids **6** and **7** were prepared by hydrolysis (**13,14**) of the commercially available esters in ethanol with potassium hydroxide.

(1-Methyl-1*H*-1,2,4-triazol-5-yl)-phosphonic acid **8** was prepared by electrophilic substitution (**15**) of diethylchlorophosphonate, followed by hydrolysis of the diester with bromotrimethylsilane. (2-Thienyl)-phosphonic acid **9** was synthesized by electrophilic substitution on 2-bromothiophene with diethylchlorophosphonate and hydrolysis with bromotrimethylsilane.

The pyrazolyl and pyrimidinyl phosphonic acids were prepared using phosphonic enamines, and reacting those with either methyl hydrazine or guanidine. The hydrolysis of the esters gave different products for the pyrimidinyl phosphonates, depending on whether 6*N* HCl or bromotrimethylsilane was used. The phosphonic enamines **12** were prepared (**16,17**) as shown in Scheme 1 and reacted with guanidine to yield either (2-amino-5-pyrimidinyl)-phosphonic acid, diethyl ester **13** or (2-amino-4-methyl-5-pyrimidinyl)-phosphonic acid, diethyl ester **14** depending upon the R' substitution in **10**. Reacting the same phosphonic

enamines with methylhydrazine provided (1-methyl-1*H*-pyrazol-4-yl)-phosphonic acid, diethyl ester **15** or (1,5-dimethyl-1*H*-pyrazol-4-yl)-phosphonic acid, diethyl ester **16**. The hydrolysis of the pyrazole phosphonates could be affected either with 10% aqueous HCl or bromotrimethylsilane to give (1-methyl-1*H*-pyrazol-4-yl)-phosphonic acid **17** or (1,5-dimethyl-1*H*-pyrazol-4-yl)-phosphonic acid **18**. The structure of **18** was verified by NOE experiments, and had been formed in 78:22 ratio over the regioisomer (1,3-dimethyl-1*H*-pyrazol-4-yl)-phosphonic acid, which was not isolated in pure form.

Figure 1: Carboxylic Acids

Figure 2: Phosphonic Acids

Upon hydrolysis of the pyrimidinyl diesters with 6N HCl, the hydroxy compounds were formed. (2-Hydroxy-5-pyrimidinyl)-phosphonic acid 19 and (2-hydroxy-4-methyl-5-pyrimidinyl)-phosphonic acid 20 existed as a tautomeric mixture, exhibiting a dynamic equilibrium in solution, as determined by line broadening in the nuclear magnetic resonancing (NMR), while having a carbonyl in the infrared (IR) in the crystalline state. Three pKa values were measured for 19 and 20 supporting the triprotic hydroxy structure in solution.

The pyrimidinyl phosphonic acids were obtained as the amino compounds upon reaction with

bromotrimethylsilane, giving (2-amino-5-pyrimidine)-phosphonic acid 21 and (2-amino-4-methyl-5-pyrimidine)-phosphonic acid 22.

RESULTS AND DISCUSSION

The measurements of pKa and log P were done potentiometrically, using a Sirius PCA101 (Sirius Analytical Instruments, Ltd, East Sussex, UK), and the data were processed with their pKaLOGP, Version 4.02 software.

For the carboxylic acids, the electrode was standardized before each set of runs with a blank; for the phosphonic acids, the electrode was standardized using a calibration

Scheme 1: Synthesis of Pyrimidine and Pyrazole Phosphonic Acids

with KH_2PO_4 dissolved in ion strength adjusted (ISA) water, 0.15M KCl, comparable in ionic strength to that of blood water. The sample was run under a blanket of in

ert gas, and was corrected for dissolved carbon dioxide. The samples were run from high pH to low pH. Before and after each run, the electrode was standardized against a phosphate buffer reference solution. The temperature was also measured, and a temperature correction was done against the buffer for that run. The volume of ISA water used was 10 mL, and the amount of compound required was 1.5 mg to 2 mg for the carboxylic acids, and 9 mg to 12 mg for the phosphonic acids. The masses were accurate to 0.001 mg.

When the compound was not soluble in the volume of water used, a partition derived pK_a method was used. The system has an internal calibration for mixtures of

either methanol-ISA water or dimethyl sulfoxide (DMSO)-ISA water. In this situation, the compound was dissolved in a specific amount of organic solvent, then diluted with ISA water, for a total volume of 10 mL, such that no precipitation occurs. Multiple runs are performed, using varying amounts of organic solvent-ISA water ratios, and the derived pK_a is extrapolated to zero organic solvent, using Yasuda-Shedlovsky plots (18,19). This method is expected to overestimate the extrapolated pK_a value for weak acids by 0.34 (20). No correction factor to the values obtained by the Yasuda-Shedlovsky plots was assigned.

Table 1 lists the data for the heterocyclic carboxylic acids, Table 2 lists the heterocyclic phosphonic acids, and Table 3 has the measured values for the aromatic phosphonic acids.

Compound		Compound	
<div>1</div> <div>Log P < 0 $\text{pK}_1 = 6.88$ Temp = 24.2° C</div>		<div>6</div> <div>Log P = insoluble $\text{pK}_1 = \text{insoluble}$</div>	
<div>2</div> <div>Log P = -0.04 ± 0.11 $\text{pK}_1 = 4.02$ (Y-S) Temp = 24.0° C</div>		<div>7</div> <div>Log P = insoluble $\text{pK}_1 = 2.77$ (Y-S)</div>	
<div>3</div> <div>Log P = insoluble $\text{pK}_1 = 2.95$ (Y-S)</div>		<div></div> <div>Log P = 1.57 ± 0.02 $\text{pK}_1 = 4.54$ Temp = 23.5° C</div>	
<div>4</div> <div>Log P = 0.88 ± 0.02 $\text{pK}_1 = 3.79$ Temp = 24.3° C</div>		<div></div> <div>Log P = < 0 $\text{pK}_1 = 3.04$ Temp = 23.9° C</div>	
<div>5</div> <div>Log P = 0.66 ± 0.08 $\text{pK}_1 = 4.52$ Temp = 23.7° C</div>		<div></div> <div>Log P = 1.46 ± 0.01 $\text{pK}_1 = 3.37$ Temp = 24.0° C</div>	

Table I: Log P and pK_a Values for Heterocyclic Carboxylic Acids

	Compound			Compound	
8		Log P = 0.11 ± 0.09 $pK_1 = 2.28$ $pK_2 = 5.32$ Temp = 24.4°C	19		Log P = <0 $pK_1 = 1.52$ $pK_2 = 5.60$ $pK_3 = 9.24$ Temp = 24.0°C
9		Log P = 0.66 ± 0.08 $pK_1 = 1.10$ $pK_2 = 6.43$ Temp = 24.0°C	20		Log P = 0.97 ± 0.12 $pK_1 = 2.51$ $pK_2 = 5.92$ $pK_3 = 10.03$ Temp = 24.2°C
17		Log P = 0.44 ± 0.22 $pK_1 = 1.84$ $pK_2 = 6.76$ Temp = 24.4°C	21		Log P = -0.04 ± 0.27 $pK_1 = 2.94$ $pK_2 = 6.15$ Temp = 24.4°C
18		Log P = 0.67 ± 0.12 $pK_1 = 2.10$ $pK_2 = 7.15$ Temp = 24.4°C	22		Log P = insoluble $pK_1 = \text{insoluble}$ $pK_2 = \text{insoluble}$

(Y-S) Yasuda-Shedlovsky plots. Log p < 0 indicates a log P value of <0, with the instrument unable to assign a specific value within a reasonable standard deviation.

Table II: Log P and pKa Values for Heterocyclic Phosphonic Acids

Compound	Log P	Temp	pK ₁	pK ₂	pK ₃

R = H	0.88 ± 0.17	23.8° C	1.42	6.92	
R = COOH	0.98 ± 0.22	24.3° C	1.32	3.84	6.77
R = OCH ₂ CH ₃	1.07 ± 0.06	23.9° C	1.71	7.08	
R = CH ₃	1.21 ± 0.09	23.8° C	1.55	7.05	
R = NO ₂	1.22 ± 0.06	23.7° C	n.c.	6.10	
R = Cl	1.70 ± 0.13	23.6° C	1.09	6.65	

Table III: Log P and pKa Values for Reference Phosphonic Acids

Compound	Log P	temp	pK ₁	pK ₂

R = H	2.04 (1)	25° C	4.19 (2)	
R = COOH	1.57 (3)	25° C	3.20 (4)	4.30 (4)
R = CH ₃	2.26 (1)	25° C	4.36 (2)	
R = OCH ₂ CH ₃	2.45 (1)	25° C	4.48 (5)	
R = NO ₂	1.84 (1)	25° C	3.41 (2)	
R = Cl	2.62 (1)	25° C	3.98 (2)	

Table IV: Log P and pKa Values for Reference Carboxylic Acids

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Figure 3: Log P Values for Aromatic Compounds

Figure 4. pK₁ Values for Aromatic Compounds

The relationship among the aromatic phosphonic, carboxylic, sulfonamides, and tetrazoles is shown in Figure 3 and Figure 4 from data in Table 3, which were measured for the phosphonic acids, and Table 4 and Table 5 data, which were taken from literature values or calculated values as indicated.

Compounds	Log P	pKa	temp	Compounds	Log P	pKa	temp

R = H	0.35 (1)	10 (2)	20° C	R = H	1.49 (5)	4.54 (6)	25° C
R = COOH	0.55 (3)	3.47 (4)	25° C	R = COOH	1.24 (5)	3.63 (6)	25° C
R = OCH ₃	0.45 (1)	10.22 (2)	20° C	R = OCH ₃	1.41 (5)	4.23 (7)	20° C
R = CH ₃	0.80 (1)	10.17 (2)	20° C	R = CH ₃	1.99 (5)	4.82 (6)	25° C
R = NO ₂	0.75 (1)	n.a.		R = NO ₂	1.24 (5)	3.08 (7)	20° C
R = Cl	1.10 (1)	9.77 (2)	20° C	R = Cl	2.20 (5)	4.49 (6)	25° C

Table 5. Reference Sulfonamides and Tetrazoles

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Partition Coefficients

As shown in Figure 3, the **logP** values for the aromatic phosphonic acids are 0.7 to 1.7, and for the aromatic carboxylic acids, 1.57 to 2.45. The aromatic phosphonic acids are approximately one log P unit lower than that of the corresponding carboxylic acids. The aromatic sulfonamide log P values are 0.35 to 1.10 and for the aromatic tetrazoles, 1.24 to 2.20.

The values for the *N*-heteroaromatic phosphonic acids are less than 0 to 0.67, and for the carboxylic acids, less than 0 to 0.9, and are comparable for the aromatic sulfonamides. The values for the *N*-heteroaromatic carboxylic acids are approximately 1 log P unit lower than the aromatic carboxylic acids and comparable to the aromatic tetrazole reference compounds. Replacing a phosphonic acid group with a sulfonamide for the aromatic reference series showed little change in log P value. In general, replacing a carboxylic acid or a tetrazole group on a molecule with a phosphonic acid group can be expected to decrease the log P by at least 1 log P unit while replacement with a sulfonamide decreases log P about 1.5 units. Within the aromatic reference series, substitution with a chlorine gave the highest log P value. While no substitution (hydrogen) often gave the lowest log P value, substitution rankings between the aromatic carboxylic acids and aromatic tetrazoles had the closest parallel.

Ionization Constants

As shown in Figure 4, the pK_1 values for the reference aromatic phosphonic acids are 1.09 to 1.7, and for the carboxylic acids, 3.2 to 4.48. The values for the *N*-heteroaromatic phosphonic acids are 1.5 to 2.9, and for the corresponding carboxylic acids, 3.2 to 4.5, with the imidazole compound an outlier at 6.88. Pyrazole-4-carboxylic acid (**2**) has a pK_1 value about 2 log units less acidic than the (pyrazol-4-yl)-phosphonic acid (**17**). The aromatic tetrazole references had values of 3.08 to 4.82, which is comparable to the carboxylic acids. The pK_1 values for the reference sulfonamides are decidedly basic, with values of 9.77 to 10.22 for the sulfonamide group.

As shown in Table 3, the pK_2 values for the aromatic phosphonic acids are from 6.1 to 7.1, and for the heteroaromatic phosphonic acids, 5.3 to 7.15. In this study, there is little difference in pK_2 values in either the aromatic or heteroaromatic compounds studied.

CONCLUSIONS

The values for pK_a and $\log P$ are very important parameters in drug design. Functional group manipulations are important methods for optimizing drug candidate properties. The interchange of carboxylic acid for tetrazole and sulfonamide has been extensively studied and often results in useful drugs. In angiotensin II antagonist drug development, there has been extensive use of the tetrazole as a carboxylic acid surrogate, which has improved oral absorption. This study indicates that substituting a phosphonic acid for a carboxylic acid group will lower the value for $\log P$ by about 1 log unit, expected to be comparable to that of a tetrazole moiety. There is an increase in acidity however, which may be a limiting factor in the absence of active transport. The increase in acidity is in the range of 1.0 to 1.5 pH units.

Replacing a carboxylic acid group with a phosphonic acid group gives a much more acidic compound; with a sulfonamide group, a much less acidic compound results; and with a tetrazole replacement, acidity is essentially unchanged.

If it is desired to lower the $\log P$, and increased acidity of the compound was not a limiting factor, substitution of a phosphonic acid group for a carboxylic acid would be a viable approach. At physiological pH, a phosphonic acid would be a dianion. While all the

phosphonic acids synthesized in this study would enter a cell by passive diffusion, there are phosphonic acids in the World Drug Index that have a molecular weight greater than that expected for passive diffusion. The presence of marketed drugs containing a phosphonic acid group indicates that phosphonic acids can and do play a role in drug design.

EXPERIMENTAL SECTION

All melting points were obtained in a Thomas-Hoover apparatus ($< 200^\circ\text{C}$) or in a Mel-TempTM ($> 200^\circ\text{C}$) in capillary tubes and are uncorrected. Proton NMR were recorded on a Bruker AC400 (400 MHz) (Bruker Instruments, Billerica, MA) unless indicated otherwise in CDCl_3 or d_6 -DMSO with TMS, or in D_2O with TSP ([3-(trimethylsilyl)-1-propane sulfonic acid, sodium salt]) as an internal reference. ^{13}C NMR were recorded on a Bruker AMX 360 or AMX 400. Mass spectra were measured on a Micromass Platform II (Micromass UK, Wythenshawe, Manchester, UK) single quadrupole mass spectrometer, and exact mass MS were acquired by infusing a sample on a Finnegan T70 FT/MS (Thermal Finnigan Austin, Austin, TX) equipped with a 7.0 T superconducting magnet. Ten accumulations were summed per spectrum (in 60 seconds), and 3 spectra were acquired. For each spectrum, the mass calibration was corrected using a single internal lock mass ($\text{C}_{12}\text{H}_{30}\text{O}_8\text{P}_2\text{Na}$; m/z 387), and the masses of 26 ions corresponding to $[\text{M}+\text{H}]^+$, $[\text{M}+\text{Na}]^+$, $[2\text{M}+\text{H}]^+$, $[2\text{M}+\text{Na}]^+$, $[3\text{M}+\text{H}]^+$, $[3\text{M}+\text{Na}]^+$, and the respective ^{13}C isotopes, where visible, were averaged. Capillary Gas Chromatography (GC) were performed on a Fison 8130 (Thermal Quest Austin, Austin, TX) capillary GC, using J&W; DB-5 ms 15 M $\times$.32 mm ID, 0.25 μ film thickness ((Agilent Technologies, Wilmington, DE), operated in split mode and recorded and integrated with ChromPerfect software (Justice Laboratory Solutions, Mountain View, CA). Fourier transform infra-red spectroscopy (FT-IR) was obtained on a Nicolet Instruments Impact 400D (Madison, WI). Column chromatography was done on Silica Gel 60, 230-400 mesh (E. Merck, Darmstadt, Germany). Thin-layer chromatography (TLC) was performed on Uniplat Silica Gel GHLF plates (Analtech, Newark, DE). All solvent extractions were washed with brine and dried over MgSO_4 . All reactions were carried out under an argon atmosphere. All starting materials were obtained from commercial sources, and the 3 aromatic phosphonic acids (4-

nitrophenylphosphonic, 4-methylphenylphosphonic, and 4-phosphonobenzoic acid), which were obtained from Sigma-Aldrich Rare Chemicals (Milwaukee, WI) were further characterized. All reactions were run under inert atmosphere. Elemental analyses were performed by Quantitative Technologies, Inc (Whitehouse, NJ). Compounds were found to be within 0.4% of their theoretical values, unless otherwise indicated.

1-Methyl-1H-imidazole-2-carboxylic acid (1). 1-Methyl-1H-imidazole (6.56 g, 79.8 mmol) was dissolved in a mixture of 32.8 mL acetonitrile and 16.4 mL of triethylamine, and cooled in an ice bath to -30°C. Carbobenzoxy chloride (27.4 g, 191.74 mmol) was added at a rate to maintain the temp lower than -20°C, over a period of 4 hours. The reaction mixture became very hard to stir. The cooling bath was removed, and the reaction mixture was allowed to warm to ambient temperature. (Maintaining the temperature cold for 24 hours did not improve the product mixture.) The reaction mixture was stirred at ambient temperature for 24 hours, filtered, and concentrated under reduced pressure to give an oil, which partially solidified. NMR indicated a complex mixture. Column chromatography (CHCl₃-methanol, 95:5) was done twice to give an oil, phenylmethylene-1-methyl-1H-imidazole-2-carboxylate, 1.28 g. ¹H NMR (CDCl₃) δ 4.00 (s, 3H), 5.38 (s, 2H), 7.03 (s, 1H), 7.15 (s, 1H), 7.31 (m, 4H), 7.47 (d, 2H, *J*_{AB} = 4.75 Hz). Phenylmethylene-1-methyl-1H-imidazole-2-carboxylate (1.28 g, 5.92 mmol) was hydrogenated on a Parr shaker in 250 mL ethanol with 120 mg 10% Pd/C. After 60 minutes, the reaction was filtered, and concentrated to a solid, which was triturated with ether. The ether was filtered, and the solids were dissolved in methanol and concentrated under reduced pressure at ambient temperature to give a solid film that was triturated with ether and filtered to give crystals, 0.41 g, (1), 3.25 mmol (59.2%), mp 110°C (d), (lit (21) mp for monohydrate, 121.5°C). NMR analysis indicated 4% decarboxylated material. ¹H NMR (*d*₆ DMSO) δ 4.01 (s, 3H), 7.28 (d, *J*_{AB} = 1 Hz, 1H), 7.51 (d, *J*_{AB} = 1 Hz, 1H).

1-Methyl-1H-pyrazole-4-carboxylic acid (2). 1-Methyl-1H-pyrazole, (9.50 g, 115.69 mmol) was dissolved in 22 mL dimethylformamide and heated on a steam bath. Dropwise, POCl₃ (18.0 g, 117.4 mmol) was added. The reaction mixture was heated for 1.5 hours, cooled, then poured over ice/water. The reaction

mixture was extracted with CHCl₃, filtered, and concentrated under reduced pressure to an oil. Distillation afforded a heavy liquid, bp 110°C to 112°C/20 mm, 2.48 g (19.4%) of 1-methyl-1H-pyrazole-4-carboxaldehyde. TLC (ethyl acetate) showed a single component, (+) 2,4-DNP spray. ¹H NMR (CDCl₃) δ 3.97 (s, 3H), 7.91 (s, 1H), 7.96 (s, 1H), 9.85 (s, 1H). To 1-methyl-1H-pyrazole-4-carboxaldehyde (1.40 g, 12.7 mmol) in a mixture of 25 mL water and 5 mL 10% aqueous NaOH was added KMnO₄ (2.81 g, 12.7 mmol) in 100 mL water. The reaction was refluxed for 30 minutes, cooled and filtered, and the colorless solution was acidified with 10% aqueous HCl. This acidic solution was extracted twice with ethyl acetate. This extract was dried, filtered, and concentrated under reduced pressure to give a white solid, 0.50 g, (2), 6.25 mmol (49.2%), mp 203-204°C, (lit [10] mp 205-206°C). ¹H NMR (*d*₆ DMSO) δ 3.86 (s, 3H), 7.76 (s, 1H), 8.20 (s, 1H). Anal. C₅H₆N₂O₂ C, H, N.

1-Methyl-1H-1,2,3-triazole-4-carboxylic acid (3). The reaction was run as described (22) to give 13.7 g, 108 mmol (89.7%), mp 222°C (d) (lit mp 224°C [d] (22)). 1.10 g of these crystals was recryst from water to give 1.02 g, (3), mp 234°C (d). IR (KBr) 1687 cm⁻¹. ¹H NMR (*d*₆ DMSO) δ 4.09 (s, 3H), 8.61 (s, 1H). Anal. C₄H₅N₃O₂ C, H, N.

1-Methyl-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (4). Ethyl-2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutyrate (5.00 g, 20.8 mmol) was stirred in 50 mL ether, and cooled to -5°C. Methylhydrazine (1.04 g, 26.0 mmol) was added dropwise at a rate to maintain the temperature at lower than 0°C, requiring 45 minutes. After this addition, the reaction was stirred at -5°C for 15 minutes, then 60 minutes at ambient temperature. The reaction was concentrated under reduced pressure to an oil, ethyl-1-methyl-3(5)-trifluoro-methyl-1H-pyrazole-4-carboxylate, 4.75 g. The oil solidified, and GC analysis indicated a mixture of 87:12. ¹H NMR (CDCl₃) δ 1.35 (t, *J*_{AB} = 5.3 Hz, 3H), 3.97 (s, 2.64 H), 4.07 (s, 0.36H), 4.32 (q, *J*_{AB} = 5.3 Hz, 2H), 7.92 (s, 0.26H), 7.96 (s, 1.74H). The mixture of the two regioisomers (1.10 g, 4.95 mmol) were refluxed in a mixture of 5 mL ethanol and 5 mL 10% aqueous NaOH for 60 minutes. The reaction mixture was concentrated under reduced pressure to a solid, which was dissolved in 10 mL water, filtered, and acidified with 10% aqueous HCl to give cream yellow

crystals, 0.71 g, (4), 3.90 mmol (90.7% yield based on 86.8% regioisomer purity of starting ester), mp 200°C to 200.5°C (lit mp 199°C to 200°C) (15). ¹H NMR (CDCl₃) δ 4.00 (s, 3H), 8.02 (s, 1H). NOE difference experiments support the structure. The 5-H gave a positive NOE effect to the 1-methyl, and the 1-methyl gave a positive NOE effect to the 5-H. Anal. C₆H₅F₃N₂O₂ C,H,N.

1,3-Dimethyl-1H-pyrazole-4-carboxylic acid (5).

Reaction performed as described (12) to give 50 mg (5), 0.36 mmol (22%), mp 184-186°C, (lit mp 188°C to 189°C) (13) FT-IR (KBr) 3156, 3067, 1735, 1171, 1504 cm⁻¹. ¹H NMR (CDCl₃) δ 2.47 (s, 3H), 3.87 (s, 3H), 7.87 (s, 1H). A positive NOE was observed between the 1-methyl and the 5-H, but no NOE effect from the 3-methyl was detected.

2-Amino-4-methylpyrimidine-5-carboxylic acid (6).

To a suspension of ethyl 2-amino-4-methylpyrimidine-5-carboxylate (1.00 g, 5.55 mmol) was added 5 mL of a methanol solution containing KOH (0.93 g, 16.5 mmol). The reaction mixture was refluxed for 18 hours and concentrated under reduced pressure to a paste, which was diluted with 20 mL water, filtered, and made acidic with 6N HCl. White crystals were obtained, 0.81 g (6), 5.29 mmol (95.4%), mp 316°C to 320°C (lit mp > 300°C) (14). FT-IR (KBr) 3273, 3177, 1672, 1585, 1296 cm⁻¹. ¹H NMR (d₆ DMSO) δ 2.52 (s, 3H), 7.25 (br s, 2H), 8.63 (s, 1H). Anal. C₆H₇N₃O₂ C,H,N.

2-Amino-4-trifluoromethylpyrimidine-5-carboxylic acid (7).

Ethyl 2-amino-4-trifluoromethylpyrimidine-5-carboxylate (1.00 g, 4.25 mmol) was hydrolyzed to give white crystals, 0.76 g (7), 3.67 mmol (86.3%), mp 288°C to 290°C (d) (lit mp 292°C to 294°C) (23) ¹H NMR (d₆ DMSO) δ 3.35 (br, 1H), 7.94 (br d, 2H), 8.83 (s, 1H). Anal. C₆H₄F₃N₃O₂ C,H,N.

(1-Methyl-1H-1,2,4-triazol-5-yl)-phosphonic acid (8).

1-Methyl-1H-1,2,4-triazole (1.05 g, 12.65 mmol) was dissolved in 25 mL anhydrous THF, and cooled to -78°C. A 2.5 M hexane solution of *n*-BuLi (13.28 mmol) was added via syringe over a period of 0.5 hour. The reaction was stirred for 1.5 hours at -78°C. A pale yellow heterogeneous mixture resulted. To this was added diethylchlorophosphonate (12.95 mmol, 2.18 g) over 15 minutes; the reaction was allowed to slowly warm to ambient temperature over several hours, then stirred at ambient temperature for 16 hours. The

reaction was quenched with water and extracted with ethyl acetate. The ethyl acetate solution was dried, filtered, and concentrated under reduced pressure to give an oil (1-methyl-1H-1,2,4-triazol-5-yl)-phosphonic acid, diethyl ester, 1.93 g, 8.80 mmol (69.6%). ¹H NMR (CDCl₃) δ 1.32-1.42 (m, 6H), 4.08 - 4.21 (m, 7H), 8.00 (s, 1H). This crude oil was reacted with bromotrimethylsilane (8.26 g, 54 mmol) in an oil bath at 40°C for 16 hours. The solvents were removed under reduced pressure under anhydrous conditions to give an oil, which was diluted with 25 mL anhydrous THF and filtered free of some insolubles. The THF solution was diluted with 0.33 mL water to give white solids. The solids were filtered, washed with methanol. White crystals, 0.70 g (8), 4.29 mmol (48.8%), mp 210°C to 210.5°C. ¹H NMR (d₆ DMSO) δ 4.06 (s, 3H), 6.30 (br, exchangeable), 8.14 (s, 1H). Anal. Calcd for C₃H₆N₃O₃P: C, 22.10; H, 3.71; N, 25.77. Found C, 22.52; H, 3.46; N, 24.38. Exact mass: C₃H₆N₃O₃P 163.0147 ± 2 ppm.

(2-Thienyl)-phosphonic acid (9).

2-Bromothiophene (5.00 g, 30.67 mmol) was dissolved in 40 mL anhydrous THF and cooled to less than -65°C. A 1.7 M solution of *t*-BuLi (33.73 mmol) was added at a rate to maintain the temperature lower than -60°C, requiring 1 hour. The reaction was stirred for 1 hour, then diethylchlorophosphonate (3.50 g, 32.2 mmol) was added dropwise, maintaining the temperature lower than -50°C (addition was very exothermic). The reaction was a clear orange color, and was allowed to slowly warm to ambient temperature, and stirred at ambient for 16 hours. The reaction was poured into water, extracted with ether, dried, filtered, and concentrated under reduced pressure to give an oil, 3.00 g. Column chromatography with ethyl acetate gave pure material, (2-thienyl)-phosphonic acid, diethyl ester, 0.40 g plus an additional 0.90 g of crude material enriched in product. ¹H NMR (CDCl₃) δ 1.32 - 1.36 (m, 6H), 4.07-4.21 (m, 4H), 7.17-7.19 (m, 1H), 7.65-7.71 (m, 2H). MS, *m/z* 220 (M⁺). The oil (0.40 g, 1.82 mmol) was reacted with bromotrimethylsilane (1.67 g, 10.91 mmol) to give an oil, which was diluted with 5.0 mL THF followed by 0.1 mL water, which gave a heavy oil that crystallized to give ([2-thienyl]-phosphonic acid) (9), 0.245 g, mp 119°C to 120°C. MS *m/z* 164 (M⁺). C,H,S analysis was not within an acceptable range. The crystals were dissolved in water, and eluted through a 2.0 g Mega Bond Elut C18

column (Varian Associates, Harbor City, CA). Lyophilizing the eluant gave crystals, 140 mg, mp 107°C to 109°C. The elemental analysis was outside of normal limits. One hundred ten milligrams were subjected to reverse phase high-performance liquid chromatography (HPLC) (ODS-3) giving a single component, 70 mg (**9**), mp 106°C to 107°C. MS m/z 220 (M⁺). ¹H NMR (360 MHz), (D₂O) δ 7.21 (m, J = 2.0, 2.7 Hz, 1H), 7.53 (qd, J = 1.1, 4.5 Hz, 1H), 7.73 (dt, J = 1.1, 4.5 Hz, 1H). ¹³C NMR (90.56 MHz), (D₂O) 131.1 (d, ³ J_{PCCC} = 17.3 Hz), 134.6 (³ J_{PSC} = 6.9 Hz), 136.9 (³ J_{PSC} = 11.8 Hz), 137 (³ J_{PSC} = 196.7 Hz). HNQC (360 MHz) analysis also supported the structure. Anal. Calcd for C₄H₅O₃PS: C, 29.27; H, 3.07; S, 19.54. Found: C, 25.40; H, 3.14; S, 15.53. By NMR, no other organic component observed, and HPLC gave enough retention to remove inorganic impurities.

(2-amino-5-pyrimidinyl)-phosphonic acid, diethyl ester (13**).** The phosphonic-enamine (**12**, R = Et, R' = H, 3.00 g, 12.76 mmol) (prepared by the method of Aboujaoude and coworkers (16,17) and used without further purification) was added to a stirred suspension of guanidine hydrochloride (1.21 g, 12.76 mmol) in 12.76 mmol of a 25% methanol solution of sodium methoxide, 12 mL THF, and 4 mL absolute ethanol. This mixture was refluxed for 4 hours, cooled, and concentrated under reduced pressure and the solids obtained were triturated with CHCl₃ and filtered through 20 g neutral Al₂O₃ (Woelm, 70-230 mesh, E. Merck, Darmstadt, Germany). A total of 100 mL CHCl₃ was eluted. Concentration under reduced pressure gave white solids, 2.09 g. Recrystallization from CH₂Cl₂-hexane gave white crystals, 1.51 g (**13**), 6.54 mmol (51.2%), mp 108°C to 108.5°C. ¹H NMR (CDCl₃) δ 1.33-1.36 (m, 6H), 4.07-4.20 (m, 4H), 5.58 (br s, 2H), 8.61 (d, ³ J_{PH} = 7.2 Hz, 2H). FT-IR (KBr) 3315, 3184, 1648, 1246 cm⁻¹. MS m/z 231 (M⁺). Anal. C₈H₁₄N₃O₃P C,H,N.

(2-amino-4-methyl-5-pyrimidinyl)-phosphonic acid, dimethyl ester (14**).** In the same fashion, (**14**) was prepared from the phosphonic-enamine (**12**, R = CH₃, R' = CH₃) to give a solid, 1.24 g, which was recrystallized from CH₂Cl₂-hexane and gave white crystals, 0.47 g (**14**), 2.16 mmol (12.8%), mp 126°C to 127.5°C. ¹H NMR (CDCl₃) δ 2.55 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 5.60 (br s, 1H), 8.61 (d, ³ J_{PH} = 7.2 Hz). FT-IR (KBr) 3302, 3161, 1673, 1584, 1011 cm⁻¹. Anal. C₇H₁₂N₃O₃P C,H,N.

(1-Methyl-1H-pyrazol-4-yl)-phosphonic acid (17**).** The phosphonic-enamine (**12**, R' = H, 3.00 g, 12.76 mmol) and methylhydrazine hydrosulfate (1.84 g, 12.76 mmol) were dissolved in 85 mL absolute ethanol, to which was added triethylamine (6.46 g, 68.82 mmol), and refluxed for 4 hours. The reaction was concentrated under reduced pressure to an oil, which was partitioned between ethyl acetate and 5% aqueous Na₂CO₃. The ethyl acetate solution was dried, filtered, and concentrated to an oil, 1.82 g (**15**), 8.34 mmol (65.4%). Column chromatography (CHCl₃-methanol 9:1) gave an oil, 1.73 g (**15**), 7.93 mmol (62.2%). ¹H NMR (CDCl₃) δ 1.33 (t, J_{AB} = 7 Hz, 6H), 3.95 (s, 3H), 4.06 - 4.13 (m, 4H), 7.72 (s, 1H), 7.74 (d, ³ J_{PH} = 1.9 Hz, 1H). (1-Methyl-1H-pyrazol-4-yl)-phosphonic acid, diethyl ester (**15**, 0.75 g, 3.44 mmol) was reacted with bromotrimethylsilane (3.16 g, 20.64 mmol) as previously described to give an oil, which was dissolved in water, filtered, and lyophilized to give a semisolid, 0.54g (**17**), 3.33 mmol (97%), mp 109°C to 121°C. ¹H NMR (d₆ DMSO) δ 3.86 (s, 1H), 5.73 (br), 7.53 (s, 1H), 7.92 (d, ³ J_{PH} < 0.5 Hz, 1H), 8.27 (br s, 5H). Anal. C₄H₇N₂O₃P_{0.4} HBr C,H,N,Br.

(1,5-Dimethyl-1H-pyrazol-4-yl)-phosphonic acid (18**).** The phosphonic-enamine (**12**, 16.05 mmol) prepared from diethyl-2-oxopropyl phosphonate and dimethylformamide dimethylacetal was used without further purification. Methylhydrazine hydrosulfate (2.43 g, 16.87 mmol), diluted with 125 mL absolute ethanol, to which was added triethylamine (10.24 g, 101.2 mmol), followed by the phosphonate. The reaction was refluxed for 4 hours, and concentrated to an oil that was partitioned between ethyl acetate and 5% aqueous Na₂CO₃. The ethyl acetate solution was dried, filtered, and concentrated to an oil, 3.76 g. Capillary GC analysis indicated a mixture of 2 components, 78:22 ratio. NMR supported a mixture of 2 regioisomers. Column chromatography (CHCl₃-methanol 95:5) on 1.87 g of the crude oil gave 0.68 g of (**16**), pure by GC, and corresponding to the major component. ¹H NMR (CDCl₃) δ 1.32 (t, J_{AB} = 7 Hz, 6H), 2.46 (d, J_{PH} = 1 Hz, 3H), 3.82 (s, 3H), 4.08 (m, 4H), 7.64 (s, 1H). A positive NOE was obtained between the 1-methyl and the 5-methyl groups, verifying the structure. The 3-H gave no NOE to another peak. Anal. C₉H₁₇N₂O₃P_{0.2} H₂O C,H,N.

(1,5-Dimethyl-1H-pyrazol-4-yl)-phosphonic acid, diethyl ester (16**, 0.68 g, 2.93 mmol)** was reacted with

bromotrimethylsilane (2.69 g, 15.58 mmol) as previously described to give a gum. The gum was dissolved in water, filtered, and lyophilized to give a gum that solidified, 0.32 g (**18**), 1.82 mmol (62.1%), mp 122°C to 123°C. ¹H NMR (d6 DMSO) δ 2.36 (s, 3H), 3.73 (s, 3H), 7.41 (s, 1H), 7.59 (br, exchangeable). Anal. C₅H₉N₂O₃P·0.75 H₂O·0.4 HBr C, H, N, Br.

(2-Hydroxy-5-pyrimidinyl)-phosphonic acid (19). (2-Amino-5-pyrimidinyl)-phosphonic acid, diethyl ester (**13**, 0.25 g, 1.08 mmol) was refluxed in 2 mL 6N HCl for 18 hours, diluted with toluene and concentrated under reduced pressure to an oil, which was diluted with water, filtered, and lyophilized to give crystals, 120 mg. Recrystallization from water-CH₃CN to give light tan crystals, 60 mg (**19**), 0.34 mmol (31.5%), mp higher than 200°C. (Changes in mp above 200°C; decomposition observed.) ¹H NMR (D₂O) δ 8.65 (d, ²J_{PH} = 6.8 Hz, 2H). ¹³C (100 MHz) 116 (J_{PC} = 188.6 Hz), 157.44, 163 (³J_{PCC} = 13.7 Hz). FT-IR (KBr) 3045, 1733, 1584 cm⁻¹. MS m/z 176 (M⁺). Anal. C₄H₅N₂O₃P C, H, N.

(2-Hydroxy-4-methyl-5-pyrimidinyl)-phosphonic acid (20). (2-amino-4-methyl-5-pyrimidinyl)-phosphonic acid, diethyl ester (**14**, 0.21 g, 0.97 mmol) was refluxed in 2 mL 6N HCl for 18 hours, diluted with toluene, and concentrated under reduced pressure to an oil, which solidified. Recrystallization from water-CH₃CN to give cream yellow crystals, 47 mg (**20**), 0.25 mmol (25.5%), mp 229°C (d). ¹H NMR (d6 DMSO) δ 2.42 (d, 3H, ³J_{PH} = 2 Hz), 8.20 (br, 2H). ¹H NMR (360 MHz) (D₂O, TSP, 0.01% TFA) δ 8.77 (d, 1H, ²J_{PH} = 8.8 Hz). FT-IR (KBr) 3146, 1749, 1576, 1176 cm⁻¹. MS m/z 190 (M⁺). Exact mass MS, C₅H₇N₂O₄P, 190.0141 ± 2 ppm. Anal. C₅H₇N₂O₄P C, H, N.

(2-Amino-5-pyrimidine)-phosphonic acid (21). (2-amino-5-pyrimidinyl)-phosphonic acid, diethyl ester (**13**, 0.50 g, 2.16 mmol) was reacted with bromotrimethylsilane (1.99 g, 12.99 mmol) as previously described to give crystals, 0.54 g (**21**). Recrystallization from water-CH₃CN to give white crystals as needles, 0.38 g (**21**), (100%), mp 232°C to 234°C. ¹H NMR (d6 DMSO) δ 5.65 (br), 8.46 (d, 3 J_{PH} = 6.5 Hz). MS m/z 175 (M⁺). Exact mass MS, C₄H₆N₃O₃P, 175.0147 ± 2 ppm. Anal. C₄H₆N₃O₃P C, H, N.

(2-Amino-4-methyl-5-pyrimidine)-phosphonic acid (22). (2-amino-4-methyl-5-pyrimidinyl)-phosphonic acid, diethyl ester (**14**, 400 mg, 1.84 mmol) was reacted with bromotrimethylsilane (1.69 g, 11.05 mmol) to give white crystals, from water-CH₃CN, 207 mg (**22**), 1.09 mmol (59.5%), mp 173.5°C to 175°C. ¹H NMR (360 MHz) (D₂O, no TSP, 0.01% TFA) δ 1.96 (d, 3H, ³J_{PH} = 2 Hz), 8.20, (d, 1H, ²J_{PH} = 5 Hz). MS m/z 189 (M⁺). Anal. C₅H₈N₃O₃P·1/2 H₂O C, H, N.

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