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# Phosphorus, Sulfur, and Silicon and the Related Elements

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First Synthesis of Phosphorylated Thienopyridines from 2amino-3-cyanothiophenes and βketophosphonates

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# FIRST SYNTHESIS OF PHOSPHORYLATED THIENOPYRIDINES FROM 2-AMINO-3-CYANOTHIOPHENES AND β-KETOPHOSPHONATES

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#### **GRAPHICAL ABSTRACT**



**Abstract** In a simple procedure, treatment of 2-amino-3-cyanothiophenes with  $\beta$ -ketophosphonates, under acid catalysis, leads to new 4-amino-5-phosphonothieno[2,3-b]pyridines in good to excellent yields. The structure of obtained products was confirmed by NMR ( ${}^{1}H$ ,  ${}^{31}P$ ,  ${}^{13}C$ ) and IR spectroscopies, and by mass spectrometry.

**Keywords** Thienopyridines; phosphonothienopyridines; phosphorylated heterocycles; fused heterocycles;  $\beta$ -ketophosphonates; 2-amino-3-cyanothiophenes

#### INTRODUCTION

Thienopyridines are very important heterocyclic compounds due to their broad spectrum of biological properties including anticancer,<sup>1,2</sup> antithrombotic,<sup>3,4</sup> anti-inflammatory,<sup>5</sup> and antimicrobial<sup>6,7</sup> activities. Certain thienopyridine derivatives have also found uses as anticonvulsants,<sup>8</sup> antidepressants,<sup>9</sup> and calcium channel modulators.<sup>10</sup>

Various synthetic procedures for thienopyridines were reported in the literature.<sup>11</sup> Among them, the condensation of 2-amino-3-cyanothiophenes with alkyl acetoacetates in the presence of stannic chloride<sup>11,12</sup> is one of the most used methods.

With this in mind, and pursuing our research program concerning the preparation of new phosphorylated heterocycles with possible biological properties,<sup>13</sup> we report here,

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for the first time, the synthesis of thienopyridine derivatives bearing a phosphonate or a phosphine oxide group. These phosphorus substituents could regulate important biological functions and could improve the biological activity of such compounds, in a similar way to that reported for other pharmaceuticals.<sup>14</sup>

The target compounds were obtained, in a simple one-pot protocol, from easily made 2-amino-3-cyanothiophenes and  $\beta$ -ketophosphonates, as starting materials.

## **RESULTS AND DISCUSSION**

The starting 2-amino-3-cyanothiophenes  $1^{15}$  and  $\beta$ -ketophosphonates  $2^{16}$  were easily prepared according to the reported procedures. Our initial attempts at synthesizing the desired phosphonothienopyridines involved the coupling of the former reactants in the presence of stannic chloride as acid catalyst. Unfortunately, the reaction failed and gave only the starting materials even after refluxing the mixture in toluene for long periods of time. A great improvement was observed when the reaction was performed with *p*-toluenesulfonic acid (TsOH) instead of stannic chloride. Indeed, the condensation of thiophenes 1 with  $\beta$ ketophosphonates 2, performed in refluxing toluene, for 72 h, in the presence of a catalytic amount of TsOH, led to the formation of 4-amino-5-phosphonothieno[2,3-*b*]pyridines 3 in 62–97% yield (Scheme 1). In order to demonstrate the efficiency and generality of this protocol, we examined the reactions of various 2-amino-3-cyanothiophenes and  $\beta$ ketophosphonates (Table 1). All substrates react to give the corresponding thienopyridines in good to high yields.

A plausible mechanism for the formation of compounds **3** is depicted in Scheme 2. The transformation is believed to proceed via a nucleophilic attack of the amino group on the  $\beta$ -ketophosphonate, giving rise to an imine intermediate. A subsequent intramolecular cyclization through the nucleophilic attack of the enamine tautomer at the nitrile group, leads to the final products **3**.

The structures of phosphonothienopyridines **3** were established through IR, NMR (<sup>1</sup>H, <sup>31</sup>P, <sup>13</sup>C), and mass spectral data. The IR spectra revealed the presence of absorption bands toward 1250 and 3300 cm<sup>-1</sup> corresponding to the P = O and NH<sub>2</sub> vibrators, respectively. The <sup>1</sup>H NMR spectrum of each compound **3** showed, in particular, a broad singlet at 4–5 ppm, ascribable to the NH<sub>2</sub> protons. The <sup>31</sup>P NMR shift recorded for compounds **3** was  $\delta = 20$ –27 ppm, which is consistent with the phosphoryl chemical shift values. The <sup>13</sup>C NMR spectra display the characteristic signals of all carbons and particularly those corresponding to the heterocyclic ring. Of particular note is the C–P carbon that



Entry	$\mathbf{R}^1$	R <sup>2</sup>	R <sup>3</sup>	$\mathbb{R}^4$	Product	Yield <sup>a</sup> (%)
1	(CH <sub>2</sub> ) <sub>4</sub>	OEt	CH <sub>3</sub>	3a	91	91
2	(CH <sub>2</sub> ) <sub>4</sub>	OMe	CH <sub>3</sub>	3b	90	90
3	(CH <sub>2</sub> ) <sub>4</sub>	Ph	Ph	3c	97	97
4	(CH <sub>2</sub> ) <sub>3</sub>	OEt	CH <sub>3</sub>	3d	68	68
5	(CH <sub>2</sub> ) <sub>3</sub>	Ph	Ph	3e	84	84
6	Ph-CH <sub>2</sub>	Ph	OEt	Ph	3f	94
7	Ph-CH <sub>2</sub>	Ph	OMe	Ph	3g	96
8	Ph-CH <sub>2</sub>	Ph	OMe	CH <sub>3</sub>	3h	78
9	Ph	Н	Ph	Ph	3i	93
10	CH <sub>3</sub>	Ph-CH <sub>2</sub>	OMe	CH <sub>3</sub>	3j	62
11	CH <sub>3</sub>	Ph-CH <sub>2</sub>	OMe	Ph	3k	71
12	CH <sub>3</sub>	Ph	OMe	Ph	31	76
13	CH <sub>3</sub>	Ph	OEt	CH <sub>3</sub>	3m	72
14	CH <sub>3</sub>	<i>i</i> Pr	OEt	Ph	3n	67
15	CH <sub>3</sub>	CH <sub>3</sub>	OEt	Ph	30	86
16	CH <sub>3</sub>	Н	OEt	CH <sub>3</sub>	3р	79

 Table 1
 Synthesis of 4-amino-5-phosphonothieno[2,3-b]pyridines 3

<sup>a</sup>Isolated yield.

resonates as a doublet around 90–120 ppm. Such a doublet is characteristic of the coupling with phosphorus with a  ${}^{1}J_{CP}$  coupling constant of about 80–130 Hz. The structures of the compounds **3** were supported additionally by the mass spectra, which showed the correct molecular ion peaks.



Scheme 2

#### CONCLUSION

A simple and efficient methodology has been developed for the synthesis of 4-amino-5-phosphonothieno[2,3-*b*]pyridines, from easily made 2-amino-3-cyanothiophenes and  $\beta$ ketophosphonates. To the best of our knowledge, this is the first synthesis of thienopyridine derivatives bearing a phosphonate or a phosphine oxide group.

### **EXPERIMENTAL**

The <sup>1</sup>H, <sup>31</sup>P, and <sup>13</sup>C NMR spectra were recorded with CDCl<sub>3</sub> as the solvent, on a Bruker-300 spectrometer. The chemical shifts are reported in ppm relative to tetramethyl-silane (TMS) (internal reference) for the <sup>1</sup>H and <sup>13</sup>C NMR and relative to 85% H<sub>3</sub>PO<sub>4</sub> (external reference) for the <sup>31</sup>P NMR. The coupling constants are reported in hertz. For the <sup>1</sup>H NMR, the multiplicities of signals are indicated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; qp, quintet; sept, septuplet; and m, multiplet. Sample <sup>1</sup>H, <sup>13</sup>C, and <sup>31</sup>P spectra for 3d and 3c are shown in Figures S1–S6 in the Supplemental Materials (posted online only).

Mass spectra were determined on a Micromass Quatro Ultima Pt spectrometer, under electrospray ionization (ESI) conditions, or on an Agilent 5975B spectrometer, under electronic impact (EI) conditions. The IR spectra were recorded on a Nicolet IR200 spectrometer. Purification of products was performed by column chromatography using silica gel 60 (Fluka).

General procedure for the synthesis of 4-amino-5-phosphonothieno[2,3b]pyridines 3. A mixture of 2-amino-3-cyanothiophene 1 (0.005 mol),  $\beta$ -ketophosphonate 2 (0.005 mol), and TsOH (0.1 g) in dry toluene (25 mL) was refluxed for 72 h in Dean–Stark apparatus. The reaction mixture was cooled and extracted with a saturated sodium bicarbonate solution (30 mL) and then with water (2 × 30 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude product was purified by chromatography on a silica gel column using diethylether as eluent.

**3a:** Light brown solid; mp = 174–176 °C; <sup>31</sup>P NMR (121.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 20.5 ppm; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.19 (t, 6H, <sup>3</sup>J<sub>H-H</sub> = 6.0 Hz, CH<sub>3</sub>–CH<sub>2</sub>); 1.55–2.33 (m, 8H, cyclic H); 2.44 (s, 3H, CH<sub>3</sub>–C=N); 3.98 (qp, 4H, <sup>3</sup>J<sub>H-H</sub> = <sup>3</sup>J<sub>P-H</sub> = 6.0 Hz, CH<sub>3</sub>–CH<sub>2</sub>); 5.04 (broad s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 16.0 (d, <sup>3</sup>J<sub>CP</sub> = 6.0 Hz, CH<sub>3</sub>–CH<sub>2</sub>–O); 21.8 (s, CH<sub>2</sub>–CH<sub>2</sub>–C=C=S); 22.9 (s, CH<sub>2</sub>–CH<sub>2</sub>–CH<sub>2</sub>–C=C=S); 23.5 (s, CH<sub>2</sub>–(CH<sub>2</sub>)<sub>3</sub>–C=C–S); 24.0 (s, CH<sub>2</sub>–C=C–S); 31.0 (s, CH<sub>3</sub>–C=N); 61.7 (d, <sup>2</sup>J<sub>CP</sub> = 6.0 Hz, CH<sub>2</sub>–O); 104.5 (d, <sup>1</sup>J<sub>CP</sub> = 104.2 Hz, C–P=O); 116.8 (s, C=C–S); 122.3 (s, CH<sub>2</sub>–C=C–S); 128.7 (s, CH<sub>2</sub>–C=S); 130.8 (d, <sup>2</sup>J<sub>CP</sub> = 23.4 Hz, C–NH<sub>2</sub>); 148.7 (s, N–C=S); 162.5 (d, <sup>2</sup>J<sub>CP</sub> = 22.6 Hz, C=N); IR (neat):  $\nu_{P=O}$  = 1262 cm<sup>-1</sup>;  $\nu_{NH2}$  = 3211–3410 cm<sup>-1</sup>; ESI-MS: *m*/*z* = 355.2 ([M+H]<sup>+</sup>); EI-HRMS: calculated for C<sub>16</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub>PS, 354.1167 (M<sup>+</sup>); found: 354.1164.

**3b:** Light brown solid; mp = 115–117 °C; <sup>31</sup>P NMR (121.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 22.1 ppm; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.65–2.39 (m, 8H, cyclic H); 2.23 (s, 3H, CH<sub>3</sub>–C=N); 3.71 (d, 6H, <sup>3</sup>J<sub>P-H</sub> = 12.0 Hz, CH<sub>3</sub>–O); 4.62 (broad s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 21.2 (s, <u>CH<sub>2</sub>–CH<sub>2</sub>–C=C=S); 22.4 (s, CH<sub>2</sub>–CH<sub>2</sub>–CH<sub>2</sub>–C=C=C=S); 23.2 (s, <u>CH<sub>2</sub>–(CH<sub>2</sub>)<sub>3</sub>–C=C=S); 23.5 (s, <u>CH<sub>2</sub>–C=C=S); 30.5 (s, <u>CH<sub>3</sub>–C=N); 52.2 (d</u>, <sup>2</sup>J<sub>CP</sub> = 6.8 Hz, <u>CH<sub>3</sub>–O); 116.3 (d</u>, <sup>1</sup>J<sub>CP</sub> = 104.1 Hz, C–P=O); 118.5 (s, C=C–S); 124.8 (s, CH<sub>2</sub>–C=C=S); 130.9 (s, CH<sub>2</sub>–C=S); 141.1 (d,</u></u></u>

 ${}^{2}J_{CP} = 19.6 \text{ Hz}, \underline{C}-NH_{2}$ ; 144.0 (s, N- $\underline{C}$ -S); 163.8 (d,  ${}^{2}J_{CP} = 26.8 \text{ Hz}, \underline{C}$ =N); IR (neat):  $\nu_{P=0} = 1234 \text{ cm}^{-1}$ ;  $\nu_{NH2} = 3211-3432 \text{ cm}^{-1}$ ; ESI-MS: m/z=327.1 ([M+H]<sup>+</sup>).

**3c:** Light brown solid; mp = 198–199 °C; <sup>31</sup>P NMR (121.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 27.3 ppm; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.63–2.53 (m, 8H, cyclic H); 3.76 (broad s, 2H, NH<sub>2</sub>); 7.12–7.95 (m, 15H, arom-H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 22.0 (s, <u>CH<sub>2</sub>-CH<sub>2</sub>-C=C=C); 23.0 (s, <u>CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-C=C=C); 24.1 (s, <u>CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-C=C=S); 24.6 (s, <u>CH<sub>2</sub>-C=C=S); 92.0 (d, <sup>1</sup>J<sub>CP</sub> = 105.7 Hz, <u>C</u>-P=O); 114.6 (s, <u>C</u>=C-S); 127.1 (s, <u>CH<sub>2</sub>-C=C=S); 130.9 (s, CH<sub>2</sub>-<u>C</u>-S); 132.2 (d, <sup>2</sup>J<sub>CP</sub> = 33.2 Hz, <u>C</u>-NH<sub>2</sub>); 156.5 (s, N-<u>C</u>-S); 161.8 (d, <sup>2</sup>J<sub>CP</sub> = 16.6 Hz, <u>C</u>=N); Phenyl carbons: 128.2, 128.5, 128.7, 129.1, 130.1, 131.0, 131.3, 131.7, 133.4, 134.0, 134.8, 138.0; IR (neat):  $\nu_{P=0} = 1262$  cm<sup>-1</sup>;  $\nu_{NH2} = 3211$ –3410 cm<sup>-1</sup>; ESI-MS: *m/z*=481.2 ([M+H]<sup>+</sup>); EI-HRMS: calculated for C<sub>29</sub>H<sub>25</sub>N<sub>2</sub>OPS, 480.1425 (M<sup>+</sup>); found: 480.1426.</u></u></u></u></u>

**3d:** Light brown solid; mp = 98–100 °C; <sup>31</sup>P NMR (121.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 20.3 ppm; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.24 (t, 6H, <sup>3</sup>J<sub>H-H</sub> = 6.0 Hz, C<u>H</u><sub>3</sub>–CH<sub>2</sub>); 1.59–2.81 (m, 6H, cyclic H); 2.31 (s, 3H, CH<sub>3</sub>–C=N); 4.10 (qp, 4H, <sup>3</sup>J<sub>H-H</sub> = <sup>3</sup>J<sub>P-H</sub> = 6.0 Hz, CH<sub>3</sub>–C<u>H</u><sub>2</sub>); 5.08 (broad s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 15.2 (d, <sup>3</sup>J<sub>CP</sub> = 6.0 Hz, C<u>H</u><sub>3</sub>–CH<sub>2</sub>–O); 26.4 (s, C<u>H</u><sub>2</sub>–CH<sub>2</sub>–C=C=S); 27.4 (s, C<u>H</u><sub>2</sub>–C=C=S); 28.6 (s, C<u>H</u><sub>2</sub>–(CH<sub>2</sub>)<sub>2</sub>–C=C=S); 30.4 (s, C<u>H</u><sub>3</sub>–C=N); 61.6 (d, <sup>2</sup>J<sub>CP</sub> = 6.0 Hz, C<u>H</u><sub>2</sub>–O); 111.9 (d, <sup>1</sup>J<sub>CP</sub> = 103.4 Hz, C\_P=O); 115 (s, C=C–S); 123.5 (s, CH<sub>2</sub>–C=C–S); 128.6 (s, CH<sub>2</sub>–C-S); 137.0 (d, <sup>2</sup>J<sub>CP</sub> = 21.9 Hz, C–NH<sub>2</sub>); 143.7 (s, N–C–S); 165.2 (d, <sup>2</sup>J<sub>CP</sub> = 25.7 Hz, C=N); IR (neat):  $\nu_{P=O}$  = 1262 cm<sup>-1</sup>;  $\nu_{NH2}$  = 3215–3422 cm<sup>-1</sup>; ESI-MS: m/z=341.1 ([M+H]<sup>+</sup>).

**3e:** Light brown solid; mp = 119–120 °C; <sup>31</sup>P NMR (121.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 27.4 ppm; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.05–2.52 (m, 6H, cyclic H); 5.31 (broad s, 2H, NH<sub>2</sub>); 6.96–7.88 (m, 15H, arom-H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 27.3 (s, CH<sub>2</sub>–CH<sub>2</sub>–C=C–S); 28.4 (s, CH<sub>2</sub>–C=C–S); 29.2 (s, CH<sub>2</sub>–(CH<sub>2</sub>)<sub>2</sub>–C=C–S); 116.2 (s, C=C–S); 104.8 (d, <sup>1</sup>J<sub>CP</sub> = 100.4 Hz, C–P = O); 127.9 (s, CH<sub>2</sub>–C = C–S); 131.7 (s, CH<sub>2</sub>–C–S); 133.3 (d, <sup>2</sup>J<sub>CP</sub> = 36.2 Hz, C–NH<sub>2</sub>); 141.5 (s, N–C–S); 166.8 (d, <sup>2</sup>J<sub>CP</sub> = 29.4 Hz, C=N); Phenyl carbons: 128.1, 128.2, 128.5, 128.7, 129.1, 130.7, 131.1, 131.3, 131.5, 132.1, 132.6, 137.0; IR (neat):  $\nu_{P=O}$  = 1262 cm<sup>-1</sup>;  $\nu_{NH2}$  = 3211–3410 cm<sup>-1</sup>; ESI-MS: m/z = 467.3 ([M+H]<sup>+</sup>).

**3f:** Light brown solid; mp = 132–134 °C; <sup>31</sup>P NMR (121.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 19.9 ppm; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.20 (t, 6H, <sup>3</sup>J<sub>H-H</sub> = 6.0 Hz, CH<sub>3</sub>–CH<sub>2</sub>); 3.59 (s, 2H, CH<sub>2</sub>-Ph); 4.06 (qp, 4H, <sup>3</sup>J<sub>H-H</sub> = <sup>3</sup>J<sub>P-H</sub> = 6.0 Hz, CH<sub>3</sub>–CH<sub>2</sub>); 4.37 (broad s, 2H, NH<sub>2</sub>); 7.04–7.94 (m, 15H, arom-H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 15.2 (d, <sup>3</sup>J<sub>CP</sub> = 6.0 Hz, CH<sub>3</sub>–CH<sub>2</sub>–O); 32.6 (s, CH<sub>2</sub>–C=C–S); 61.7 (d, <sup>2</sup>J<sub>CP</sub> = 6.8 Hz, CH<sub>2</sub>–O); 113.6 (d, <sup>1</sup>J<sub>CP</sub> = 122.3 Hz, C–P = O); 124.3 (s, C = C–S); 126.0 (s, CH<sub>2</sub>–C = C–S); 132.1 (s, CH<sub>2</sub>–C–S); 132.2 (d, <sup>2</sup>J<sub>CP</sub> = 18.9 Hz, C–NH<sub>2</sub>); 143.6 (s, N–C–S); 160.8 (d, <sup>2</sup>J<sub>CP</sub> = 28.3 Hz, C=N); Phenyl carbons: 125.3, 126.7, 126.8, 127.2, 127.5, 127.6, 127.8, 128.0, 128.3, 128.8, 135.5, 138.0; IR (neat):  $\nu_{P=O}$  = 1278 cm<sup>-1</sup>;  $\nu_{NH2}$  = 3207–3352 cm<sup>-1</sup>; ESI-MS: *m/z* = 529.2 ([M+H]<sup>+</sup>).

**3g:** Light brown solid; mp = 120–122 °C; <sup>31</sup>P NMR (121.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 22.9 ppm; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 3.59 (d, 6H, <sup>3</sup>J<sub>P-H</sub> = 6.0 Hz, CH<sub>3</sub>–O); 4.37 (s, 2H, CH<sub>2</sub>-Ph); 5.43 (broad s, 2H, NH<sub>2</sub>); 7.01–7.89 (m, 15H, arom-H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 32.9 (s, <u>CH<sub>2</sub>-Ph</u>); 52.4 (d, <sup>2</sup>J<sub>CP</sub> = 6.8 Hz, <u>CH<sub>3</sub>–O</u>); 112.9 (d, <sup>1</sup>J<sub>CP</sub> = 118.5 Hz, <u>C</u>–P = O); 122.5 (s, <u>C</u> = C–S); 126.2 (s, CH<sub>2</sub>–<u>C</u> = C–S); 129.1 (s, Ph–<u>C</u>–S); 132.2 (d, <sup>2</sup>J<sub>CP</sub> = 18.8 Hz, <u>C</u>–NH<sub>2</sub>); 144.1 (s, N–<u>C</u>–S); 161.2 (d, <sup>2</sup>J<sub>CP</sub> = 24.2 Hz,

<u>C</u>=N); Phenyl carbons: 124.5, 127.3, 127.4, 127.5, 127.7, 127.8, 127.9, 128.0, 128.2, 128.7, 137.0, 138.3; IR (neat):  $\nu_{P=0} = 1272 \text{ cm}^{-1}$ ;  $\nu_{NH2} = 3211-3342 \text{ cm}^{-1}$ ; ESI-MS:  $m/z = 501.1 \text{ ([M+H]}^+\text{)}.$ 

**3h:** Light brown solid; mp = 112–114 °C; <sup>31</sup>P NMR (121.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 22.5 ppm; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.35 (s, 3H, CH<sub>3</sub>–C=N); 3.70 (d, 6H, <sup>3</sup>J<sub>P-H</sub> = 9.0 Hz, CH<sub>3</sub>–O); 3.89 (s, 2H, CH<sub>2</sub>-Ph); 4.71 (broad s, 2H, NH<sub>2</sub>); 7.04–7.89 (m, 10H, arom-H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 28.5 (s, CH<sub>3</sub>–C=N); 32.6 (s, Ph-CH<sub>2</sub>); 60.8 (d, <sup>2</sup>J<sub>CP</sub> = 5.3 Hz, CH<sub>3</sub>–O); 112.9 (d, <sup>1</sup>J<sub>CP</sub> = 123.0 Hz, C–P = O); 114.4 (s, C = C–S); 125.0 (s, CH<sub>2</sub>–C = C–S); 131.2 (s, Ph-C–S); 132.4 (d, <sup>2</sup>J<sub>CP</sub> = 27.2 Hz, C–NH<sub>2</sub>); 143.9 (s, N–C–S); 160.5 (d, <sup>2</sup>J<sub>CP</sub> = 29.4 Hz, C=N); Phenyl carbons: 125.4, 126.5, 127.3, 127.5, 127.8, 128.3, 128.9, 138.0; IR (neat):  $\nu_{P=O}$  = 1245 cm<sup>-1</sup>;  $\nu_{NH2}$  = 3219–3460 cm<sup>-1</sup>; ESI-MS: *m/z* = 439.1 ([M+H]<sup>+</sup>).

**3i:** Light brown solid; mp = 138–140 °C; <sup>31</sup>P NMR (121.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 27.5 ppm; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 6.18 (broad s, 2H, NH<sub>2</sub>); 6.96–8.18 (m, 21H, arom-H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 96.1 (d, <sup>1</sup>J<sub>CP</sub> = 110.9 Hz, <u>C</u>–P = O); 124.6 (s, <u>C</u> = C–S); 125.3 (s, Ph-<u>C</u> = C–S); 128.6 (s, H–<u>C</u>-S); 132.4 (d, <sup>2</sup>J<sub>CP</sub> = 30.2 Hz, <u>C</u>–NH<sub>2</sub>); 141.7 (s, N–<u>C</u>–S); 166.4 (d, <sup>2</sup>J<sub>CP</sub> = 27.9 Hz, <u>C</u>=N); Phenyl carbons: 127.3, 127.9, 128.3, 128.5, 128.7, 129.0, 129.1, 129.6, 131.0, 131.1, 131.2, 131.7, 132.2, 133.1, 133.6, 137.0; IR (neat):  $\nu_{P=O}$  = 1276 cm<sup>-1</sup>;  $\nu_{NH2}$  = 3211–3345 cm<sup>-1</sup>; ESI-MS: m/z = 503.2 ([M+H]<sup>+</sup>).

**3j:** Light brown solid; mp = 114–116 °C; <sup>31</sup>P NMR (121.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 22.5 ppm; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.03 (s, 3H, CH<sub>3</sub>–C=C); 2.38 (s, 3H, CH<sub>3</sub>–C=N); 3.60 (d, 6H, <sup>3</sup>J<sub>P-H</sub> = 9.0 Hz, CH<sub>3</sub>–O); 3.78 (s, 2H, CH<sub>2</sub>-Ph); 4.98 (broad s, 2H, NH<sub>2</sub>); 6.95–7.72 (m, 5H, arom-H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 20.6 (s, CH<sub>3</sub>–C=C); 29.0 (s, CH<sub>3</sub>–C=N); 32.6 (s, Ph-CH<sub>2</sub>); 55.2 (d, <sup>2</sup>J<sub>CP</sub> = 6.8 Hz, CH<sub>3</sub>–O); 116.6 (d, <sup>1</sup>J<sub>CP</sub> = 122.6 Hz, C–P = O); 120.2 (s, C = C–S); 125.0 (s, CH<sub>3</sub>–C=S); 131.1 (s, CH<sub>2</sub>–C–S); 140.1 (d, <sup>2</sup>J<sub>CP</sub> = 21.1 Hz, C–NH<sub>2</sub>); 141.9 (s, N–C–S); 163.9 (d, <sup>2</sup>J<sub>CP</sub> = 34.7 Hz, C=N); Phenyl carbons: 124.3, 126.6, 127.8, 143.9; IR (neat):  $\nu_{P=O} = 1271 \text{ cm}^{-1}$ ;  $\nu_{NH2} = 3211–3340 \text{ cm}^{-1}$ ; ESI-MS: *m/z* = 377.0 ([M+H]<sup>+</sup>).

**3k:** Light brown solid; mp = 118–119 °C; <sup>31</sup>P NMR (121.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 22.9 ppm; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.47 (s, 3H, CH<sub>3</sub>–C=C); 3.65 (d, 6H, <sup>3</sup>J<sub>P-H</sub> = 9.0 Hz, CH<sub>3</sub>–O); 3.92 (s, 2H, CH<sub>2</sub>-Ph); 4.78 (broad s, 2H, NH<sub>2</sub>); 7.03–7.91 (m, 10H, arom-H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 11.9 (s, CH<sub>3</sub>–C=C); 35.5 (s, Ph-CH<sub>2</sub>); 52.1 (d, <sup>2</sup>J<sub>CP</sub> = 6.8 Hz, CH<sub>3</sub>–O); 110.6 (d, <sup>1</sup>J<sub>CP</sub> = 132.1 Hz, C–P = O); 120.1 (s, C = C–S); 125.1 (s, CH<sub>3</sub>–C = C–S); 130.4 (s, CH<sub>2</sub>–C–S); 137.7 (d, <sup>2</sup>J<sub>CP</sub> = 33.2 Hz, C–NH<sub>2</sub>); 139.9 (s, N–C–S); 159.8 (d, <sup>2</sup>J<sub>CP</sub> = 33.2 Hz, C=N); Phenyl carbons: 124.3, 126.8, 127.2, 127.7, 128.0, 129.1, 132.7, 143.8; IR (neat):  $\nu_{P=O}$  = 1272 cm<sup>-1</sup>;  $\nu_{NH2}$  = 3219–3340 cm<sup>-1</sup>; ESI-MS: *m/z* = 439.2 ([M+H]<sup>+</sup>).

**31:** Light brown solid; mp = 85–87 °C; <sup>31</sup>P NMR (121.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 23.1 ppm; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.34 (s, 3H, CH<sub>3</sub>–C=C); 3.55 (d, 6H, <sup>3</sup>J<sub>P-H</sub> = 11.4 Hz, CH<sub>3</sub>–O); 5.33 (broad s, 2H, NH<sub>2</sub>); 6.91–7.79 (m, 10H, arom-H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 14.1 (s, <u>C</u>H<sub>3</sub>–C=C); 53.2 (d, <sup>2</sup>J<sub>CP</sub> = 6.0 Hz, <u>C</u>H<sub>3</sub>–O); 116.5 (d, <sup>1</sup>J<sub>CP</sub> = 80.8 Hz, <u>C</u>–P = O); 121.2 (s, <u>C</u> = C–S); 125.3 (s, CH<sub>3</sub>–<u>C</u> = C–S); 130.5 (s, Ph-<u>C</u>–S); 133.6 (d, <sup>2</sup>J<sub>CP</sub> = 27.2 Hz, <u>C</u>–NH<sub>2</sub>); 138.4 (s, N–<u>C</u>–S); 161.9 (d, <sup>2</sup>J<sub>CP</sub> = 24.9 Hz, <u>C</u>=N); Phenyl carbons: 123.0, 128.3, 128.6, 128.7, 128.9, 129.2, 133.1, 137.1; IR (neat):  $\nu_{P=O}$  = 1273 cm<sup>-1</sup>;  $\nu_{NH2}$  = 3217–3340 cm<sup>-1</sup>; ESI-MS: *m/z* = 425.1 ([M+H]<sup>+</sup>); EI-HRMS: calculated for C<sub>22</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub>PS, 424.1010 (M<sup>+</sup>); found: 424.1014.

**3m:** Light brown solid; mp = 189–191 °C; <sup>31</sup>P NMR (121.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 21.9 ppm; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.34 (t, 6H, <sup>3</sup>J<sub>H-H</sub> = 6.0 Hz, CH<sub>3</sub>–CH<sub>2</sub>); 2.21 (s, 3H, CH<sub>3</sub>–C=N); 2.31 (s, 3H, CH<sub>3</sub>–C=C); 4.16 (qp, 4H, <sup>3</sup>J<sub>H-H</sub> = <sup>3</sup>J<sub>P-H</sub> = 6.0 Hz, CH<sub>3</sub>–CH<sub>2</sub>); 5.56 (broad s, 2H, NH<sub>2</sub>); 6.63–7.49 (m, 5H, arom-H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 14.2 (s, CH<sub>3</sub>–C=C); 16.2 (d, <sup>3</sup>J<sub>CP</sub> = 6.0 Hz, CH<sub>3</sub>–CH<sub>2</sub>–O); 31.3 (s, CH<sub>3</sub>–C=N); 62.6 (d, <sup>2</sup>J<sub>CP</sub> = 6.0 Hz, CH<sub>2</sub>–O); 111.5 (d, <sup>1</sup>J<sub>CP</sub> = 114.7 Hz, C–P = O); 121.1 (s, C = C–S); 126.0 (s, CH<sub>3</sub>–C = C–S); 128.6 (s, Ph-C–S); 130.0 (d, <sup>2</sup>J<sub>CP</sub> = 28.7 Hz, C–NH<sub>2</sub>); 138.4 (s, N–C–S); 161.8 (d, <sup>2</sup>J<sub>CP</sub> = 29.4 Hz, C=N); Phenyl carbons: 126.2, 127.0, 129.2, 135.5; IR (neat):  $\nu_{P=O}$  = 1262 cm<sup>-1</sup>;  $\nu_{NH2}$  = 3215–3367 cm<sup>-1</sup>; ESI-MS: m/z = 391.3 ([M+H]<sup>+</sup>).

**3n:** Light brown solid; mp = 150–152 °C; <sup>31</sup>P NMR (121.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 20.0 ppm; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 0.79 (d, 6H, <sup>3</sup>J<sub>H-H</sub> = 6.0 Hz, (CH<sub>3</sub>)<sub>2</sub>CH); 1.17 (t, 6H, <sup>3</sup>J<sub>H-H</sub> = 6.0 Hz, CH<sub>3</sub>–CH<sub>2</sub>); 2.19 (s, 3H, CH<sub>3</sub>–C=C); 3.55 (sept, 1H, <sup>3</sup>J<sub>H-H</sub> = 6.0 Hz, (CH<sub>3</sub>)<sub>2</sub>CH); 4.02 (qp, 4H, <sup>3</sup>J<sub>H-H</sub> = <sup>3</sup>J<sub>P-H</sub> = 6.0 Hz, CH<sub>3</sub>–CH<sub>2</sub>); 5.32 (broad s, 2H, NH<sub>2</sub>); 6.99–8.01 (m, 5H, arom-H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 12.6 (s, CH<sub>3</sub>–C=C); 16.3 (d, <sup>3</sup>J<sub>CP</sub> = 6.8 Hz, CH<sub>3</sub>–CH<sub>2</sub>–O); 22.3 (s, (CH<sub>3</sub>)<sub>2</sub>CH); 26.5 (s, (CH<sub>3</sub>)<sub>2</sub>CH); 62.5 (d, <sup>2</sup>J<sub>CP</sub> = 6.8 Hz, CH<sub>2</sub>–O); 114.1 (d, <sup>1</sup>J<sub>CP</sub> = 128.3 Hz, C=P = O); 125.2 (s, C = C-S); 127.2 (s, CH<sub>3</sub>–C=C-S); 131.5 (s, CH–C=S); 137.2 (d, <sup>2</sup>J<sub>CP</sub> = 26.4 Hz, C=NH<sub>2</sub>); 140.9 (s, N–C–S); 160.3 (d, <sup>2</sup>J<sub>CP</sub> = 27.2 Hz, C=N); Phenyl carbons: 127.7, 128.5, 133.0, 143.2; IR (neat):  $\nu_{P=O} = 1277$  cm<sup>-1</sup>;  $\nu_{NH2} = 3220$ –3343 cm<sup>-1</sup>; ESI-MS: *m/z* = 419.2 ([M+H]<sup>+</sup>).

**30:** Light brown solid; mp = 155–156 °C; <sup>31</sup>P NMR (121.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 19.9 ppm; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.06 (t, 6H, <sup>3</sup>J<sub>H-H</sub> = 6.0 Hz, CH<sub>3</sub>–CH<sub>2</sub>); 2.12 (s, 3H, CH<sub>3</sub>–C=C); 2.36 (s, 3H, CH<sub>3</sub>–C–S); 3.93 (qp, 4H, <sup>3</sup>J<sub>H-H</sub> = <sup>3</sup>J<sub>P-H</sub> = 6.0 Hz, CH<sub>3</sub>–CH<sub>2</sub>); 5.31 (broad s, 2H, NH<sub>2</sub>); 6.92–7.95 (m, 5H, arom-H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 12.3 (s, CH<sub>3</sub>–C–S); 13.0 (s, CH<sub>3</sub>–C=C); 16.0 (d, <sup>3</sup>J<sub>CP</sub> = 6.0 Hz, CH<sub>3</sub>–CH<sub>2</sub>–O); 62.5 (d, <sup>2</sup>J<sub>CP</sub> = 6.8 Hz, CH<sub>2</sub>–O); 105.7 (d, <sup>1</sup>J<sub>CP</sub> = 113.2 Hz, C–P = O); 120.1 (s, C = C–S); 127.6 (s, CH<sub>3</sub>–C = C–S); 131.2 (s, CH<sub>3</sub>–C–S); 136.7 (d, <sup>2</sup>J<sub>CP</sub> = 39.2 Hz, C–NH<sub>2</sub>); 138.5 (s, N–C–S); 160.3 (d, <sup>2</sup>J<sub>CP</sub> = 38.5 Hz, C=N); Phenyl carbons: 125.2, 128.5, 129.0, 137.5; IR (neat):  $\nu_{P=0} = 1271$  cm<sup>-1</sup>;  $\nu_{NH2} = 3217–3340$  cm<sup>-1</sup>; ESI-MS: *m/z* = 391.1 ([M+H]<sup>+</sup>).

**3p:** Light brown solid; mp = 113–115 °C; <sup>31</sup>P NMR (121.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 19.7 ppm; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.28 (t, 6H, <sup>3</sup>J<sub>H-H</sub> = 6.0 Hz, CH<sub>3</sub>–CH<sub>2</sub>); 2.09 (s, 3H, CH<sub>3</sub>–C=C); 2.23 (s, 3H, CH<sub>3</sub>–C=N); 4.08 (qp, 4H, <sup>3</sup>J<sub>H-H</sub> = <sup>3</sup>J<sub>P-H</sub> = 6.0 Hz, CH<sub>3</sub>–CH<sub>2</sub>); 5.16 (broad s, 2H, NH<sub>2</sub>); 7.70 (s, 1H, arom-H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 14.2 (s, CH<sub>3</sub>–C=C); 15.3 (d, <sup>3</sup>J<sub>CP</sub> = 6.8 Hz, CH<sub>3</sub>–CH<sub>2</sub>–O); 30.4 (s, CH<sub>3</sub>–C=N); 61.6 (d, <sup>2</sup>J<sub>CP</sub> = 6.8 Hz, CH<sub>2</sub>–O); 115.1 (d, <sup>1</sup>J<sub>CP</sub> = 113.2 Hz, C–P = O); 124.3 (s, C = C–S); 127.2 (s, CH<sub>3</sub>–C = C–S); 128.8 (s, H–C–S); 132.4 (d, <sup>2</sup>J<sub>CP</sub> = 23.3 Hz, C–NH<sub>2</sub>); 143.7 (s, N–C–S); 162.2 (d, <sup>2</sup>J<sub>CP</sub> = 26.4 Hz, C=N); IR (neat):  $\nu_{P=0}$  = 1266 cm<sup>-1</sup>;  $\nu_{NH2}$  = 3235–3338 cm<sup>-1</sup>; ESI-MS: *m*/*z* = 315.2 ([M+H]<sup>+</sup>).

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