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# Facile synthesis and nematicidal activity evaluation of thiophosphinyl amide [(Pz)<sub>2</sub>P(S)NHR] and thiophosphonyl diamide [(Pz)P(S)(NHR)<sub>2</sub>] (Pz = 1,3,5-trimethylpyrazole, R = biphenyl derivatives)<sup>†</sup>

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A series of thiophosphinyl amide [(Pz)<sub>2</sub>P(S)NHR] and thiophosphonyl diamide [(Pz)P(S)(NHR)<sub>2</sub>] compounds, where Pz = 1,3,5-trimethylpyrazole and N(H)R = derivatives of 2-aminobiphenyl, were synthesized via a facile two-step process. Reaction of pyrazolyl substituted bromophosphine with 2-aminobiphenyl derivatives and further reaction with elemental sulphur affords the corresponding thiophosphinyl amide and thiophosphonyl diamide. The intermediate species was used without prior purification for reaction with sulphur to yield the target compounds. The nematicidal activity evaluation suggests that some compounds could manifest moderate nematicidal activity towards *Meloidogyne incognita*, which is higher than that of their amide analogue bixafen.

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## Introduction

The biological activities of organophosphorus compounds are well documented and their action mode is in part related to the presence of the phosphate group in nucleotides and cell membranes.<sup>1–4</sup> In the medical field, the phosphate containing drug remdesivir has been developed,<sup>5,6</sup> while in the agricultural industry this approach has also garnered success, as exemplified by the pesticide Imicyafos.<sup>7–9</sup> It should be noted that compared with the highly investigated small molecule organophosphorus compounds (like phosphate esters),<sup>4,10–13</sup> there is comparatively little research on the synthesis and bio-activity of their pyrazole derivatives,<sup>14–20</sup> an area of research that is particularly relevant since the bio-activity of such compounds is well documented.<sup>21–24</sup> Indeed, some of the phosphonyl pyrazole derivatives have been shown to possess biological activity, like antimicrobial, anticancer and antioxidant activities.<sup>25–29</sup>

Our primary interest in the bioactivity of organophosphorus prompted us to investigate agricultural pesticides, in particular those that act as a succinate dehydrogenase inhibitor (SDHI). To date, 23 SDHI compounds have been listed by the Fungicide Resistance Action Committee (FRAC) (selected SDHIs are listed in Fig. 1). Previous investigation suggests that fluopyram, one of these SDHI, could inhibit the growth of *Meloidogyne incognita*, with a 2 h EC<sub>50</sub> value of 5.18 mg mL<sup>−1</sup>.<sup>30</sup> This nematicide activity was higher than those of the other tested SDHIs, like boscalid,

flutolanil, penthiopyrad and benzovindiflupyr.<sup>30</sup> In this fertile area, a number of novel SDHI-based compounds and their nematicidal activity are currently under investigation, some of which will be released into the market soon, such as the new nematicide named cyclobutrifluram, developed by Syngenta.<sup>31</sup> The promising nematicidal activity of fluopyram and cyclobutrifluram suggests that further research of SDHI-based compounds as effective nematicidal agents is warranted.<sup>32,33</sup> Considering the potential bio-activity of organophosphorus compounds, we believe that a successful approach could involve the synergistic combination of the basic molecular scaffold of existing SDHIs with the biologically active organophosphorus moiety.

Herein, we report the facile synthesis of 16 novel thiophosphinyl amides and thiophosphonyl diamides, together

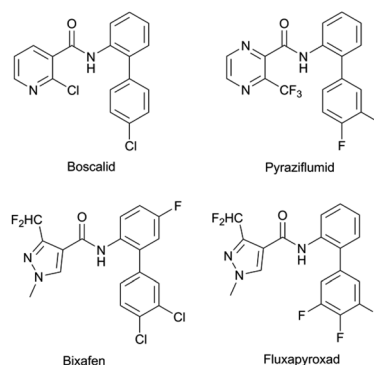


Fig. 1 Molecular structures of selected SDHIs (boscalid, pyraziflumid, bixafen and fluxapyroxad).

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with data on their nematocidal activity towards *Meloidogyne incognita*.

## Results and discussion

Target compounds were designed by combination of specific structural features of certain SDHIs and the biologically active organophosphorus moiety, which should act synergistically to promote their biological activity. Among the 23 SDHIs listed by FRAC, 12 contain a 1-methylpyrazole group, which includes isoflucypram, penflufen, pydiflumetofen, flupoxad, and sedaxane, underscoring the importance of pyrazole groups for biological activity. Furthermore, the SDHIs of acaricide pyflubumide similarly possess a 1,3,5-trimethylpyrazole group.<sup>34,35</sup>

Based on these precedents, we decided to incorporate the 1,3,5-trimethylpyrazole moiety in our novel thiophosphine based nematocides. A C-5 methyl group should prevent migration of a phosphine group between C-2 and C-3, a process that has been widely observed for other pyrazole derivatives.<sup>36,37</sup> In addition, some analogues of 2-aminobiphenyl have been employed as pesticidal agents.

The 1,3,5-trimethylpyrazole substituted bromophosphine (**1** and **2**) were prepared following a previously published protocol.<sup>15</sup> Due to the  $\pi$ -rich character of a pyrazol ring,  $\text{PBr}_3$  can directly react with 1,3,5-trimethylpyrazole in the presence of pyridine, which acts as both a solvent and an acid acceptor, leading to the corresponding phosphorylation products **1** and **2**. After a standard reaction of **1** (or **2**) with the corresponding analogues of 2-aminobiphenyl, in the presence of triethylamine, the resulting crude phosphinylamine (phosphonyldiamine) directly reacted with stoichiometric amount of  $\text{S}_8$ , giving the desired compounds **1a–1h** (or **2a–2h**) (Fig. 2). Tedious

purification procedures such as column chromatography could be avoided, and crystallization proceeded smoothly after a simple workup procedure. The crude products **1a–1h** were directly isolated after the removal of a violet filtrate, followed by washing with petroleum ether. Spectroscopically pure compounds were obtained after crystallization from ethyl acetate/petroleum ether ( $v/v = 1:1$ ), affording products in moderate to high yields. To obtain the purified products **2a–2h**, petroleum ether was added directly to a partially concentrated crude mixture, giving two separate layers, with the interface acting as a vehicle for slow crystallization of the products obtained in moderate yields.

In the  $^1\text{H}$  NMR spectra, the  $-\text{NH}$  signals at around 5 ppm were observed as doublets in all compounds, which indicated the existence of  $^2J_{\text{PH}}$  coupling and the formation of P–N bonds. IR spectroscopy analysis confirmed the presence of a secondary amine with a single sharp N–H stretch absorption band  $\nu(\text{NH})$  observed at around  $3380\text{ cm}^{-1}$ . Taken together, the NMR and IR data both confirmed the presence of a secondary amide where the nitrogen was bound to a phosphorus atom. Meanwhile, the single doublet indicated the presence of symmetric  $-\text{NH}$  groups in **1a–1h** in solution on the NMR timescale. Meanwhile, the P–C coupling phenomenon can be detected as well in the  $^{13}\text{C}$  NMR spectra and the coupling constants are highly consistent with that of reported bis(diethylamido)-1,3,5-trimethylpyrazol-4-ylthiophosphonate.<sup>15</sup> In the  $^{31}\text{P}$  NMR spectra, a singlet was observed at around 41 ppm for compounds **1a–1h** (Table 1).

The NMR spectra of **2a–2h** mirrored those of **1a–1h**. For example, the  $^1\text{H}$  NMR spectra showed that the  $-\text{NH}$  signals were also observed as doublets at similar ppm values. In addition, the methyl groups were observed as singlets indicating the presence of highly symmetric pyrazole groups in **2a–2h** in

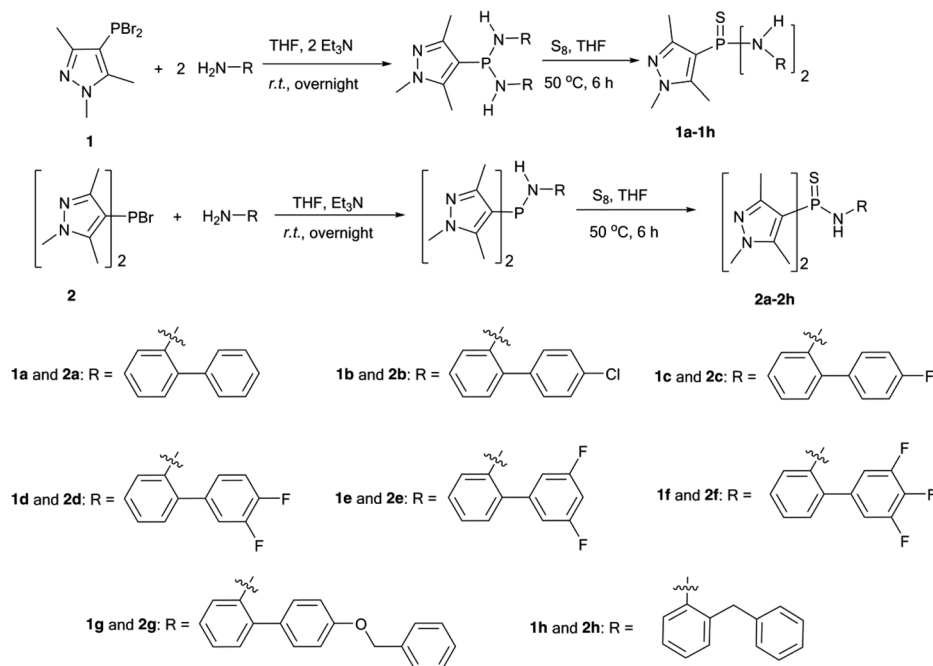


Fig. 2 Synthesis and molecular structures of thiophosphinyl amide (**1a–1h**) and thiophosphonyl diamide (**2a–2h**).

Table 1  $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{31}\text{P}$  NMR and IR data of the compounds **1a–2h**

$^1\text{H}$ NMR (ppm)				$^{13}\text{C}$ NMR (ppm) ( $J_{\text{P-C}}$ , Hz)						$^{31}\text{P}$ NMR (ppm)	IR ( $\text{cm}^{-1}$ )
1- $\text{CH}_3$	3- $\text{CH}_3$	5- $\text{CH}_3$	-NH ( $^2J_{\text{PH}}$ , Hz)	1- $\text{CH}_3$	3- $\text{CH}_3$	5- $\text{CH}_3$	C-3	C-4	C-5		-NH
<b>1a</b> 3.63	2.18	1.94	5.42, 5.39 (8.3)	36.36	13.78	11.27	144.08, 143.91 (25.5)	109.56, 108.54 (153.0)	148.73, 148.64 (13.5)	40.40	3381
<b>1b</b> 3.66	2.26	2.00	5.28, 5.25 (7.1)	36.44	13.94	11.44	144.32, 144.14 (27.0)	109.35, 108.32 (154.5)	148.76, 148.68 (12.0)	41.26	3385
<b>1c</b> 3.66	2.31	1.94	5.67, 5.65 (8.2)	36.43	13.93	11.41	144.17, 144.00 (25.5)	109.47, 108.44 (154.5)	148.71, 148.63 (12.0)	42.20	3386
<b>1d</b> 3.68	2.31	2.05	5.23, 5.21 (6.5)	36.44	13.96	11.50	144.50, 144.33 (25.5)	109.45, 108.42 (154.5)	148.70, 148.61 (13.5)	41.48	3388
<b>1e</b> 3.67	2.34	2.04	5.25, 5.23 (6.7)	36.44	14.00	11.51	144.53, 144.36 (25.5)	109.16, 108.13 (154.5)	148.78, 148.70 (12.0)	41.90	3382
<b>1f</b> 3.63	2.32	2.09	5.49, 5.47 (6.7)	36.48	14.13	11.59	144.61, 144.44 (25.5)	109.10, 108.07 (154.5)	148.80, 148.71 (13.5)	42.20	3387
<b>1g</b> 3.64	2.22	2.00	5.45, 5.42 (8.9)	36.41	13.89	11.36	144.09, 143.92 (25.5)	109.65, 108.62 (154.5)	148.76, 148.68 (12.0)	40.53	3373
<b>1h</b> 3.65	2.10	1.84	4.89, 4.86 (8.0)	36.31	13.75	11.26	144.60, 144.43 (25.5)	109.58, 108.56 (153.0)	149.27, 149.18 (13.5)	40.36	3385
<b>2a</b> 3.70	2.29	1.97	5.26, 5.24 (7.7)	36.36	14.00	11.44	144.65, 144.49 (24.0)	108.79, 107.92 (130.5)	149.36, 149.28 (12.0)	29.61	3400
<b>2b</b> 3.68	2.28	1.95	5.09, 5.07 (6.6)	36.41	14.06	11.52	144.70, 144.54 (24.0)	108.68, 107.82 (129.0)	149.34, 149.26 (12.0)	29.97	3402
<b>2c</b> 3.68	2.28	1.95	5.09, 5.07 (5.3)	36.40	14.04	11.51	144.69, 144.53 (24.0)	108.72, 107.85 (130.5)	149.31, 149.24 (12.0)	29.86	3402
<b>2d</b> 3.69	2.32	1.96	5.03, 5.01 (6.9)	36.41	14.06	11.56	144.75, 144.59 (24.0)	108.65, 107.79 (129.0)	149.30, 149.22 (12.0)	30.25	3395
<b>2e</b> 3.70	2.31	1.96	5.02, 5.00 (7.3)	36.39	14.02	11.56	144.78, 144.62 (24.0)	108.64, 107.78 (129.0)	149.31, 149.23 (12.0)	30.31	3400
<b>2f</b> 3.69	2.35	1.96	4.93, 4.91 (7.2)	36.43	14.06	11.62	144.84, 144.68 (24.0)	108.61, 107.75 (129.0)	149.30, 149.23 (10.5)	30.71	3401
<b>2g</b> 3.67	2.28	1.95	5.24, 5.22 (6.8)	36.38	14.04	11.49	144.65, 144.49 (24.0)	108.79, 107.92 (130.5)	149.36, 149.28 (12.0)	29.61	3402
<b>2h</b> 3.69	2.20	1.84	4.77, 4.75 (7.3)	36.34	13.90	11.46	144.67, 144.51 (24.0)	108.89, 108.03 (129.0)	149.46, 149.39 (10.5)	29.09	3402

Table 2 Nematicidal activity of **1a–1h**, **2a–2h** and bixafen towards *M. incognita* at 40  $\text{mg L}^{-1}$ 

Compound	Inhibition (%)	Compound	Inhibition (%)
<b>1a</b>	34.2 $\pm$ 1.2	<b>2a</b>	26.7 $\pm$ 1.0
<b>1b</b>	23.7 $\pm$ 1.6	<b>2b</b>	31.5 $\pm$ 1.8
<b>1c</b>	62.1 $\pm$ 0.8	<b>2c</b>	—
<b>1d</b>	24.8 $\pm$ 1.7	<b>2d</b>	—
<b>1e</b>	—	<b>2e</b>	37.3 $\pm$ 2.2
<b>1f</b>	—	<b>2f</b>	—
<b>1g</b>	—	<b>2g</b>	—
<b>1h</b>	—	<b>2h</b>	—
Bixafen	—		

solution on the NMR timescale. Compared with **1a–1h**, the single sharp -NH stretch absorption bands  $\nu(\text{NH})$  of **2a–2h** were shifted to approximately 3400  $\text{cm}^{-1}$ , a slightly higher wave-number. The coupling constants in **2a–2h** are identify with that of in **1a–1h**, except for a slightly lower constants for P-C4, which was influenced by the variation of substitutes on the P atom. The singlets in the  $^{31}\text{P}$  NMR spectra were shifted downfield to approximately 30 ppm in **2a–2h** (Table 1).

The *in vitro* nematicidal activity was evaluated according to the classic protocol reported by Faske and Hurd.<sup>30</sup> After exploring a concentration of 40  $\text{mg L}^{-1}$  for 24 h, no obvious inhibitory activity could be detected for the lead compound bixafen towards *M. incognita*. In contrast, moderate nematicidal activities were observed for compounds **1a–1d**, **2a**, **2b** and **2e**, and particularly for **1c**, which had the highest inhibitory rate at 62.1%. Moreover, after treatment with **1c**, the activity of the surviving nematodes was highly inhibited. We thus demonstrated that modifying the basic structure scaffold present in the SDHI bixafen by incorporating an organophosphorus moiety was a successful approach for screening compounds

with encouraging nematicidal activity. Motivated by the above encouraging results, studies involving further modification of phosphorylated pyrazole derivatives and the evaluation of their nematicidal activity are currently underway.

## Experimental

### Materials and methods

All manipulations of air-sensitive materials were performed under rigorous exclusion of oxygen and moisture in Schlenk-type glassware or on a dual manifold Schlenk line, interfaced with a high vacuum line. Tetrahydrofuran, toluene and triethylamine were predried using an MBraun solvent purification system (SPS-800) and then they were degassed, dried and stored over 4 Å molecular sieves. Starting materials **1** and **2** were synthesized following the previously published procedure.<sup>15</sup> The other chemicals were purchased from commercial source and used without further purification. The  $^1\text{H}$ , and  $^{31}\text{P}$  NMR spectra were recorded on a Bruker Avance II 300 MHz NMR spectrometer.  $^{13}\text{C}$  spectra were obtained from a Bruker Avance II 600 MHz NMR spectrometer. Chemical shifts for  $^1\text{H}$  and  $^{13}\text{C}$  spectra are reported as parts per million (ppm) relative to tetramethylsilane and referenced to the residual  $^1\text{H}$  or  $^{13}\text{C}$  resonances of the deuterated solvents. The  $^{31}\text{P}$  NMR data was referenced to  $\text{H}_3\text{PO}_4$ . IR spectra, from 4000 to 400  $\text{cm}^{-1}$ , were obtained using a Nicolet IS10 FT-IR spectrometer equipped with a room temperature DLaTGS detector and a diamond ATR unit. Mass spectra (ESI) were recorded on a Bruker ultraflexxtreme MALDI-TOF instrument in positive ionization mode.

### Synthesis of compounds **1a–1h**

The corresponding primary amine (18.0 mmol) and  $\text{Et}_3\text{N}$  (1.822 g, 18.0 mmol) was dissolved in 100 mL dry THF. Then,



a THF solution of **1** (2.699 g, 9.0 mmol, in 20 mL dry THF) was added to the mixture previously cooled to 0 °C. After addition, the solution was slowly warmed to room temperature and was stirred overnight. Filtration was used to remove the formed white solid Et<sub>3</sub>N·HBr. Then, S<sub>8</sub> (0.288 g, 9.0 mmol) was added to the mixture and the mixture was further stirred for 6.0 h at 50 °C. After filtration, the violet filtrate was removed under vacuum and the residue was washed with 30 mL of petroleum ether, giving the crude product. The target compound could be further purified by crystallization using ethyl acetate/petroleum ether (v/v = 1 : 1).

**N,N'-(1,1'-Biphenyl)-2-yl)-P(1,3,5-trimethyl-1H-pyrazol-4-yl)phosphonothioic diamide (1a).** White solid. Yield: 3.16 g, 68.9%. <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 300 MHz, 298 K): 7.47–7.00 (m, 18H, Ph), 5.42, 5.39 (d, 2H, <sup>2</sup>J<sub>PH</sub> = 8.3 Hz, NH), 3.63 (s, 3H, 1-CH<sub>3</sub>), 2.18 (s, 3H, 3-CH<sub>3</sub>), 1.94 (s, 3H, 5-CH<sub>3</sub>). <sup>13</sup>C NMR (151 MHz, CD<sub>2</sub>Cl<sub>2</sub>): 148.69 (d, J<sub>P-C</sub> = 13.5 Hz), 144.00 (d, J<sub>P-C</sub> = 25.5 Hz), 138.63, 137.31, 132.27, 132.22, 130.75, 129.67, 129.56, 128.52, 128.39, 122.12, 118.07, 118.04, 109.01 (d, J<sub>P-C</sub> = 153.0 Hz), 36.36, 13.78, 11.27. <sup>31</sup>P NMR (CD<sub>2</sub>Cl<sub>2</sub>, 121.5 MHz, 298 K): δ = 40.4 ppm. IR (ATR, cm<sup>-1</sup>): 3380, 3056, 3028, 1595, 1578, 1499, 1480, 1434, 1400, 1379, 1298, 1379, 1269, 1212, 1178, 1112, 1051, 1008, 994, 946, 931, 909, 838, 802, 754, 770, 736, 721, 704, 681, 643, 590, 549, 483, 473, 457. MS (ESI, pos.) *m/z*: found: 509.11 [M + H]<sup>+</sup>, calculated: 508.19. Anal. calcd for C<sub>30</sub>H<sub>29</sub>N<sub>4</sub>PS (508.62): C, 70.84; H, 5.75; N, 11.02; S, 6.30%; found: C, 70.67; H, 5.82; N, 10.89; S, 6.12%.

**N,N'-(4'-Chloro-[1,1'-biphenyl]-2-yl)-P(1,3,5-trimethyl-1H-pyrazol-4-yl)phosphonothioic diamide (1b).** White solid. Yield: 3.96 g, 76.1%. <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 300 MHz, 298 K): 7.44–7.02 (m, 16H, Ph), 5.28, 5.25 (d, 2H, <sup>2</sup>J<sub>PH</sub> = 7.1 Hz, NH), 3.66 (s, 3H, 1-CH<sub>3</sub>), 2.26 (s, 3H, 3-CH<sub>3</sub>), 2.00 (s, 3H, 5-CH<sub>3</sub>). <sup>13</sup>C NMR (151 MHz, CD<sub>2</sub>Cl<sub>2</sub>, 298 K): 148.72 (d, J<sub>P-C</sub> = 12.0 Hz), 144.23 (d, J<sub>P-C</sub> = 27.0 Hz), 137.23, 137.13, 134.32, 131.29, 131.23, 131.15, 130.82, 129.65, 128.85, 122.47, 118.65, 118.62, 108.84 (d, J<sub>P-C</sub> = 154.5 Hz), 36.44, 13.94, 11.44. <sup>31</sup>P NMR (CD<sub>2</sub>Cl<sub>2</sub>, 121.5 MHz, 298 K): δ = 41.3 ppm. IR (ATR, cm<sup>-1</sup>): 3385, 3357, 3029, 1607, 1591, 1579, 1500, 1479, 1449, 1397, 1381, 1295, 1283, 1272, 1205, 1179, 1160, 1101, 1084, 1051, 1018, 1007, 935, 917, 832, 801, 764, 693, 671, 651, 617, 595, 547, 502, 489, 470, 448. MS (ESI, pos.) *m/z*: found: 577.07 [M + H]<sup>+</sup>, calculated: 576.11. Anal. calcd for C<sub>30</sub>H<sub>27</sub>Cl<sub>2</sub>N<sub>4</sub>PS (577.51): C, 62.39; H, 4.71; N, 9.70; S, 5.55%; found: C, 62.11; H, 4.88; N, 9.83; S, 5.67%.

**N,N'-(4'-Fluoro-[1,1'-biphenyl]-2-yl)-P(1,3,5-trimethyl-1H-pyrazol-4-yl)phosphonothioic diamide (1c).** White solid. Yield: 3.83 g, 78.0%. <sup>1</sup>H NMR (CD<sub>3</sub>CN, 300 MHz, 298 K): 7.43–7.02 (m, 16H, Ph), 5.67, 5.65 (d, 2H, <sup>2</sup>J<sub>PH</sub> = 8.2 Hz, NH), 3.66 (s, 3H, 1-CH<sub>3</sub>), 2.31 (s, 3H, 3-CH<sub>3</sub>), 1.99 (s, 3H, 5-CH<sub>3</sub>). <sup>13</sup>C NMR (151 MHz, CD<sub>2</sub>Cl<sub>2</sub>, 298 K): 162.89 (d, J<sub>C-F</sub> = 247.6 Hz), 148.67 (d, J<sub>P-C</sub> = 12.0 Hz), 144.09 (d, J<sub>P-C</sub> = 25.5 Hz), 137.41, 131.54 (d, J<sub>C-F</sub> = 7.6 Hz), 131.34, 131.29, 130.94, 128.69, 122.29, 118.30 (d, J<sub>C-F</sub> = 4.5 Hz), 116.44 (d, J<sub>C-F</sub> = 21.1 Hz), 108.96 (d, J<sub>P-C</sub> = 154.5 Hz), 36.43, 13.93, 11.41. <sup>31</sup>P NMR (CD<sub>3</sub>CN, 121.5 MHz, 298 K): δ = 41.8 ppm. IR (ATR, cm<sup>-1</sup>): 3386, 3063, 3038, 2923, 1597, 1579, 1512, 1487, 1448, 1406, 1383, 1370, 1295, 1286, 1273, 1219, 1158, 1111, 1093, 1051, 1009, 940, 916, 839, 802, 766, 751, 710,

684, 673, 664, 639, 618, 601, 555, 546, 499, 487, 464, 435. MS (ESI, pos.) *m/z*: found: 545.13 [M + H]<sup>+</sup>, calculated: 544.17.

**N,N'-(3',4'-Difluoro-[1,1'-biphenyl]-2-yl)-P(1,3,5-trimethyl-1H-pyrazol-4-yl)phosphonothioic diamide (1d).** White solid. Yield: 4.11 g, 78.5%. <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 300 MHz, 298 K): 7.35–7.05 (m, 14H, Ph), 5.23, 5.21 (d, 2H, <sup>2</sup>J<sub>PH</sub> = 6.5 Hz, NH), 3.68 (s, 3H, 1-CH<sub>3</sub>), 2.31 (s, 3H, 3-CH<sub>3</sub>), 2.05 (s, 3H, 5-CH<sub>3</sub>). <sup>13</sup>C NMR (151 MHz, CD<sub>2</sub>Cl<sub>2</sub>, 298 K): 151.50 (dd, J<sub>C-F</sub> = 249.5, 11.7 Hz), 149.84 (dd, J<sub>C-F</sub> = 251.5, 12.1 Hz), 148.70 (d, J<sub>P-C</sub> = 13.5 Hz), 144.42 (d, J<sub>P-C</sub> = 25.5 Hz), 137.18, 135.66–135.60 (m), 130.91, 130.56, 130.50, 129.14, 126.13–126.07 (m), 122.63, 118.98 (d, J<sub>C-F</sub> = 18.1 Hz), 118.88, 118.85, 118.38 (d, J<sub>C-F</sub> = 17.9 Hz), 108.94 (d, J<sub>P-C</sub> = 154.5 Hz), 36.44, 13.96, 11.50. <sup>31</sup>P NMR (CD<sub>2</sub>Cl<sub>2</sub>, 121.5 MHz, 298 K): δ = 41.5 ppm. IR (ATR, cm<sup>-1</sup>): 3389, 3030, 2925, 1604, 1579, 1515, 1491, 1453, 1410, 1383, 1311, 1279, 1261, 1228, 1212, 1181, 1160, 1116, 1107, 1052, 943, 922, 897, 874, 840, 821, 802, 768, 755, 708, 685, 674, 665, 634, 619, 586, 577, 546, 492, 450. MS (ESI, pos.) *m/z*: found: 581.08 [M + H]<sup>+</sup>, calculated: 580.15.

**N,N'-(3',5'-Difluoro-[1,1'-biphenyl]-2-yl)-P(1,3,5-trimethyl-1H-pyrazol-4-yl)phosphonothioic diamide (1e).** White solid. Yield: 3.89 g, 74.4%. <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 300 MHz, 298 K): 7.37–6.85 (m, 14H, Ph), 5.25, 5.23 (d, 2H, <sup>2</sup>J<sub>PH</sub> = 6.7 Hz, NH), 3.67 (s, 3H, 1-CH<sub>3</sub>), 2.34 (s, 3H, 3-CH<sub>3</sub>), 2.04 (s, 3H, 5-CH<sub>3</sub>). <sup>13</sup>C NMR (151 MHz, CD<sub>2</sub>Cl<sub>2</sub>, 298 K): 163.71 (dd, J<sub>C-F</sub> = 250.7, 12.1 Hz), 148.74 (d, J<sub>P-C</sub> = 12.0 Hz), 144.50 (d, J<sub>P-C</sub> = 25.5 Hz), 142.03 (t, J<sub>C-F</sub> = 9.7 Hz), 136.99, 130.61, 130.44, 130.40, 129.43, 122.71, 119.13, 112.88 (dd, J<sub>C-F</sub> = 20.4, 4.5 Hz), 108.64 (d, J<sub>P-C</sub> = 154.5 Hz), 103.81 (t, J<sub>C-F</sub> = 25.7 Hz), 36.44, 14.00, 11.51. <sup>31</sup>P NMR (CD<sub>2</sub>Cl<sub>2</sub>, 121.5 MHz, 298 K): δ = 41.9 ppm. IR (ATR, cm<sup>-1</sup>): 3382, 3056, 2976, 2928, 1601, 1577, 1500, 1482, 1436, 1422, 1406, 1381, 1364, 1295, 1275, 1211, 1178, 1160, 1113, 1073, 1050, 1009, 992, 915, 838, 795, 774, 757, 742, 731, 707, 692, 647, 622, 606, 587, 553, 538, 509, 489, 457. MS (ESI, pos.) *m/z*: found: 581.09 [M + H]<sup>+</sup>, calculated: 580.15.

**N,N'-(3',4',5'-Trifluoro-[1,1'-biphenyl]-2-yl)-P(1,3,5-trimethyl-1H-pyrazol-4-yl)phosphonothioic diamide (1f).** White solid. Yield: 4.41 g, 79.4%. <sup>1</sup>H NMR (CD<sub>3</sub>CN, 300 MHz, 298 K): 7.37–7.08 (m, 12H, Ph), 5.49, 5.47 (d, 2H, <sup>2</sup>J<sub>PH</sub> = 6.7 Hz, NH), 3.63 (s, 3H, 1-CH<sub>3</sub>), 2.32 (s, 3H, 3-CH<sub>3</sub>), 2.09 (s, 3H, 5-CH<sub>3</sub>). <sup>13</sup>C NMR (151 MHz, CD<sub>2</sub>Cl<sub>2</sub>, 298 K): 151.69 (ddd, J<sub>C-F</sub> = 252.2, 10.1, 4.1 Hz), 148.76 (d, J<sub>P-C</sub> = 13.5 Hz), 144.53 (d, J<sub>P-C</sub> = 25.5 Hz), 139.93 (dt, J<sub>C-F</sub> = 253.7, 16.6 Hz), 137.0, 134.78 (td, J<sub>C-F</sub> = 7.7, 5.9 Hz), 130.81, 129.93, 129.88, 129.54, 122.92, 119.46, 119.43, 114.21 (dd, J<sub>C-F</sub> = 16.6, 4.5 Hz), 108.63 (d, J<sub>P-C</sub> = 154.5 Hz), 36.48, 14.13, 11.59. <sup>31</sup>P NMR (CD<sub>3</sub>CN, 121.5 MHz, 298 K): δ = 44.2 ppm. IR (ATR, cm<sup>-1</sup>): 3387, 2950, 2923, 1606, 1590, 1580, 1515, 1497, 1476, 1451, 1408, 1381, 1363, 1296, 1272, 1199, 1175, 1113, 1098, 1083, 1048, 1016, 1006, 908, 835, 794, 762, 743, 692, 643, 609, 588, 541, 510, 495, 463, 426. MS (ESI, pos.) *m/z*: found: 617.06 [M + H]<sup>+</sup>, calculated: 616.13.

**N,N'-(4'-(benzyloxy)-[1,1'-biphenyl]-2-yl)-P(1,3,5-trimethyl-1H-pyrazol-4-yl)phosphonothioic diamide (1g).** White solid. Yield: 5.01 g, 77.2%. <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 300 MHz, 298 K): 7.47–6.98 (m, 26H, Ph), 5.45, 5.42 (d, 2H, <sup>2</sup>J<sub>PH</sub> = 8.9 Hz, NH), 5.11 (s, 4H, CH<sub>2</sub>), 3.64 (s, 3H, 1-CH<sub>3</sub>), 2.22 (s, 3H, 3-CH<sub>3</sub>), 2.00 (s, 3H, 5-CH<sub>3</sub>). <sup>13</sup>C NMR (151 MHz, CD<sub>2</sub>Cl<sub>2</sub>, 298 K): 159.00, 148.72 (d, J<sub>P-C</sub>

= 12.0 Hz), 144.01 (d,  $J_{\text{P-C}} = 25.5$  Hz), 137.56, 137.35, 131.90, 131.84, 130.96, 130.93, 128.97, 128.43, 128.28, 127.98, 122.05, 117.98, 117.95, 115.80, 109.12 (d,  $J_{\text{P-C}} = 154.5$  Hz), 70.46, 36.41, 13.89, 11.36.  $^{31}\text{P}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 121.5 MHz, 298 K):  $\delta = 41.3$  ppm. IR (ATR,  $\text{cm}^{-1}$ ): 3373, 3055, 3018, 2964, 2926, 1604, 1578, 1493, 1452, 1409, 1384, 1361, 1287, 1239, 1200, 1180, 1161, 1100, 1074, 1044, 1012, 992, 935, 918, 896, 858, 838, 760, 738, 725, 702, 691, 674, 644, 624, 615, 606, 585, 557, 503, 473, 463, 440. MS (ESI, pos.)  $m/z$ : found: 721.24  $[\text{M} + \text{H}]^+$ , calculated: 720.27. Anal. calcd for  $\text{C}_{44}\text{H}_{41}\text{N}_4\text{O}_2\text{PS}$  (720.87): C, 73.31; H, 5.73; N, 7.77; O, 4.44; S, 4.45%; found: C, 73.22; H, 5.95; N, 7.59; O, 4.30; S, 4.71%.

***N,N'*-(2-Benzylphenyl)-*P,P*-bis(1,3,5-trimethyl-1*H*-pyrazol-4-yl)phosphonothioic diamide (1h).** White solid. Yield: 3.72 g, 76.9%.  $^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 300 MHz, 298 K): 7.21–6.97 (m, 18H, Ph), 4.89, 4.86 (d, 2H,  $^2J_{\text{PH}} = 8.0$  Hz, NH), 3.86 (s, 4H,  $\text{CH}_2$ ), 3.65 (s, 3H, 1- $\text{CH}_3$ ), 2.10 (s, 3H, 3- $\text{CH}_3$ ), 1.84 (s, 3H, 5- $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (151 MHz,  $\text{CD}_2\text{Cl}_2$ , 298 K): 149.20 (d,  $J_{\text{P-C}} = 13.5$  Hz), 144.52 (d,  $J_{\text{P-C}} = 25.5$  Hz), 139.14, 138.79, 131.59, 129.72, 129.67, 129.29, 128.78, 127.78, 127.13, 122.46, 119.55, 109.07 (d,  $J_{\text{P-C}} = 153.0$  Hz), 38.92, 36.31, 13.75, 11.26.  $^{31}\text{P}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 121.5 MHz, 298 K):  $\delta = 41.3$  ppm. IR (ATR,  $\text{cm}^{-1}$ ): 3385, 3028, 2923, 1607, 1591, 1579, 1499, 1479, 1449, 1398, 1381, 1295, 1272, 1205, 1179, 1160, 1101, 1085, 1051, 1018, 1007, 935, 917, 865, 832, 801, 764, 693, 671, 651, 617, 596, 547, 489, 470, 448. MS (ESI, pos.)  $m/z$ : found: 537.18  $[\text{M} + \text{H}]^+$ , calculated: 536.22. Anal. calcd for  $\text{C}_{32}\text{H}_{33}\text{N}_4\text{PS}$  (536.68): C, 71.62; H, 6.20; N, 10.44; S, 5.97%; found: C, 71.47; H, 5.89; N, 10.55; S, 6.18%.

**Synthesis of compounds 2a–2h.** The corresponding primary amine (9.0 mmol) and  $\text{Et}_3\text{N}$  (0.911 g, 9.0 mmol) was dissolved in 100 mL dry toluene. Then, a toluene solution of **2** (2.963 g, 9.0 mmol, in 20 mL dry toluene) was added to the mixture and cooled to 0 °C. After addition, the mixture was slowly warmed to room temperature and was stirred overnight. The formed white solid  $\text{Et}_3\text{N} \cdot \text{HBr}$  was removed by filtration. Then,  $\text{S}_8$  (0.288 g, 9.0 mmol) was added to the mixture and it was stirred for another 6.0 h at 50 °C. After filtration, the filtrate was concentrated to approximately 20 mL. Then, 40 mL of petroleum ether was layered on top of the toluene solution. After one day, crystals of the target compound could be obtained at the border of the two layers.

***N*-[1,1'-Biphenyl]-2-yl)-*P,P*-bis(1,3,5-trimethyl-1*H*-pyrazol-4-yl)phosphonothioic amide (2a).** White solid. Yield: 1.90 g, 46.9%.  $^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 300 MHz, 298 K): 7.48–6.95 (m, 9H, Ph), 5.23, 5.20 (d, 1H,  $^2J_{\text{PH}} = 7.7$  Hz, NH), 3.67 (s, 6H, 1- $\text{CH}_3$ ), 2.26 (s, 6H, 3- $\text{CH}_3$ ), 1.94 (s, 6H, 5- $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (151 MHz,  $\text{CD}_2\text{Cl}_2$ , 298 K): 149.32 (d,  $J_{\text{P-C}} = 12.0$  Hz), 144.57 (d,  $J_{\text{P-C}} = 24.0$  Hz), 138.92, 137.92, 131.93, 131.88, 130.62, 129.83, 129.53, 128.31, 128.25, 121.30, 118.10, 118.06, 108.36 (d,  $J_{\text{P-C}} = 130.5$  Hz), 36.36, 14.00, 11.44.  $^{31}\text{P}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 121.5 MHz, 298 K):  $\delta = 29.6$  ppm. IR (ATR,  $\text{cm}^{-1}$ ): 3400, 3037, 2934, 1601, 1577, 1516, 1491, 1443, 1407, 1381, 1362, 1312, 1287, 1262, 1230, 1214, 1179, 1112, 1051, 1014, 992, 922, 895, 838, 774, 752, 704, 687, 677, 645, 639, 609, 595, 586, 548, 508, 482, 459, 412. MS (ESI, pos.)  $m/z$ : found: 450.16  $[\text{M} + \text{H}]^+$ , calculated: 449.18. Anal. calcd for  $\text{C}_{24}\text{H}_{28}\text{N}_5\text{PS}$  (449.56): C, 64.12; H, 6.28; N, 15.58; S, 7.13%; found: C, 63.88; H, 5.95; N, 15.85; S, 7.52%.

***N*-(4'-Chloro-[1,1'-biphenyl]-2-yl)-*P,P*-bis(1,3,5-trimethyl-1*H*-pyrazol-4-yl)phosphonothioic amide (2b).** White solid. Yield: 2.18 g, 50.1%.  $^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 300 MHz, 298 K): 7.42–6.98 (m, 8H, Ph), 5.09, 5.07 (d, 1H,  $^2J_{\text{PH}} = 6.6$  Hz, NH), 3.68 (s, 6H, 1- $\text{CH}_3$ ), 2.28 (s, 6H, 3- $\text{CH}_3$ ), 1.95 (s, 6H, 5- $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (151 MHz,  $\text{CD}_2\text{Cl}_2$ , 298 K): 149.30 (d,  $J_{\text{P-C}} = 12.0$  Hz), 144.62 (d,  $J_{\text{P-C}} = 24.0$  Hz), 137.92, 137.48, 134.26, 131.33, 130.69, 130.61, 130.56, 129.67, 128.58, 121.44, 118.41, 118.37, 108.25 (d,  $J_{\text{P-C}} = 129.0$  Hz), 36.41, 14.06, 11.52.  $^{31}\text{P}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 121.5 MHz, 298 K):  $\delta = 30.0$  ppm. IR (ATR,  $\text{cm}^{-1}$ ): 3402, 3087, 3062, 3041, 2979, 2958, 2917, 1621, 1590, 1494, 1465, 1442, 1424, 1406, 1380, 1362, 1338, 1290, 1278, 1231, 1189, 1164, 1118, 1066, 1040, 1003, 982, 920, 885, 865, 844, 837, 753, 692, 677, 650, 638, 619, 606, 586, 577, 548, 540, 506, 463. MS (ESI, pos.)  $m/z$ : found: 484.13  $[\text{M} + \text{H}]^+$ , calculated: 483.14. Anal. calcd for  $\text{C}_{24}\text{H}_{27}\text{ClN}_5\text{PS}$  (484.00): C, 59.56; H, 5.62; N, 14.47; S, 6.62%; found: C, 60.02; H, 5.86; N, 14.11; S, 6.98%.

***N*-(4'-Fluoro-[1,1'-biphenyl]-2-yl)-*P,P*-bis(1,3,5-trimethyl-1*H*-pyrazol-4-yl)phosphonothioic amide (2c).** White solid. Yield: 2.21 g, 52.5%.  $^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 300 MHz, 298 K): 7.35–6.95 (m, 8H, Ph), 5.09, 5.07 (d, 1H,  $^2J_{\text{PH}} = 5.3$  Hz, NH), 3.68 (s, 6H, 1- $\text{CH}_3$ ), 2.28 (s, 6H, 3- $\text{CH}_3$ ), 1.95 (s, 6H, 5- $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (151 MHz,  $\text{CD}_2\text{Cl}_2$ , 298 K): 162.85 (d,  $J_{\text{C-F}} = 247.6$  Hz), 149.28 (d,  $J_{\text{P-C}} = 12.0$  Hz), 144.61 (d,  $J_{\text{P-C}} = 24.0$  Hz), 138.04, 134.94, 131.69 (d,  $J_{\text{C-F}} = 7.6$  Hz), 130.80, 128.44, 121.36, 118.25 (d,  $J_{\text{C-F}} = 5.2$  Hz), 116.43 (d,  $J_{\text{C-F}} = 21.1$  Hz), 108.29 (d,  $J_{\text{P-C}} = 130.5$  Hz), 36.40, 14.04, 11.51.  $^{31}\text{P}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 121.5 MHz, 298 K):  $\delta = 29.9$  ppm. IR (ATR,  $\text{cm}^{-1}$ ): 3402, 3053, 3026, 2978, 2956, 2920, 1611, 1577, 1527, 1493, 1443, 1421, 1405, 1379, 1361, 1290, 1279, 1248, 1229, 1212, 1163, 1108, 1039, 992, 924, 884, 854, 837, 752, 691, 676, 647, 637, 606, 586, 549, 511, 496, 473. MS (ESI, pos.)  $m/z$ : found: 468.17  $[\text{M} + \text{H}]^+$ , calculated: 467.17.

***N*-(3',4'-Difluoro-[1,1'-biphenyl]-2-yl)-*P,P*-bis(1,3,5-trimethyl-1*H*-pyrazol-4-yl)phosphonothioic amide (2d).** White solid. Yield: 2.37 g, 54.2%.  $^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 300 MHz, 298 K): 7.38–6.96 (m, 7H, Ph), 5.03, 5.01 (d, 1H,  $^2J_{\text{PH}} = 5.9$  Hz, NH), 3.69 (s, 6H, 1- $\text{CH}_3$ ), 2.32 (s, 6H, 3- $\text{CH}_3$ ), 1.96 (s, 6H, 5- $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (151 MHz,  $\text{CD}_2\text{Cl}_2$ , 298 K): 151.45 (dd,  $J_{\text{C-F}} = 251.1$ , 12.1 Hz), 149.85 (dd,  $J_{\text{C-F}} = 249.7$ , 11.9 Hz), 149.26 (d,  $J_{\text{P-C}} = 12.0$  Hz), 144.67 (d,  $J_{\text{P-C}} = 24.0$  Hz), 137.94, 136.02 (dd,  $J_{\text{C-F}} = 5.9$ , 3.7 Hz), 130.72, 129.80, 129.75, 128.84, 126.30 (dd,  $J_{\text{C-F}} = 6.2$ , 3.4 Hz), 121.52, 119.45 (d,  $J_{\text{C-F}} = 16.6$  Hz), 118.68, 118.64, 118.41 (d,  $J_{\text{C-F}} = 18.1$  Hz), 108.2 (d,  $J_{\text{P-C}} = 129.0$  Hz), 36.41, 14.06, 11.56.  $^{31}\text{P}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 121.5 MHz, 298 K):  $\delta = 30.3$  ppm. IR (ATR,  $\text{cm}^{-1}$ ): 3395, 2928, 1598, 1575, 1510, 1492, 1443, 1422, 1402, 1381, 1360, 1294, 1275, 1224, 1158, 1111, 1093, 1050, 1006, 994, 914, 838, 817, 790, 759, 705, 686, 646, 610, 587, 559, 539, 509, 490, 472, 421. MS (ESI, pos.)  $m/z$ : found: 468.13  $[\text{M} + \text{H}]^+$ , calculated: 485.16.

***N*-(3',5'-Difluoro-[1,1'-biphenyl]-2-yl)-*P,P*-bis(1,3,5-trimethyl-1*H*-pyrazol-4-yl)phosphonothioic amide (2e).** White solid. Yield: 2.45 g, 53.9%.  $^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 300 MHz, 298 K): 7.39–6.82 (m, 7H, Ph), 5.05, 5.02 (d, 1H,  $^2J_{\text{PH}} = 7.3$  Hz, NH), 3.69 (s, 6H, 1- $\text{CH}_3$ ), 2.33 (s, 6H, 3- $\text{CH}_3$ ), 1.96 (s, 6H, 5- $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (151 MHz,  $\text{CD}_2\text{Cl}_2$ , 298 K): 163.68 (dd,  $J_{\text{C-F}} = 249.9$ , 12.1 Hz), 149.27 (d,  $J_{\text{P-C}} = 12.0$  Hz), 144.70 (d,  $J_{\text{P-C}} = 24.0$  Hz), 142.36 (t,  $J_{\text{C-F}} = 9.5$



Hz), 137.75, 130.40, 129.64, 129.59, 129.08, 121.60, 118.92, 118.88, 113.01 (dd,  $J_{C-F} = 20.1$ , 4.5 Hz), 108.21 (d,  $J_{P-C} = 129.0$  Hz), 103.70 (t,  $J_{C-F} = 24.2$  Hz), 36.39, 14.02, 11.56.  $^{31}\text{P}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 121.5 MHz, 298 K):  $\delta = 30.5$  ppm. IR (ATR,  $\text{cm}^{-1}$ ): 3400, 3037, 2934, 1600, 1577, 1516, 1491, 1443, 1408, 1380, 1362, 1312, 1286, 1262, 1230, 1213, 1179, 1111, 1050, 1014, 992, 923, 895, 837, 774, 752, 704, 689, 644, 609, 583, 548, 507, 482, 459, 419. MS (ESI, pos.)  $m/z$ : found: 486.12  $[\text{M} + \text{H}]^+$ , calculated: 485.16.

***N*-(3',4',5'-Trifluoro-[1,1'-biphenyl]-2-yl)-*P,P*-bis(1,3,5-trimethyl-1*H*-pyrazol-4-yl)phosphinothioic amide (2f).** White solid. Yield: 2.17 g, 47.8%.  $^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 300 MHz, 298 K): 7.39–6.95 (m, 6H, Ph), 4.94, 4.91 (d, 1H,  $^2J_{\text{PH}} = 7.2$  Hz, NH), 3.69 (s, 6H, 1- $\text{CH}_3$ ), 2.35 (s, 6H, 3- $\text{CH}_3$ ), 1.96 (s, 6H, 5- $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (151 MHz,  $\text{CD}_2\text{Cl}_2$ , 298 K): 151.79 (ddd,  $J_{C-F} = 249.2$ , 12.1, 4.7 Hz), 149.27 (d,  $J_{P-C} = 10.5$  Hz), 144.76 (d,  $J_{P-C} = 24.0$  Hz), 139.80 (dt,  $J_{P-C} = 252.2$ , 15.6 Hz), 137.82, 135.15 (td,  $J_{C-F} = 8.1$ , 6.1 Hz), 135.15, 130.59, 129.23, 128.94, 121.73, 119.18, 119.14, 114.33 (dd,  $J_{C-F} = 16.2$ , 4.5 Hz), 108.18 (d,  $J_{P-C} = 129.0$  Hz), 36.43, 14.06, 11.62.  $^{31}\text{P}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 121.5 MHz, 298 K):  $\delta = 30.7$  ppm. IR (ATR,  $\text{cm}^{-1}$ ): 3401, 3037, 2977, 2955, 1600, 1577, 1516, 1491, 1443, 1407, 1380, 1362, 1312, 1287, 1262, 1230, 1214, 1179, 1112, 1051, 1015, 992, 922, 895, 858, 774, 752, 705, 687, 677, 645, 638, 609, 595, 589, 548, 507, 482, 459, 438, 419. MS (ESI, pos.)  $m/z$ : found: 504.14  $[\text{M} + \text{H}]^+$ , calculated: 503.15.

***N*-(4'-(benzyloxy)-[1,1'-biphenyl]-2-yl)-*P,P*-bis(1,3,5-trimethyl-1*H*-pyrazol-4-yl)phosphinothioic amide (2g).** White solid. Yield: 2.51 g, 50.1%.  $^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 300 MHz, 298 K): 7.45–6.95 (m, 13H, Ph), 5.24, 5.22 (d, 1H,  $^2J_{\text{PH}} = 6.8$  Hz, NH), 5.09 (s, 2H,  $\text{CH}_2$ ), 3.67 (s, 6H, 1- $\text{CH}_3$ ), 2.28 (s, 6H, 3- $\text{CH}_3$ ), 1.95 (s, 6H, 5- $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (151 MHz,  $\text{CD}_2\text{Cl}_2$ , 298 K): 158.92, 149.32 (d,  $J_{P-C} = 12.0$  Hz), 144.57 (d,  $J_{P-C} = 24.0$  Hz), 138.15, 137.31, 131.51, 131.46, 131.24, 131.02, 130.84, 128.95, 128.42, 128.00, 127.95, 121.23, 117.99, 117.95, 115.76, 108.36 (d,  $J_{P-C} = 130.5$  Hz), 70.43, 36.38, 14.04, 11.49.  $^{31}\text{P}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 121.5 MHz, 298 K):  $\delta = 29.6$  ppm. IR (ATR,  $\text{cm}^{-1}$ ): 3402, 3053, 3027, 2978, 2956, 2934, 1611, 1577, 1527, 1493, 1443, 1421, 1405, 1380, 1361, 1291, 1279, 1248, 1230, 1213, 1163, 1108, 1040, 992, 924, 884, 854, 838, 752, 715, 691, 677, 648, 647, 606, 586, 549, 540, 511, 497, 473, 418. MS (ESI, pos.)  $m/z$ : found: 556.19  $[\text{M} + \text{H}]^+$ , calculated: 555.22. Anal. calcd for  $\text{C}_{31}\text{H}_{34}\text{N}_5\text{OPS}$  (555.68): C, 67.01; H, 6.17; N, 12.60; O, 2.88; S, 5.77%; found: C, 67.46; H, 6.32; N, 12.33; S, 6.59%.

***N*-(2-Benzylphenyl)-*P,P*-bis(1,3,5-trimethyl-1*H*-pyrazol-4-yl)phosphinothioic amide (2h).** White solid. Yield: 1.98 g, 47.3%.  $^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 300 MHz, 298 K): 7.29–6.91 (m, 9H, Ph), 4.78, 4.75 (d, 1H,  $^2J_{\text{PH}} = 7.3$  Hz, NH), 3.92 (s, 2H,  $\text{CH}_2$ ), 3.68 (s, 6H, 1- $\text{CH}_3$ ), 2.20 (s, 6H, 3- $\text{CH}_3$ ), 1.84 (s, 6H, 5- $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (151 MHz,  $\text{CD}_2\text{Cl}_2$ , 298 K): 149.43 (d,  $J_{P-C} = 10.5$  Hz), 144.59 (d,  $J_{P-C} = 24.0$  Hz), 139.40, 139.20, 131.62, 129.26, 128.77, 128.62, 128.57, 127.52, 127.17, 121.55, 119.14, 119.10, 108.46 (d,  $J_{P-C} = 129.0$  Hz), 39.09, 36.34, 13.90, 11.46.  $^{31}\text{P}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 121.5 MHz, 298 K):  $\delta = 29.1$  ppm. IR (ATR,  $\text{cm}^{-1}$ ): 3402, 3087, 3062, 3036, 2978, 2957, 2917, 1621, 1590, 1494, 1465, 1442, 1424, 1406, 1380, 1362, 1338, 1290, 1278, 1231, 1189, 1164, 1118, 1066, 1040, 1003, 982, 921, 885, 864, 844, 837, 752, 692, 677, 650, 638, 619, 606, 586, 548, 540, 506, 463. MS (ESI, pos.)  $m/z$ : found:

464.17  $[\text{M} + \text{H}]^+$ , calculated: 463.20. Anal. calcd for  $\text{C}_{25}\text{H}_{30}\text{N}_5\text{PS}$  (463.58): C, 64.77; H, 6.52; N, 15.11; S, 6.92%; found: C, 64.98; H, 6.89; N, 15.49; S, 7.32%.

**Nematicidal activity.** The nematicidal activities of the synthesized compounds were determined at the China Agricultural University following the published procedure.<sup>30,38</sup> Pure compounds **1a–2h** and bixafen were initially dissolved in 0.5 mL of DMSO, and were further diluted with distilled water to 1.0 L to obtain 80 mg L<sup>−1</sup> dilutions for bioassays. Thus, the final concentration of DMSO was less than 1% v/v. The nematodes *M. incognita* used in experiments were originally isolated from tomato plants. *M. incognita* eggs were extracted using the NaClO (0.5%, 3 min) procedure described by Hussey and Barker<sup>39</sup> and second-stage juveniles (J2) were hatched over 2–3 days in Baermann funnels at 26 °C. All J2s hatched in the first 3 days were discarded and a further 24 h was allowed to elapse before J2 nematodes were collected for use in these experiments. Bixafen at a concentration of 80 mg L<sup>−1</sup> served as a positive control. The negative control was carried out by following the same experimental procedure in the absence of the tested compounds. Solutions of test compounds (0.5 mL) and approximately 50 *M. incognita* J2s in 0.5 mL of water were mixed and plated in 24-well plates. The plates were then wrapped in parafilm and stored in the dark at 26 °C for 24 h. The nematodes were considered immotile if they did not respond to being touched by a small probe under an inverted microscope. Moreover, the percentage of immotile nematodes was calculated for each compound and the results are listed in Table 2.

## Conclusions

A series of thiophosphinyl amide and thiophosphonyl diamide compounds were synthesized and purified by facile purification methods and characterized by standard spectroscopic/analytic techniques. Our preliminary nematicidal activity investigation shows that some compounds manifested higher nematicidal activity than the lead compound bixafen. Hence, the modification of SDHI by the incorporation of an organothiophosphorus group could be a successful approach for the synthesis of nematicidal compounds with improved activities.

## Conflicts of interest

The authors have no conflicts to declare.

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