An approach to biologically important chromenes bearing P-S-heterocycles. Based on the chemistry of Lawesson’s reagent

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Abstract
A series of chromenes bearing P-S-heterocycles, were prepared in reasonable yields from the reaction of 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide (Lawesson’s reagent, LR, 1) with a variety of substituted chromones. The antibacterial and/or antifungal activities for some of the new products obtained were evaluated.

Keywords: Lawesson’s Reagent, substituted chromones, P-S-heterocycles, thiation, antibacterial activity, antifungal activity

Introduction
The activity of 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide (Lawesson’s reagent, LR, 1) as a thiating agent, has been studied in diverse classes of carbonyl compounds.1-3 At elevated temperatures, LR exists in equilibrium with the monomeric species 1A4 (Figure 1), which allows it to undergo [2 + 4] cycloaddition with acyclic α-β-unsaturated ketones1,2,5 to give various heterocyclic compounds. Additionally, the ability of LR to produce 5- and 6-membered P-S-heterocycles from bifunctional systems has been previously discussed in the literature.6-8 Furthermore, the utility of LR for producing 4-membered P-S-heterocycles was previously reported by us.9 In continuation of this work, the present study has focused on the synthesis of bioactive P-S-heterocyclic systems. The methodology centered on the application of Lawesson’s reagent with some chromone derivatives 2, 7, 11, and 15. The structure-activity relationships of some of the isolated products are also briefly discussed.
Results and Discussion

3-Formylchromone (2) was allowed to react with LR in boiling toluene to give a mixture of two products that could be separated by column chromatography. The first (20%) is formulated as 4-thioxo-4-chromene-3-carbothialdehyde (3) based upon analytical and spectroscopic arguments. The second product (60%), is formulated as 2-(4-methoxyphenyl)-5H-10aH-[1,3,2]oxathiaphosphinino[4,5-b]chromene-5-thione-2-sulfide (6) (Scheme 1).
The constitutions of the isolated products 3 and 6 were in accord with elemental analyses and spectroscopic properties. The structure of the oxathiaphosphinino chromene 6 was based on the following data: its $^{31}$P-NMR signal (in CDCl$_3$, vs. 85% H$_3$PO$_4$) was at $\delta$ 93.39 which matches a cyclic structure.$^{10,11}$ The IR spectrum of 6 revealed the absence of an absorption band around 1640 cm$^{-1}$ corresponding to (C=O), instead, absorption bands at 1220 (C=S), 1580, 1600 (C=C, aromatic) cm$^{-1}$ were present. Moreover, an absorption band at 650 cm$^{-1}$ corresponding to (P=S) was present in the spectrum of 6. The $^1$H NMR spectrum of 6 (in CDCl$_3$, $\delta$ ppm) revealed the presence of signals at 3.85 (s, 3H, OCH$_3$), 7.4 (d, $^3J_{HP} = 11.3$, 1H, P-S-CH). The AB system due to the four aromatic protons of the substituent aromatic ring appeared as two sets of doublet of doublets at 6.95 and 7.56 each with $J_{HH} = 9$ Hz, $^3J_{HP} = 11$ Hz, whereas the aromatic protons of the chromene ring appeared at 7.95, 8.7 (2d, 2H, $J_{HH} = 7$ Hz), 6.8, 7.1 (2t, 2H, $=$CH-CH=), 8.8 (d, $^3J_{HP} = 10.5$, 1H, P-O-CH=C). The $^{13}$C NMR showed signals at 55.30 (OCH$_3$), 84.71 (d, $^2J_{CP} = 40.1$, O-CH-S), 112.05 (S=C-C=C), 112.88, 119.06, 124.19, 125.66, 129.53, 132.51, 134.51, 134.55, 150.66, 151.11, 152.33, 158.80 (C=C, aromatic), 150.57 (d, $^2J_{CP} = 38.9$, C=C-O-P=S), 216.77 (C=S).

The formation of compound 6 can be interpreted in terms of nucleophilic attack by the S-anion of the monomeric species 1A on the initially formed chromone thionine intermediate 4 to give the transient dipolar structure 5, followed by ring closure.

The reactions of 3-(aryliminomethyl)chromones 7a-d with LR were also studied. The isolated products are formulated as 3-{(E)-[4-aryliminomethyl]}-4H-chromene-4-thione (8a-d) and 3-[3-aryl-2-(4-methoxyphenyl)-2-sulfido-1,3,2-thiazaphosphetidin-4-yl]-4H-chromene-4-thione (10a-d) (Scheme 2).
The structure elucidation of $8a-d$ and $10a-d$ was based on their elemental analyses, molecular weight determinations (MS) and their spectroscopic data. For instance, the IR spectrum (in KBr, cm$^{-1}$) of 3-[3-(4-methoxyphenyl)-2-(4-methoxyphenyl)-2-sulfido-1,3,2-thiazaphosphetidin-4-yl]-4H-chromene-4-thione ($10b$) showed the presence of absorption bands at 645 cm$^{-1}$ corresponding to (P=S), 1200 cm$^{-1}$ (C=S) instead of a lactone-carbonyl frequency at 1650 cm$^{-1}$. The $^1$H NMR spectrum of $10b$ (CDCl$_3$, $\delta$ ppm) revealed the presence of a signal at 5.34 (d, 1H, $^3J_{HP} = 12$Hz, S-C$_2$H-N), also two singlets due to the two (OC$_3$H$_3$) groups at 3.50 and 3.82 ppm. The aromatic protons (13H) appeared as a multiplet at $\delta_H = 6.45$-8.32 ppm. The $^{13}$C NMR (CDCl$_3$, $\delta$ ppm) spectrum of $10b$ had signals at $\delta$ 54.59, 55.21 (2 $\times$ OCH$_3$), 67.57 (d, $^2J_{CP}$ = 42, P-S-CH), 115.35, 117.17, 118.33, 119.45, 122.56, 124.92, 129.84, 132.55, 134.64, 135.22, 139.99, 149.85, 153.40, 155.55, 158.34, 160.95 (aromatic carbon atoms), 205.67(C=S).

According to Scheme 2, the formation of $10a-d$ is believed to occur via nucleophilic attack of the monomeric species $1A$ on compound $8$ to give intermediate $9$, followed by ring closure to afford the thiazaphosphetidin chromene $10$.

In the same sense, [(4-oxo-4H-chromen-3-yl)methylene]malononitrile $11$ reacted with LR to give a mixture of two products which could be separated by column chromatography. The first product (65%) is formulated as (2E)-2-cyano-3-(4-thioxo-4-chromen-3-yl)prop-2-ene thioamide ($12$) based upon analytical and spectroscopic data, the second product (18%) is formulated as...
2-(4-methoxyphenyl)-4-(4-thioxo-4H-chromen-3-yl)-1,2-thiaphosphetane-3,3-dicarbonitrile-2-sulfide (14) (Scheme 3).

Scheme 3

The IR spectrum (in KBr, cm\(^{-1}\)) of compound 14 showed a strong absorption band at 2275 cm\(^{-1}\) corresponding to (2 CN) groups and 1180 cm\(^{-1}\) (C=S). Its \(^1\)H NMR revealed presence of a signal at 6.39 ppm (d, \(^3\)J\(_{HP}\) =12Hz 1H, P-S-CH), a singlet at 3.75 ppm corresponding to the OCH\(_3\) protons.

Formation of the thioamide derivative 12 can be attributed to a partial hydrolysis\(^9,12\) of 11 to yield the respective α-cyano-β-substituted acrylamide intermediate which underwent ketone-to-thioketone conversion under the thiating effect\(^1-3\) of LR to afford the thioamide chromene derivative 12.

The proposed mechanism for formation 14 involves initial nucleophilic attack by 1A on 11 to give the transient intermediate 13. This process is followed by ring closure\(^13\) to give the thiaphosphetane chromene derivative 14.

Next, the reaction of ethyl (2E)-2-cyano-3-(4-oxo-4H-chromen-3-yl)acrylate 15 with Lawesson’s reagent was carried out in boiling toluene, giving (5Z)-2-(4-methoxyphenyl)-5-[(4-...
thioxo-4\textit{H}-chromen-3-yl)methylene]-1,3,2-thiazaphosphinane-4,6-dithione-2-sulfide (17) as a sole product (69% yield) (Scheme 4).

\[
\begin{align*}
\text{Ar} &= \text{C}_6\text{H}_4\text{-OCH}_3\text{-p} \\
\text{LR, 1} \quad &\xrightarrow{\text{LR, 1}} \\
15 &\quad \text{1A} \\
\quad &\quad \text{-EtOH} \\
16 &\quad 17 (69\%)
\end{align*}
\]

Scheme 4

The structure of 17 was confirmed by analytical and spectral data which showed the disappearance of both the cyano and carboxylate groups. The \textsuperscript{1}H NMR spectrum of 17 showed a singlet at 3.82 due to methoxy protons, also a singlet at 6.8 due to exocyclic ethylenic protons and a broad band at 10.94 due to the NH proton.

It is noteworthy that, in this reaction, the expected 1,2-thiaphosphetane derivative 18 was not formed. Instead, the thiazaphosphinane chromene 17 (69% yield) was isolated in a pure form. It is believed to be formed via the thioamideacrylate intermediate 16 with concomitant elimination of an alcoholic moiety. Such cyclization reactions involving Lawesson’s reagent leading to various phospha-heterocycles were previously discussed.\textsuperscript{14-16}

Note: in all the above-mentioned reactions a colorless crystalline phosphorus-containing product was isolated (or detected by TLC) and proved to be trimer 19 by comparing its m.p. as well as IR and \textsuperscript{1}H NMR spectra with those of an authentic specimen.\textsuperscript{17-19} Formation of 19 is frequently observed during thiation processes using LR.
Pharmacological evaluation
The synthesized products 6, 8b,d, 10b, 12, 14, 17 were screened against various types of fungi including *P. brevicompactum*, *As. niger* and *As. fumigatus* by adopting a food poisoning technique. Compounds 8b,d and 12 are moderately active against *P. brevicompactum* and *As. fumigatus* at 400 mg/mL concentration level, while compounds 6, 10b, 14, and 17 are more active against the same fungi at the same dose level.

Compounds 6 and 14 registered 100% spore germination inhibition in *As. niger* at 500 mg/mL whereas, compound 12 was found to have feeble activity.

The prepared products were also tested against one or the other type of bacteria including *B. subtilis*, *B. cereus* and *E. coli*. Compounds 8b,d and 12 exhibited reasonable activities whereas, the phosphorylated derivatives 6, 10b, 14 and 17 showed the highest inhibitory effect against all the tested organisms, possibly attributable to the presence of the phosphorus moiety.

On the basis of our results, compounds 6, 10b, 14 and 17 would be good candidates, lead molecules to be modified in order to improve the anti-microbial activity.

Conclusions
In summary, the present investigations describe an efficient and simple approach to the synthesis of a variety of biologically active 4- and 6-membered P-S-heterocycles in satisfactory yields, with the use of easily available starting materials.

Experimental Section

**General Procedures.** All melting points are uncorrected. IR spectra were recorded on a Perkin–Elmer spectrophotometer model 297 using KBr disc. The $^1$H and $^{13}$C NMR spectra were recorded on a JNM-GX-400 Fa Joel spectrometer, using TMS as an internal reference. $^{31}$P-NMR spectra were taken with a Varian CFT-20 (vs. external 85% H$_3$PO$_4$). The mass spectra were performed at 70 eV on an MS-50 Kratos (A.E.I.) spectrometer provided with a data system. Elemental analyses were carried out at the Microanalysis Laboratory, Cairo University, Cairo, Egypt. The appropriate precautions in handling moisture-sensitive compounds were observed.
Starting material 2 and LR, 1 were commercially available (From Aldrich Co.). Monoanils 7a,b were prepared as described by Fitton et al. The preparation of the new starting chromone derivatives 7c,d, 11 and 15 is described below (I, II, III).

**Preparation of 3-[(Z)-[4-aminophenyl]imino]methyl]-4H-chromene-4-one (7c) and 3-[(Z)-[2-aminophenyl]imino]methyl]-4H-chromene-4-one (7d). General procedure**

A solution of equimolar quantities of 3-formylchromone (2) (10 g, 0.057 mol) and 4-aminophenylamine (in case of 7c), or 2-aminophenyl amine (in case of 7d) and one crystal of p-toluenesulfonic acid in dry benzene (100 mL) was heated under reflux (Dean-Stark water trap) for 30 min. The solvent was evaporated off and the products were purified by crystallisation from ether to obtain 7c (m.p. 189-190 °C) or 7d (m.p. 170-172 °C) as red crystals (yield ≈ 85%). Elemental analyses and spectral data for compounds 7c, 7d were in agreement with the proposed structure. Elemental analyses for compound 7d: found C, 72.69; H, 4.50; N, 10.61% C\textsubscript{16}H\textsubscript{12}N\textsubscript{2}O\textsubscript{2} (264.28) requires C, 72.72; H, 4.58; N, 10.60%; IR (ν): 1610 (CH=N), 1530, 1600 (CH=CH), 3300 (NH\textsubscript{2}); \textsuperscript{1}H NMR (CDCl\textsubscript{3}) gave signals at: δ 5.75 (br.) Due to NH\textsubscript{2}, multiplet at 6.56-8.26 corresponding to the aromatic protons and a singlet (1H) at 7.68 due to the exocyclic ethylenic proton; m/z (EI): 264 [M\textsuperscript{+}] (26).

**Preparation of [(4-oxo-4H-chromen-3-yl)methylene]malononitrile (11).** A solution of 2 (10 g, 0.057 mol), malononitrile (0.1 mol), ammonium acetate (20 g) and glacial acetic acid (50 mL) in 200 mL of toluene was refluxed for 10 h with the aid of a Dean-Stark trap until the amount of water collected in the trap remained constant. The solid formed was collected then recrystallized from cyclohexane to give 11 as yellow crystals (yield 79%), m.p 186-187 °C. Elemental analyses found: C, 70.31; H, 2.68; N, 12.45% C\textsubscript{13}H\textsubscript{6}N\textsubscript{2}O\textsubscript{2} (222.207) requires: C, 70.27; H, 2.73; N, 12.61%; ν\textsubscript{max} (KBr)/ cm\textsuperscript{-1}: 1650 (C=O), 1600 (C=C), 2210 (C≡N); δ\textsubscript{H} (ppm) showed a multiplet at 7.53-8.28 due to the aromatic protons wherein gave a singlet (1H) at 7.20 due to the exocyclic ethylenic proton; m/z (EI): 222 [M\textsuperscript{+}] (28).

**Preparation of ethyl (2E)-2-cyano-3-(4-oxo-4H-chromen-3-yl)acrylate (15).** A solution of 2 (10 g, 0.057 mol), ethyl cyanoacetate (0.1 mol), ammonium acetate (20 g) and glacial acetic acid (50 mL) in 200 mL of toluene was refluxed for 18 h with the aid of a Dean-Stark trap. The solid formed was collected then recrystallized from ethanol to give compound 15 as pale yellow crystals (yield 85%), m.p 240-241 °C. Elemental analyses found: C, 66.81; H, 4.35; N, 5.41% C\textsubscript{15}H\textsubscript{11}NO\textsubscript{4} (269.26) requires: C, 66.91; H, 4.12; N, 5.20%; ν\textsubscript{max}(KBr)/ cm\textsuperscript{-1}: 1730 (C=O, acetate), 1560 (C=C, aromatic), 2200 (C=N); δ\textsubscript{H} (ppm) showed a multiplet at 7.61-8.32 due to the aromatic protons and a singlet (1H) at 7.64 due to the exocyclic ethylenic proton, 1.24 [t, 3H, (-C-CH\textsubscript{3})], 4.2 [q, 2H, (O-CH\textsubscript{2})]; m/z (EI): 269 [M\textsuperscript{+}] (22).

**Reaction of 2 with Lawesson’s reagent 1. Preparation of compounds 3 and 6. General procedure**

To a stirred solution (2 g, 11.4 mmol) of 2 in dry toluene (25 mL), Lawesson’s reagent 1 (1.4 g, 5.9 mmol) was added. The reaction mixture was refluxed with stirring for 4 h. The reaction
mixture was evaporated under reduced pressure. The resulting residue was chromatographed on silica gel using increasing amounts of -hexane/AcOEt as eluents to give compounds 3 and 6.

4-Thi oxo-4H-chromene-3-carbothialdehyde (3) was obtained (9:1 v/v) as pale yellow crystals (20% yield), m.p. 130-132 °C (from cyclohexane). Found: C, 58.43; H, 3.0; S, 31.35; Cl, 11.72; N, 4.60; S, 10.62% C = 11 Hz, δ_H (ppm): 7.3, 8.74 (2d, J_HH = 7.5 Hz, 2H, CH-ph ), 7.28, 7.34 (2t, 2H, CH-ph ), 9.67 ( s, 1H, CH-O ), 10.6 ( s, 1H, H=CH=S); δ_C (ppm) 196.21 (C=S ring), 186.45 (H=C=S), 119.88, 125.66, 129.53, 133.25, 134.55, 152.33, 162.40 (aromatic carbon atoms); m/z, (EI): 206 [M⁺](22).

2-(4-Methoxyphenyl)-5H,10aH-[1,3,2]oxathiaphosphinino[4,5-b]chromene-5-thione-2-sulfide (6) was obtained (8:2 v/v) as yellow crystals (60% yield), m.p. 180-182 °C (from ether). Found: C, 52.34; H, 3.11; P, 8.0; S, 24.73% C_{17}H_{13}O_2PS_3 (392.47) requires C, 52.03; H, 3.34; P, 7.89; S, 24.51% ; ν_{max}(KBr)/ cm⁻¹ 1220 (C=S), 1600 (C=C, aromatic ring); δ_H (ppm): 3.85 (s, 3H, OCH_3), 7.4 (d, J_HH = 11.3, 1H, P-S-CH), 6.95 and 7.56 (2dd, 4H, J_HH = 9 Hz, J_HH = 11 Hz, H=Ar), 7.95, 8.7 (2d, 2H, J_HH = 7 Hz, H=Ph), 6.8, 7.1 (2t, 2H, =CH=CH=), 8.8 (d, J_HH = 10.5, 1H, P-O-CH=C); δ_C (ppm): δ 55.30 (OCH_3), 84.71 (d, J_CP = 40.1, O-CH-S), 112.05 (S=C=C), 112.88, 119.06, 124.22, 125.66, 129.53, 132.51, 134.51, 134.55, 150.66, 151.11, 152.33, 158.80 (C=C, aromatic), 150.57 (d, J_CP = 38.9, C=C-O-P=S), 216.77 (C=S); δ_P (CDCl₃): 93.39 ppm; m/z (EI): 392 [M⁺](26).

Reaction of 3-(aryliminomethyl)chromones 7a-d with 1. Preparation of compounds 8a-d and 10a-d. To a stirred solution (11.4 mmol) of 3-(aryliminomethyl) chromones 7a-d in dry toluene (25 mL), Lawesson’s reagent 1 (1.4 g, 5.9 mmol) was added. The reaction mixture was refluxed for 6-8 h until the reaction was finished (TLC). Working up the product mixture as described in the general procedure and column chromatography furnished compounds 8a-d and 10a-d.

3-[E]-[4-Chlorophenyl]limino[methyl]-4H-chromene-4-thione (8a) was obtained (8:2 v/v) as pale yellow crystals (15% yield), m.p 136-138 °C (from cyclohexane). Found: C, 64.50; H, 3.12; Cl, 11.72; N, 4.60; S, 10.62% C_{16}H_{11}ClNO (299.78) requires C, 64.11; H, 3.36; Cl, 11.83; N, 4.67; S, 10.70%; v_{max}(KBr)/ cm⁻¹:1610 (CH=N), (CH=CH) 1570, 1600; δ_H (ppm): δ 7.28 (S, H, CH=N), 6.48, 7.21 (2d, 4H, J_HH = 8.8 Hz, H=CH=Ph ), 7.51, 8.66 (2d, 2H, J_HH =7.3 Hz, CH=ph ), 7.24, 7.48 (2t, 2H, =CH=CH=), 8.87 (s, 1H, =CH-O); δ_C (ppm): 119.55, 121.80, 122.16, 124.04, 125.22, 132.1, 128.38, 135.33, 142.35, 148.05, 151.18, 151.93, 166.20 (aromatic carbon atoms), 199.69 (C=S ring); m/z (EI): 299 [M⁺](16).

3-[E]-[4-Methoxyphenyl]limino[methyl]-4H-chromene-4-thione (8b) was obtained (8:2 v/v) as pale yellow crystals (18%, yield), m.p. 134-136 °C (from n-hexane). Found: C, 69.43; H, 4.12; N, 5.00; S, 10.92% C_{16}H_{11}NO_2S (295.37) requires C, 69.13; H, 4.44; N, 4.74; S, 10.86%; v_{max}(KBr)/ cm⁻¹ (CH=N), 1615, (CH=CH) 1540, 1600; δ_H (ppm): 3.77 (s, 3H, -OCH₃), 7.28(s, 1H, CH=N), 6.53, 7.19 ( 2d, 4H, J_HH = 8.6 Hz, H-Ph=OCH₃), 7.5, 8.67 (2d, 2H, J_HH = 7.5 Hz , CH=ph), 7.23, 7.31 (2t, 2H, =CH=CH=), 8.87 (s, 1H, =CH-O); δ_C (ppm): 114.49, 119.23, 122.75,
125.23, 128.99, 132.33, 135.45, 142.22, 148.05, 151.42, 155.82, 156.12, 166.20 (aromatic carbon atoms), 199.69 (C=S, ring): m/z (EI): 295 [M^+]+ (22).

3-[(E)-[(4-Aminophenyl)imino]methyl]-4H-chromene-4-thione (8c) was obtained (8:2 v/v) as pale yellow crystals (20% yield), m.p. 138-140 °C (from cyclohexane). Found: C, 68.64; H, 4.59; N, 9.82; S, 11.29% C_{16}H_{12}N_{2}OS (280.35) requires C, 68.55 H, 4.31; N, 9.99; S, 11.44%; v_{max}(KBr)/cm^{-1}: 1620 (CH=N), 1570, 1600 (CH=CH), 3350, 3400 (NH_{2}); δ_{H}(ppm): 5.85 (s, 2H, NH_{2}), 7.43 (s, H, CH=N), 6.42, 7.44 (2d, 4H, J_{HH} = 8.6 Hz, H-Ph-NH_{2}), 7.55, 8.69 (2d, 2H, J_{HH} = 7.5 Hz, CH-ph), 7.25, 7.47 (2t, 2H, =CH-CH=), 8.75 (s, 1H, CH-O); δ_{C}(ppm): 108.55, 110.55, 119.07, 122.35, 125.27, 128.68, 135.33, 132.20, 134.50, 132.11, 148.05, 151.18, 166.20 (aromatic carbon atoms), 199.42 (C=S, ring); m/z (EI): 280 [M^+]+ (19).

3-[(E)-[(2-Aminophenyl)imino]methyl]-4H-chromene-4-thione (8d) was obtained (8:2 v/v) as yellow crystals (18% yield), m.p 142-144 °C (from cyclohexane). Found: C, 68.31; H, 4.59; N, 9.82; S, 11.64% C_{16}H_{12}N_{2}OS (280.35) requires C, 68.55 H, 4.31; N, 9.99; S, 11.44%; v_{max}(KBr)/cm^{-1}: 1615 (CH=N), 1540, 1600 (CH=CH), 3320, 3400 (NH_{2}); δ_{H}(ppm): 3.71 (s, 2H, NH_{2}), 7.28 (s, H, CH=N), 6.26, 6.31 (2t, 2H, H-ph-NH_{2}), 6.45, 6.92 (2d, 2H, J_{HH} = 7.2 Hz, H-Ph-NH_{2}), 7.23, 7.41 (2t, 2H, =CH-CH=), 7.47, 8.21 (2d, 2H, J_{HH} = 6.4 Hz, CH-ph), 8.87 (s, 1H, =CH-O); δ_{C}(ppm): 119.07, 120.64, 122.20, 123.06, 125.27, 131.30, 135.34, 140.79, 142.15, 149.49, 151.20, 151.85, 166.20 (aromatic carbon atoms), 198.65 (C=S ring); m/z (EI): 280 [M^+]+ (16).

3-[(3-(4-Chlorophenyl)-2-(4-methoxyphenyl)-2-sulfido-1,3,2-thiazaphosphetidin-4-yl]-4H-chromene-4-thione (10a) was obtained (6:4 v/v) as yellow crystals (45% yield) m.p 155-157 °C (from ether). Found: C, 55.24; H, 3.63; Cl, 6.99; N, 2.58; P, 6.43; S, 19.24% C_{23}H_{20}ClN_{2}O_{2}PS_{3}(502.03) requires C, 55.03; H, 3.41; Cl, 7.06; N, 2.79; P, 6.17; S, 19.16%; v_{max}(KBr)/cm^{-1}: 1190 (C=S), 1530-1600 (CH=CH), 653 (P=S): δ_{H}(ppm): 3.74 (s, 3H, OCH_{3}), 5.89 (d, 1H, J_{HH} = 12 Hz, S-CH-N); 6.99-8.75 (m, 13H, aromatics); δ_{C}(ppm): 50.05 (O-CH_{3}), 67.19 (d, J_{CP} = 43, P-S-C-N), 113.53, 118.38, 119.66, 120.53, 123.87, 130.50, 131.89, 138.55, 139.22, 134.64, 136.02, 140.99, 141.52, 149.85, 153.40, 160.95 (aromatic carbon atoms), 205.68 (C=S, ring); δP(CDC_{3}): 48.43 ppm; m/z (EI): 502 [M^+]+ (26).

3-[(3-(4-Methoxyphenyl)-2-(4-methoxyphenyl)-2-sulfido-1,3,2-thiazaphosphetidin-4-yl]-4H-chromene-4-thione (10b) was obtained (1:1 v/v) as yellow crystals (50% yield) m.p 158-160 °C (from acetone / ether). Found: C, 57.66; H, 4.34; N, 3.01; P, 6.49; S, 19.55% C_{24}H_{20}NO_{2}PS_{3}(497.61) requires C, 57.93; H, 4.05; N, 2.82; P, 6.23; S, 19.33%; v_{max}(KBr)/cm^{-1}: 1570, 1600 (CH=CH), 1200 (C=S), 645 (P=S); δ_{H}(ppm): 3.50 (s, 3H, N-Ph-OCH_{3}), 3.82 (s, 3H, P-Ph-OCH_{3}), 5.34 (d, 1H, J_{HH} = 12Hz, S-CH-N), 6.45-8.32 (m, 13H, aromatics); δ_{C}(ppm): 54.59 (P-Ph-OCH_{3}), 55.21 (N-Ph-OCH_{3}), 67.57 [d, J_{CP} = 42, (PS-CH-N)], 113.56, 115.35, 119.45, 122.56, 124.92, 129.84, 130.12, 132.55, 134.64, 135.92, 139.99, 141.35, 144.81, 149.85, 153.40, 155.55, 158.34 (aromatic carbon atoms), 205.67 (C=S, ring); δP(CDC_{3}) at 48.92 ppm; m/z (EI): 497 [M^+]+ (18).

3-[(4-Aminophenyl)-2-(4-methoxyphenyl)-2-sulfido-1,3,2-thiazaphosphetidin-4-yl]-4H-chromene-4-thione (10c) was obtained (1:1 v/v) as yellow crystals (59% yield) m.p 165-166°C
(from acetone / ether). Found: C, 56.99; H, 3.79; N, 5.53; P, 6.26; S, 19.81% C_{23}H_{19}N_2O_2PS_3 (482.58) requires C, 57.24; H, 3.97; N, 5.8; P, 6.42; S, 19.93%; \nu_{\text{max}}(\text{KBr})/ \text{cm}^{-1}: 1560, 1600 (CH=CH, aromatic), 3200 (NH_2), 1190 (C=S), 650 (P=S); \delta_H (ppm): 3.82 (s, 3H, OCH_3), 5.99 (s, 2H, -NH_2), 6.03 (d, 1H, S-CH-N), \^J_{HH} = 12Hz, 6.5-8.32 (m, 13H, aromatics); \delta_C (ppm): 54.83 (Ph-OCH_3), 67.19 (d, \^J_{CP} = 40, PS-CH-N), 115.89, 117.68, 118.33,120.23, 124.82,122.88, 128.53, 129.64, 130.15, 132.11, 134.22, 140.03, 141.17, 149.58, 153.40, 158.34 (aromatic carbon atoms), 205.83 (C=S, ring); \delta_P (CDCl_3): 47.29 ppm; m/z (EI): 482[M^+] (16).

3-[3-(2-Aminophenyl)-2-(4-methoxyphenyl)-2-sulfido-1,3,2-thiazaphosphotidin-4-yl]-4H-chromene-4-thione (10d) was obtained (6:4 v/v) as yellow crystals (50% yield) m.p 159-160 °C (from acetone). Found: C, 57.59; H, 4.05; N, 5.48; P, 6.58; S, 19.80% C_{23}H_{19}N_2O_2PS_3(482.58) requires C, 57.24; H, 3.97; N, 5.8; P, 6.42; S, 19.93%; IR \nu_{\text{max}}(\text{KBr})/ \text{cm}^{-1}: 1560, 1600 (CH=CH, aromatic), 3300 (NH_2), 1180 (C=S), 640 (P=S); \delta_H (ppm): 3.82 (s, 3H, OCH_3), 4.16 (s, 2H, -NH_2), 6.51 (d, 1H, \^J_{HH} = 12Hz, S-CH-N), 6.81-8.32 (m, 13H, aromatics); \delta_C (ppm): 54.69 (Ph-OCH_3), 67.34 (d, \^J_{CP} = 43, PS-CH-N), 105.09, 115.78, 116.99, 118.20, 120.23, 122.65, 124.12, 125.91, 129.85, 134.55, 136.11, 139.11, 144.08, 147.16, 149.59, 158.34 (aromatic carbon atoms), 204.89 (C=S, ring); \delta_P (CDCl_3): 48.11 ppm; m/z (EI): 482 [M^+] (22).

Reaction of 11 with Lawesson’s reagent 1. Preparation of compounds 12 and 14

To a stirred solution (11.4 mmol) of [(4-oxo-4H-chromen-3-yl) methylene] malononitrile 10 in dry toluene (25 mL), Lawesson’s reagent 1 (1.4 g, 5.9 mmol) was added. The reaction mixture was refluxed for 8 h until the reaction was completed (TLC). Working up the product mixture as described in the general procedure and column chromatography furnished compounds 12 and 14. (2E)-2-Cyano-3-(4-thioxo-4H-chromen-3-yl)prop-2-enethioamide (12) was obtained (8:2 v/v) as colorless crystals (65% yield) m.p 152-154 °C (from cyclohexane). Found: C, 57.11, H, 2.87, N, 10.59, S, 23.22% C_{13}H_{12}N_2O_2S (272.36) requires C, 57.33, H, 2.96, N, 10.29, S, 23.55%; \nu_{\text{max}}(\text{KBr})/ \text{cm}^{-1}: 3420, 3390 (NH_2), 2200 (C=N), 1640 (C=C, ethylenic), 1230 (C=S), 1190 (C=S, ring), 1580 (C=C, aromatic); \delta_H (ppm): 6.76 (s, 1H, S=C=CH-N), 7.46, 8.85 (2d, 2H, J_{HH} = 7.5 Hz, CH-ph), 7.36, 7.39 (2t, 2H, CH-ph), 9.20 (s, 1H, CH-O), (s, 2H, NH_2, exchangeable with D_2O); \delta_C (ppm): 85.33 , 112.73, 118.55, 122.96, 124.75, 130.86, 140.34, 153.77, 161.86 (aromatic and exocyclic carbon atoms), 112.89 (C=N), 196.45 (C=S, thioamide), 201.26 (C=S, ring); m/z (EI): 272 [M^+] (35).

2-(4-Methoxyphenyl)-4-(4-thioxo-4H-chromen-3-yl)-1,2-thiaphosphetane-3,3-dicarbonitrile-2-sulfide (14) was obtained (1:1 v/v) as pale yellow crystals (18% yield) m.p 165-163 °C (from acetone / ether). Found: C, 54.68; H, 3.04; N, 6.56; P, 7.33; S, 21.69% C_{20}H_{13}N_2O_2PS_3 (440.52) requires C, 54.53; H, 2.97; N, 6.36; P, 7.03; S, 21.84%; \nu_{\text{max}}(\text{KBr})/ \text{cm}^{-1}: 2275 (C≡N), 1580 (C=C, aromatic), 1180 (C=S), 680 (P=S); \delta_H (ppm): 3.75 (s, 3H, OCH_3), 6.39 (d, 1H, \^J_{HH} = 12Hz (S-CH-C), 6.8, 7.87 (2dd, 4H, J_{HH} = 8.5 Hz, \^J_{HP} = 10.5Hz, H-Ar), 6.85, 7.9 (2d, 2H, J_{HH} = 8.2 Hz, H-Ph), 7.45, 7.55 (2t, 2H, =CH-CH=), 8.92 (s, 1H, CH-O); \delta_C (ppm): 40.59 (d, J_{CP} = 198 Hz, C≡C≡N), 42.26(d, \^J_{CP} = 32 Hz, P-S-CH), 54.69(OCH_3), 109.50, 111.60, (2d, \^J_{CP} = 30 Hz, 2 × C≡N), 119.20, 120.89, 124.30, 130.89, 131.51, 131.85,
132.60, 134.20, 149.54, 153.70, 161.64 (aromatic carbon atoms), 209.11 (C=S); $\delta_P$ (CDCl$_3$): 50.12 ppm; $m/z$ (EI): 440 [M$^+$] (22).

**Reaction of 15 with Lawesson’s reagent 1. Preparation of compound 17**

To a stirred solution (11.4 mmol) of ethyl (2E)-2-cyano-3-(4-oxo-4H-chromen-3-yl) acrylate (15) in dry toluene (25 mL), Lawesson’s reagent 1 (1.4 g, 5.9 mmol) was added. The reaction mixture was refluxed for 10 h until (TLC) and then evaporated under reduced pressure. The solid formed was collected and recrystallized from acetone/ether to give (5Z)-2-(4-methoxyphenyl)-5-[(4-thioxo-4H-chromen-3-yl)methylene]-1,3,2-thiazaphosphinane-4,6-dithione-2-sulfide (17) as yellow crystals (69% yield), m.p 179-180 °C. Found: C, 49.00, H, 2.99, N, 2.59, P, 6.61, S, 32.52% C$_{20}$H$_{14}$NO$_2$PS$_5$ (491.65) requires C, 48.86, H, 2.87, N, 2.85, P, 6.30, S, 32.61%; $\nu_{\text{max}}$(KBr)/ cm$^{-1}$: 3180 (NH), 1570 (C=C), 1180 (C=S), 1130 (S=C-NH), 1070 (S-C=S), 680 (P=S); $\delta$H (ppm): 3.82 (s, 3H, OCH$_3$), 6.8 (s, 1H, exocyclic ethylenic proton), 7.06, 8.08 (2dd, 4H, $J_{HH}$ =9 Hz, $J_{HP}$ = 10.5 Hz, H-Ar), 7.5, 8.74 (2d, 2H, $J_{HH}$ = 7.5 Hz, H-Ph), 7.26, 7.35 (2t, 2H, =CH=CH=), 9.54 (s, 1H, CH=O), 10.94 (br., 1H, NH); $\delta$C (ppm): 54.69 (OCH$_3$), 84.90, 118.55, 119.89, 120.86, 124.58, 129.85, 134.21, 138.05, 148.15, 152.40, 157.22, 158.22, 158.59 (aromatic carbon atoms), 196.10 (d, S=C-NH, $^2J_{CP}$=34 Hz), 201.16 (-C=S, ring), 221.56 (d, S=C-S, $^2J_{CP}$ =35 Hz); $\delta_P$(CDCl$_3$): 104.8 ppm; $m/z$ (EI): 491 [M$^+$] (28).

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**References**


