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 **1A**[4] (Figure 1), which allows it to undergo [2 + 4] cycloaddition with acyclic α-β-unsaturated ketones[1,2,5] 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.

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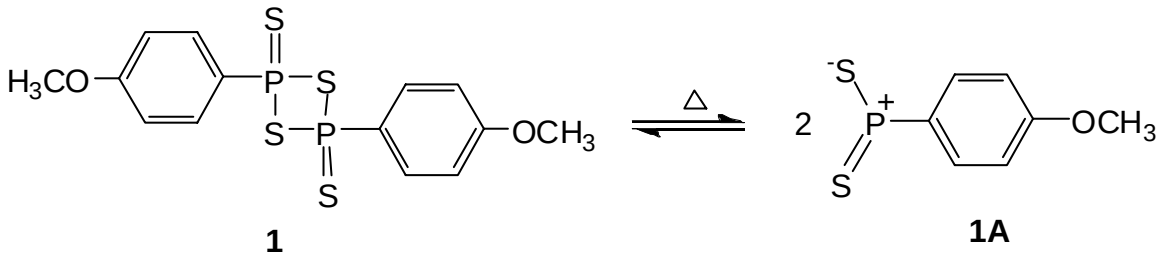
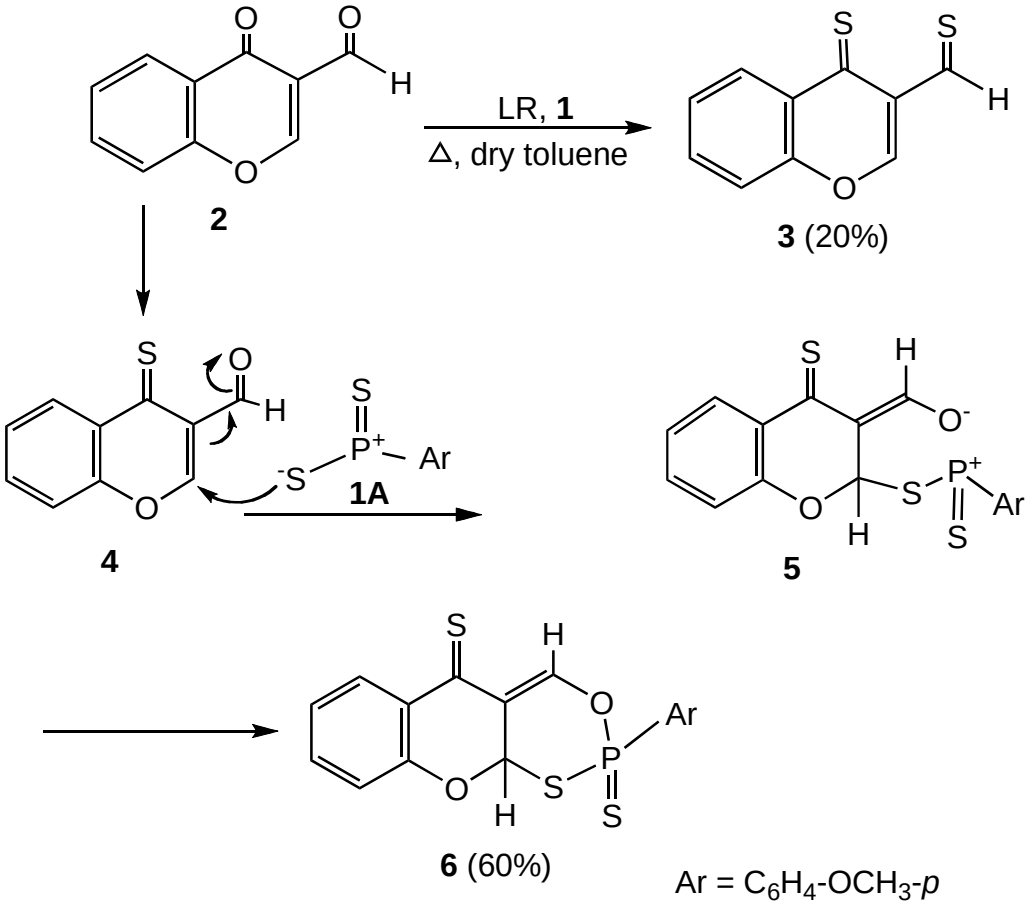


Figure 1

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)-5*H*-10a*H*-[1,3,2]oxathiaphosphinino[4,5-*b*]chromene-5-thione-2-sulfide (**6**) (Scheme 1).

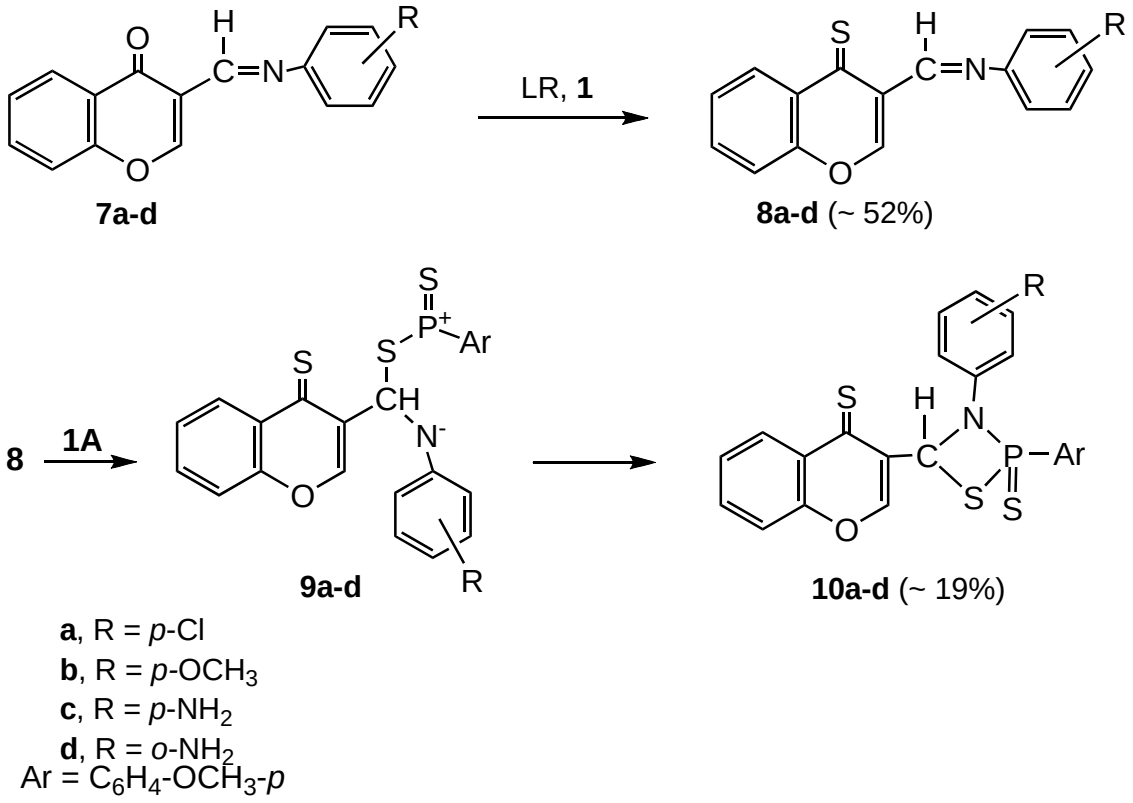


Scheme 1

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_3PO_4) was at δ 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 $CDCl_3$, δ ppm) revealed the presence of signals at 3.85 (s, 3H, OC*H*$_3$), 7.4 (d, $^3J_{HP}$ = 11.3, 1H, P-S-C*H*). The AB system due to the four aromatic protons of the substituent atomatic 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-C*H*=C). The ^{13}C NMR showed signals at 55.30 (O*C*H$_3$), 84.71 (d, $^2J_{CP}$ = 40.1, O-*C*H-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 thione 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]}-4*H*-chromene-4-thione (**8a-d**) and 3-[3-aryl-2-(4-methoxyphenyl)-2-sulfido-1,3,2-thiazaphosphetidin-4-yl]-4*H*-chromene-4-thione (**10a-d**) (Scheme 2).



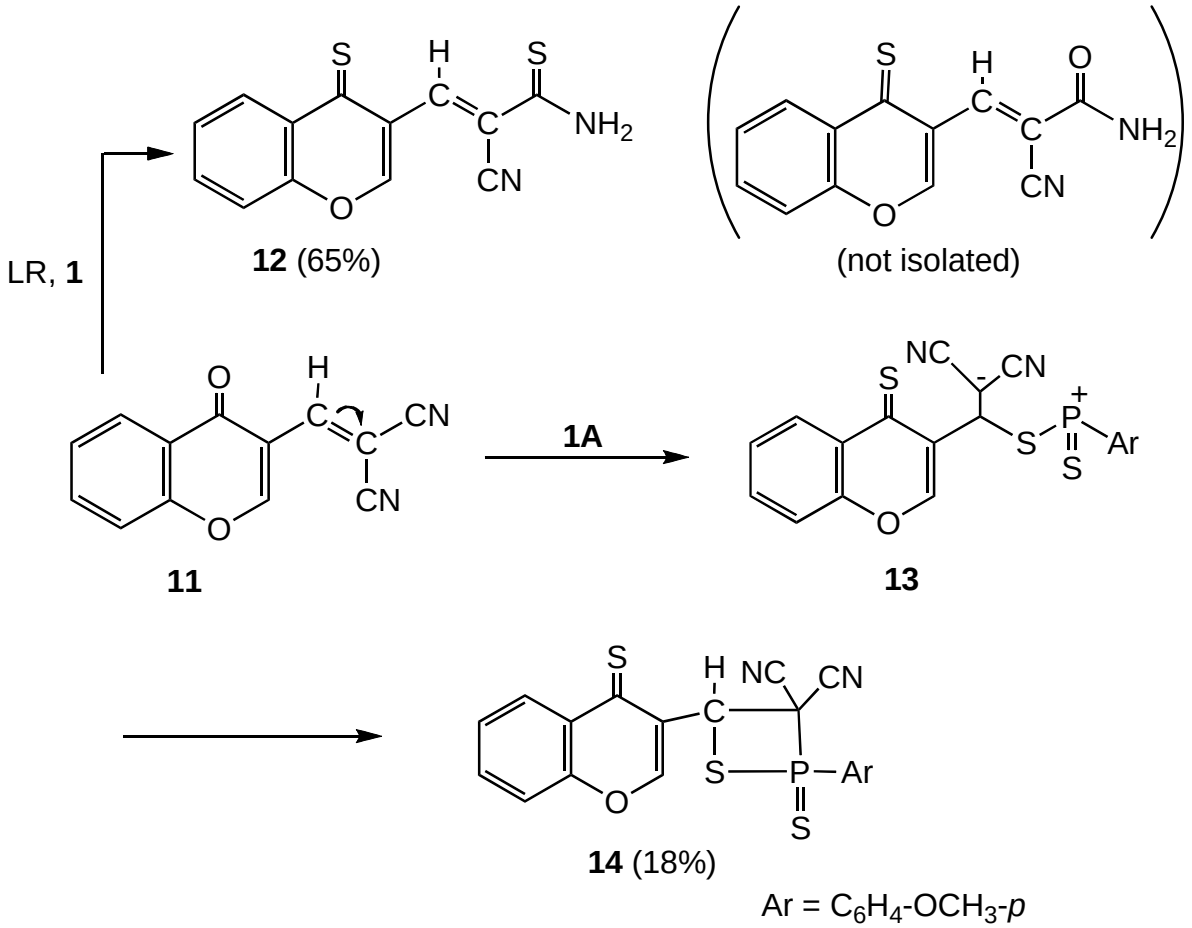
Scheme 2

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]-4*H*-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** ($CDCl_3$, δ ppm) revealed the presence of a signal at 5.34 (d, 1H, $^3J_{HP}$ = 12Hz, S-C*H*-N), also two singlets due to the two (OCH_3) groups at 3.50 and 3.82 ppm. The aromatic protons (13H) appeared as a multiplet at δ_H = 6.45-8.32 ppm. The ^{13}C NMR ($CDCl_3$, δ ppm) spectrum of **10b** had signals at δ 54.59, 55.21 (2 × O*C*H$_3$), 67.57 (d, $^2J_{CP}$ = 42, P-S-*C*H), 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-4*H*-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 (2*E*)-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-4*H*-chromen-3-yl)-1,2-thiaphosphetane-3,3-dicarbonitrile-2-sulfide (**14**) (Scheme 3).



Scheme 3

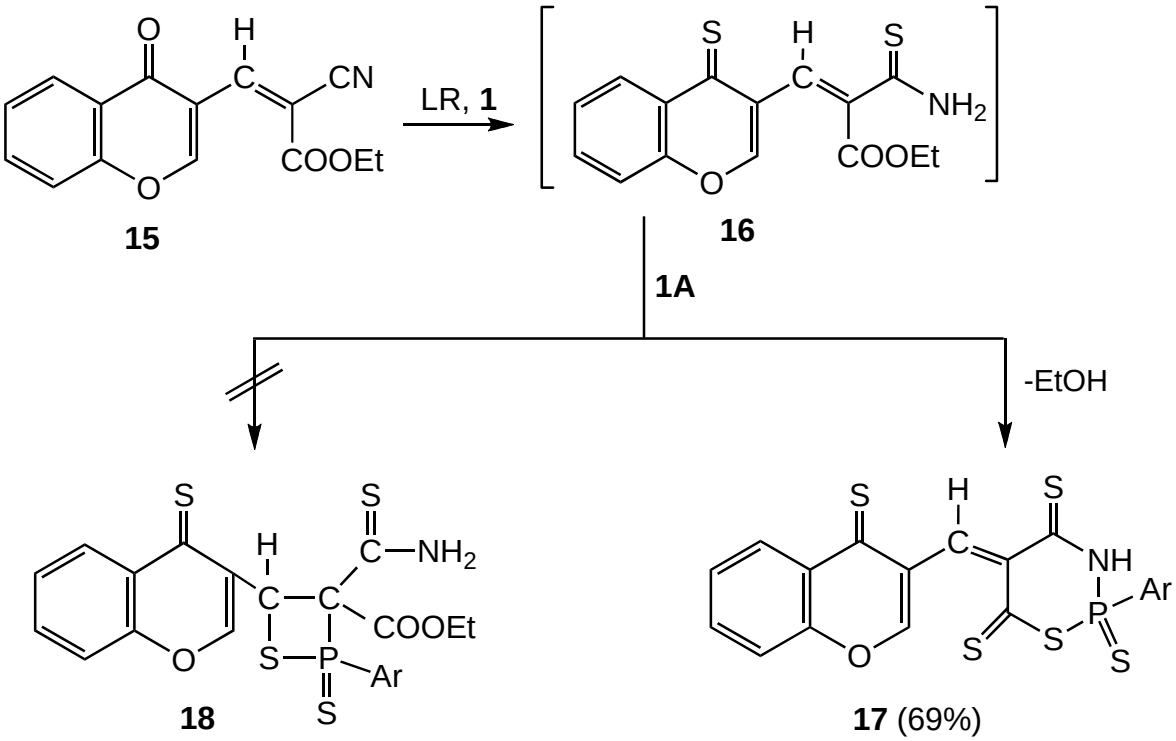
The IR spectrum (in KBr, cm^{-1}) of compound **14**-showed a strong absorption band at 2275 cm^{-1} corresponding to (2 CN) groups and 1180 cm^{-1} (C=S). Its ^{1}H NMR revealed presence of a signal at 6.39 ppm (d, $^3J_{HP}$ =12Hz 1H, P-S-C*H*), a singlet at 3.75 ppm corresponding to the OCH_3 protons.

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 (2*E*)-2-cyano-3-(4-oxo-4*H*-chromen-3-yl)acrylate **15** with Lawesson's reagent was carried out in boiling toluene, giving (5*Z*)-2-(4-methoxyphenyl)-5-[(4-

thioxo-4*H*-chromen-3-yl)methylene]-1,3,2-thiazaphosphinane-4,6-dithione-2-sulfide (**17**) as a sole product (69% yield) (Scheme 4).

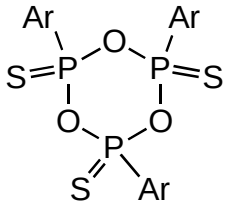


Scheme 4

The structure of **17** was confirmed by analytical and spectral data which showed the disappearance of both the cyano and carboxylate groups. The ^{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.[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 ^{1}H NMR spectra with those of an authentic specimen.[17-19] Formation of **19** is frequently observed during thiation processes using LR.



Ar = C_6H_4-OCH_3-*p*

19

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. subitilis*, *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_3PO_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 handing 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*.[20] 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% $C_{16}H_{12}N_2O_2$ (264.28) requires C, 72.72; H, 4.58; N, 10.60%; IR (ν): 1610 (CH=N), 1530, 1600 (CH=CH), 3300 (NH_2); ^{1}H NMR ($CDCl_3$) gave signals at: δ 5.75 (br.) Due to NH_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^+] (26).

Preparation of [(4-oxo-4*H*-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% $C_{13}H_6N_2O_2$ (222.207) requires: C, 70.27; H, 2.73; N, 12.61%; ν_{max}(KBr)/ cm^{-1}: 1650 (C=O), 1600 (C=C), 2210 (C≡N); δ_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^+] (28).

Preparation of ethyl (2*E*)-2-cyano-3-(4-oxo-4*H*-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 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% $C_{15}H_{11}NO_4$ (269.26) requires: C, 66.91; H, 4.12; N, 5.20%; ν_{max}(KBr)/ cm^{-1}: 1730 (C=O, acetate), 1560 (C=C, aromatic), 2200 (C≡N); δ_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-C*H*$_3$)], 4.2 [q, 2H, (O-C*H*$_2$)]; *m/z* (EI): 269 [M^+] (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-Thioxo-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%; $C_{10}H_6OS_2$ (206.29) requires; C, 58.22; H, 2.93; S, 31.09%; ν_{max}(KBr)/ cm^{-1}: 1100 (C=S, thioxo) 1190 (C=S, ald.), 1600 (C=C, aromatic ring); δ_H (ppm): 7.3, 8.74 (2d, J_{HH} =7.5 Hz, 2H, C*H*-ph), 7.28, 7.34 (2t, 2H, C*H*-ph), 9.67 (s, 1H, C*H*-O), 10.6 (s, 1H, *H*C=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,* (El): 206 [M^+](22).

2-(4-Methoxyphenyl)-5H,10a*H*-[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% $C_{17}H_{13}O_3PS_3$ (392.47) requires C, 52.03; H, 3.34; P, 7.89; S, 24.51%; ν_{max}(KBr)/ cm^{-1} 1220 (C=S) 1580, 1600 (C=C, aromatic) 650 (P=S); δ_H (ppm): 3.85 (s, 3H, OCH_3), 7.4 (d, $^3J_{HP}$ = 11.3, 1H, P-S-C*H*), 6.95 and 7.56 (2dd, 4H, J_{HH} = 9 Hz, $^3J_{HP}$ = 11 Hz, *H*-Ar), 7.95, 8.7 (2d, 2H, J_{HH} = 7 Hz, *H*-Ph), 6.8, 7.1 (2t, 2H, =C*H*-C*H*=), 8.8 (d, $^3J_{HP}$ = 10.5, 1H, P-O-C*H*=C); δ_C (ppm): δ 55.30 (O*C*H$_3$), 84.71 (d, $^2J_{CP}$ = 40.1, O-C*H*-S), 112.05 (S=C-*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, $^2J_{CP}$ = 38.9, C=*C*-O-P=S), 216.77 (*C*=S); δ_P ($CDCl_3$): 93.39 ppm; *m/z* (El): 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)imino]methyl]-4*H*-chromene-4-thione (8a) was obtained (8:2 ν/ν) 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% $C_{16}H_{10}ClNOS$ (299.78) requires C, 64.11; H, 3.36; Cl, 11.83; N, 4.67; S, 10.70%; ν_{max}(KBr)/ cm^{-1}:1610 (CH=N), (CH=CH) 1570, 1600; δ_H (ppm): δ 7.28 (S, H, C*H*=N), 6.48, 7.21 (2d, 4H, J_{HH} = 8.8 Hz, *H*-ph-Cl), 7.51, 8.66 (2d, 2H, J_{HH} =7.3 Hz, C*H*-ph), 7.24, 7.48 (2t, 2H, =C*H*-C*H*=), 8.87 (s, 1H, =C*H*-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]imino}methyl]-4*H*-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% $C_{17}H_{13}NO_2S$ (295.37) requires C, 69.13; H, 4.44; N, 4.74; S, 10.86%; ν_{max}(KBr)/ cm^{-1} (CH=N), 1615, (CH=CH) 1540, 1600; δ_H (ppm): 3.77 (s, 3H, -OCH_3), 7.28(s, 1H, C*H*=N), 6.53, 7.19 (2d, 4H, J_{HH} = 8.6 Hz, *H*-Ph-OCH$_3$), 7.5, 8.67 (2d, 2H, J_{HH} = 7.5 Hz , C*H*-ph), 7.23 ,7.31 (2t, 2H, =C*H*=C*H*=), 8.87 (s, 1H, =C*H*-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]-4*H*-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, 4.58; N, 10.02; S, 11.29% $C_{16}H_{12}N_2OS$ (280.35) requires C, 68.55 H, 4.31; N, 9.99; S, 11.44%; ν_{max}(KBr)/ cm^{-1} : 1620 (CH=N), 1570, 1600 (CH=CH), 3350, 3400 (NH_2); δ_H (ppm): 5.85 (s, 2H, N*H*$_2$), 7.43 (s, H, C*H*=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, C*H*-ph), 7.25, 7.47 (2t, 2H, =CH-CH=), 8.75 (s, 1H, C*H*-O); δ_C (ppm): 108.55, 110.55, 119.07, 122.35, 125.27, 128.68, 135.33, 132.20, 134.50, 142.11, 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]-4*H*-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% $C_{16}H_{12}N_2OS$ (280.35) requires C, 68.55; H, 4.31; N, 9.99; S, 11.44%; ν_{max}(KBr)/ cm^{-1}: 1615 (CH=N), 1540, 1600 (CH=CH), 3320, 3400 (NH_2); δ_H (ppm): 3.71 (s, 2H, N*H*$_2$), 7.28 (s, H, C*H*=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, =C*H*-C*H*=), 7.47, 8.21 (2d, 2H, J_{HH} = 7.64 Hz, C*H*-ph), 8.87 (s, 1H, =C*H*-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]-4*H*-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% $C_{23}H_{17}ClNO_2PS_3$(502.03) requires C, 55.03; H, 3.41; Cl, 7.06; N, 2.79; P, 6.17; S, 19.16%; ν_{max}(KBr)/ cm^{-1}: 1190 (C=S), 1530-1600 (CH=CH), 653 (P=S): δ_H (ppm): 3.74 (s, 3H,OC*H*$_3$), 5.89 (d, 1H, $^3J_{HP}$ = 12 Hz, S-C*H*-N); 6.99-8.75 (m, 13H, aromatics); δ_C (ppm): 56.05 (-O-CH_3), 67.19 (d, $^2J_{CP}$ = 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); δ_P ($CDCl_3$): 48.43 ppm; *m/z* (EI): 502 [M$^+$] (26).

3-[3-(4-Methoxyphenyl)-2-(4-methoxyphenyl)-2-sulfido-1,3,2-thiazaphosphetidin-4-yl]-4*H*-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% $C_{24}H_{20}NO_3PS_3$(497.61) requires C, 57.93; H, 4.05; N, 2.82; P, 6.23; S, 19.33%; ν_{max}(KBr)/ cm^{-1}: 1570, 1600 (CH=CH), 1200 (C=S), 645 (P=S); δ_H (ppm) 3.50 (s, 3H,(N-Ph-OC*H*$_3$), 3.82 (s, 3H, (P-Ph-OC*H*$_3$), 5.34 (d, 1H, $^3J_{HP}$ = 12Hz, S-C*H*-N), 6.45-8.32 (m, 13H, aromatics); δ_C (ppm): 54.59 (P-Ph-O*C*H$_3$), 55.21 (N-Ph-O*C*H$_3$), 67.57 [d, $^2J_{CP}$ = 42, (PS-*C*H-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); δ_P ($CDCl_3$) at 48.92 ppm; *m/z* (EI): 497 [M$^+$] (18).

3-[3-(4-Aminophenyl)-2-(4-methoxyphenyl)-2-sulfido-1,3,2-thiazaphosphetidin-4-yl]-4*H*-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%; ν_{max}(KBr)/ cm^{-1}: 1560, 1600 (CH=CH, aromatic), 3200 (NH_2), 1190 (C=S), 650 (P=S); δ_H (ppm): 3.82 (s, 3H,-OC*H*$_3$), 5.99 (s, 2H, -NH_2), 6.03 (d, 1H, (S-C*H*-N), $^3J_{HP}$ = 12Hz), 6.5-8.32 (m, 13H, aromatics); δ_C (ppm): 54.83 (Ph-O*C*H$_3$), 67.19 (d, $^2J_{CP}$ = 40, PS-*C*H-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); δ_P ($CDCl_3$) 47.29 ppm; *m/z* (EI): 482[M^+] (16).

3-[3-(2-Aminophenyl)-2-(4-methoxyphenyl)-2-sulfido-1,3,2-thiazaphosphetidin-4-yl]-4*H*-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 ν_{max}(KBr)/ cm^{-1}: 1560, 1600 (CH=CH, aromatic), 3300 (NH_2), 1180 (C=S), 640 (P=S): δ_H (ppm): 3.82 (s, 3H,-OC*H*$_3$), 4.16 (s, 2H, -N*H*$_2$), 6.51 (d, 1H, $^3J_{HP}$ = 12Hz, S-C*H*-N), 6.81-8.32 (m, 13H, aromatics); δ_C (ppm): 54.69 (Ph-O*C*H$_3$), 67.34 (d, $^2J_{CP}$ = 43, PS-*C*H-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); δ_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**.

(2*E*)-2-Cyano-3-(4-thioxo-4*H*-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% $C_{13}H_8N_2OS_2$ (272.36) requires C, 57.33, H, 2.96, N, 10.29, S, 23.55%; ν_{max}(KBr)/ cm^{-1}: 3420, 3390 (NH_2), 2200 (C≡N), 1640 (C=C, ethylenic), 1230 (C=S), 1190 (C=S, ring), 1580 (C=C, aromatic); δ_H (ppm): 6.76 (s, 1H, S=C-C*H*=C*H*), 7.46, 8.85 (2d, 2H, J_{HH} = 7.5 Hz, C*H*-ph), 7.36, 7.39 (2t, 2H, C*H*-ph), 9.20 (s, 1H, C*H*-O), (s, 2H, N*H*$_2$, exchangeable with D_2O); δ_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-4*H*-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%; ν_{max}(KBr)/ cm^1: 2275 (C≡N), 1580 (C=C, aromatic), 1180 (C=S), 680 (P=S); δ_H (ppm): 3.75 (s, 3H, OC*H*$_3$), 6.39 (d, 1H, $^3J_{HP}$ = 12Hz (S-C*H*-C), 6.8, 7.87 (2dd, 4H, J_{HH} =8.5 Hz, $^3J_{HP}$ = 10.5Hz, *H*-Ar), 6.85, 7.9 (2d, 2H, J_{HH} = 8.2 Hz, *H*-Ph), 7.45, 7.55 (2t, 2H, =C*H*-C*H*=), 8.92 (s, 1H, C*H*-O); δ_C (ppm): 40.59 (d, J_{CP} =198 Hz, *C*-C≡N), 42.26(d, $^2J_{CP}$ =32 Hz, P-S-*C*H), 54.69(OC*H*$_3$), 109.50, 111.60, (2d, $^2J_{CP}$ = 30 Hz, 2 × C≡N), 115.54,116.70, 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); δ_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 (2*E*)-2-cyano-3-(4-oxo-4*H*-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 (5*Z*)-2-(4-methoxyphenyl)-5-[(4-thioxo-4*H*-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% $C_{20}H_{14}NO_2PS_5$ (491.65) requires C, 48.86, H, 2.87, N, 2.85,P, 6.30, S, 32.61%; ν_{max}(KBr)/ cm^{-1}: 3180 (NH), 1570 (C=C), 1180 (C=S), 1130 (S=C-NH),1070 (S-C=S), 680 (P=S); δ_H (ppm): 3.82 (s, 3H, OC*H*$_3$), 6.8 (s, 1H, exocyclic ethylenic proton), 7.06, 8.08 (2dd, 4H, J_{HH} =9 Hz, $^3J_{HP}$ = 10.5 Hz, *H*-Ar), 7.5, 8.74 (2d, 2H, J_{HH} = 7.5 Hz, *H*-Ph), 7.26, 7.35 (2t, 2H, =C*H*-C*H*=), 9.54 (s, 1H, C*H*-O), 10.94 (br., 1H, N*H*); δ_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).; δ_P ($CDCL_3$): 104.8 ppm; *m/z* (EI): 491 [M^+] (28).

Acknowledgements

We are grateful to Dr. Latifa A. Mohamed, Division of Genetic Engineering and Biotechnology, Department of Microbial Chemistry, National Research Centre, for the pharmacological evaluation.

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