Research Article

Studies on Organo-phosphorus Compounds Part II: Synthesis and biological activities of some new benzochromeno[2,3-d][1,3,2]thiazaphosphinine derivatives

Sabry H. H. Younes[a], Shaaban K. Mohamed[b,c*], Antar A. Abdelhamid[a] ,and A. -B. A. G. Ghattas[a]
[a]Department of Chemistry, Faculty of Science, Sohag University, 82524 Sohag, Egypt.
[b]Chemistry and Environmental Division, Manchester Metropolitan University, Manchester M1 5GD, England.
[c]Chemistry Department, Faculty of Science, Minia University, 61519 El-Minia, Egypt.
*Corresponding author's E-mail: shaabankamel@yahoo.com

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ABSTRACT

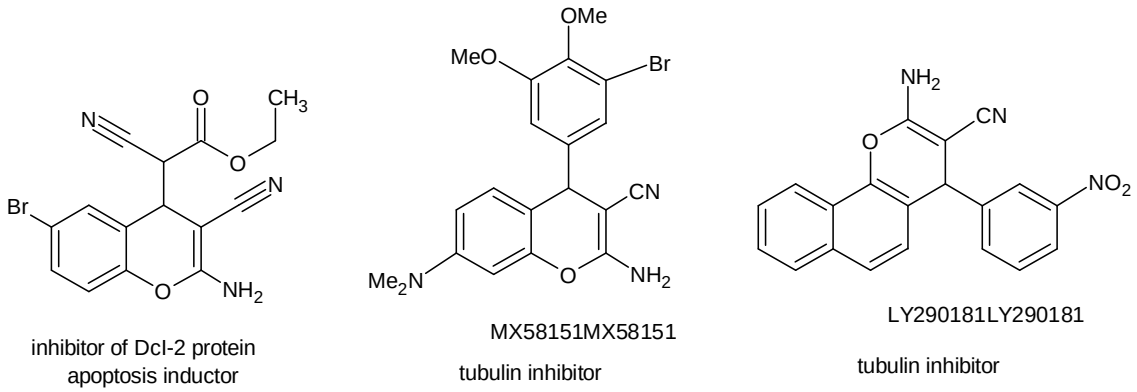
A series of novel heterocyclic chromeno[2,3-d][1,3,2]thiazaphosphinine derivatives were synthesized in a satisfactory yield via reaction of 2-aminobenzo[f]chromene with the dimer p-methoxyphenylthiophosphine sulphide (Lawesson's Reagent, LR). New structures were characterized by IR, NMR and MS spectra as well as elemental analyses. All the compounds were screened for their antibacterial, antifungal and toxicity using brine shrimp test (Artimia salina L.). Preliminary results indicated that some target compounds exhibited promising antibacterial and antifungal potency.

Keywords: Synthesis, organo-phosphorus compounds, antifungal, antibacterial.

INTRODUCTION

Chromenes are important class of oxygenated heterocyclic compounds. Among different types of chromene structures, 2-amino-4H-chromenes (especially 2-aminobenzochromenes) attracted our attention because of their occurrences in many natural products having spasmolytic, diuretic, anticoagulant, anticancer, anti-HIV and anti-anaphylactic activities[1–5]. Compounds incorporate chromenes entities have a wide range of pharmacological activities[6,7] such as antidepressant, antihypertensive, anti-tubulin, antiviral, antioxidative activity[8,9]. Chromenes are known to activate potassium channels and inhibit phosphodiesterase IV and dihydrofolate reductases[10–17].

Chromenes are also used as cosmetics, pigments[18], and potential biodegradable agrochemicals[19]. Synthetic chromene analogues have been developed over decays, and some of them have been employed as antifungal[20] and antimicrobial agents[21]. The current interest in 2-amino-4H-chromenes arises from their application in the treatment of human inflammatory TNFα-mediated diseases, such as rheumatoid and psoriatic arthritis and in cancer therapy (Fig. 1)[22-24].



inhibitor of Dcl-2 protein apoptosis inductor

MX58151MX58151

tubulin inhibitor

LY290181LY290181

tubulin inhibitor

Fig. 1: 2-Amino-4H-chromenes as privileged medicinal scaffolds

On other hand, Lawesson's Reagent is the most effective and versatile thiation reagent for carbonyl compounds[25,26]. Also Lawesson's Reagent undergoes ring closure reactions with substrates containing two functional groups[27-29] forming phosphorus heterocyclic compounds, which have a wide spectrum of biological activities such as insecticidal[30], antibacterial, antifungal[31,32] and anticancer[33].

Upon continuation of our study on developing more versatile and convenient synthesis of highly functionalized heterocycles[34-38] and extending to our applications on Lawesson's Reagent (LR)[39], we herein report a convenient synthetic protocol for new benzochromeno[2,3-d][1,3,2]thiazaphosphinine derivatives in a good to excellent yield.

MATERIALS AND METHODS

Chemistry

All melting points were recorded on Melt-Temp II melting point apparatus. IR spectra were measured as KBr pellets on a Nicolet 710 FT-IR spectrometer. ^{1}H- NMR spectra were recorded in deuterated dimethyl sulfoxide at 400 MHz on a Brucker NMR spectrometer using tetramethylsilane as an internal reference. Mass spectra were performed on a Shimadzu GCMS-QP 1000 mass spectrometer at 70 eV. The elemental analyses were carried out on an elemental analyzer 240ºC. All compounds were checked for their purity on TLC plates.

General procedures for the Synthesis of Compounds (3a-f),(5a-d) and (7a-d):

A mixture of compounds **2a-f, 4a-f** or **6a-f** (0.01 mol) and 2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulphide (Lawesson's Reagent, LR) in dry acetonitrile (50 mL) was refluxed until completion after 6 hours. The reaction was monitored by TLC. The reaction mixture was filtered off and the filtrate was evaporated under *vacuum*. The separated solid was crystallized from ethanol.

9-(4-Methoxyphenyl)-9-sulfide-12-phenyl-8,12-dihydro-9H,11H-benzo[5,6]chromeno-[2,3-d][1,3,2] thiazaphosphinin-11-imine (3a).

Yield (70%); crystallized from EtOH; mp190 ^{o}C; IR (KBr) cm^{-1}: σ 3300 (NH), 3040 ($CH_{aromt.}$), 644 (P=S); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 8.12-7.11 (m, 15H, $CH_{aromt.}$), 6.22 (s, 2H, 2NH), 4.07(s, 3H, OCH_3), 3.37(s, H, CH); MS, m/z (%): 500 (M^+) (12), 484 (18), 452 (1.7), 423 (8), 340 (4), 326 (22), 297 (29), 276 (79), 221(100). Anal. Calcd. $C_{27}H_{21}N_2O_2PS_2$ (500.56): C (64.79); H (4.23); N (5.60); P (6.19); S(12.81). Found: C (64.50); H (4.33); N (5.69); P (6.29); S(12.71).

12-(4-Chlorophenyl)-9-sulfide-9-(4-methoxyphenyl)-8,12-dihydro-9H,11H-benzo[5,6]-chromeno[2,3-d][1,3,2]thiazaphosphinin-11-imine (3b).

Yield (75%); crystallized from EtOH; mp 210 ^{o}C; IR (KBr) cm^{-1}: σ 3276 (NH), 3070 ($CH_{aromt.}$), 2910 ($CH_{aliph.}$), 619 (P=S); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 8.1-7.61 (m, 14H, $CH_{aromt.}$), 6.00 (s, 2H, 2NH), 4.36(s, 3H, OCH_3), 3.67 (s, 1H, CH); ^{13}C-NMR (100 MHz, DMSO): 160.57, 158.00, 155.41, 142.31, 140.07, 134.13, 132.44, 130.23, 129.61, 128.11, 127.05, 126.00, 125.73, 125.23, 125.00, 124.81, 124.02, 120.33, 118.12, 114.92, 114.22, 56.42, 41.99; ^{31}P (161 MHz, DMSO): 13.11. Anal. Calcd. $C_{27}H_{20}ClN_2O_2PS_2$ (535.01): C (60.61); H (3.77); Cl (6.63); N (5.24); P (5.79); S (11.98). Found: C (60.71); H (3.70); Cl (6.70); N (5.34); P (5.89); S (11.68).

9,12-Di(4-methoxyphenyl)-9-sulfide-8,12-dihydro-9H,11H-benzo[5,6]chromeno[2,3-d]-[1,3,2] thiazaphosphinin-11-imine (3c).

Yield (74%); crystallized from EtOH; mp 172 ^{o}C; IR (KBr) cm^{-1}: σ 3120 (NH), 3067 ($CH_{aromt.}$), 2922 ($CH_{aliph.}$), 625 (P=S); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 7.99-6.87 (m, 14H, $CH_{aromt.}$), 6.23 (s, 2H, 2NH), 3.96(s, 3H, OCH_3), 3.63(s, 3H, OCH_3), 3.41 (s, 1H, CH); MS, m/z (%): 530 (M^+) (65), 514 (13), 484 (0.17), 481 (3), 453 (6), 422 (7), 344 (3), 327 (32), 268 (3) 221(100), 202 (5), 139 (36). Anal. Calcd. $C_{28}H_{23}N_2O_3PS_2$ (530.59): C (63.38); H (4.37); N (5.28); P (5.84); S (12.08). Found: C (63.20); H (4.29); N (5.38); P (5.90); S (12.18).

12-(4-Hydroxyphenyl)-9-sulfide-9-(4-methoxyphenyl)-8,12-dihydro9H,11H-benzo[5,6]-chromeno[2,3-d][1,3,2]thiazaphosphinin-11-imine (3d).

Yield (68%); crystallized from EtOH; mp 187 ^{o}C; IR (KBr) cm^{-1}: σ 3173 (NH), 3030 ($CH_{aromt.}$), 2964 ($CH_{aliph.}$), 615 (P=S); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 7.78-6.45 (m, 14H, $CH_{aromt.}$), 5.97 (s, 3H, 2NH, OH), 3.81(s, 3H, OCH_3), 3.22 (s, 1H, CH). Anal. Calcd. $C_{27}H_{21}N_2O_3PS_2$ (516.56): C (62.78); H (4.11); N (5.42); P (6.00); S (12.41). Found: C (62.44); H (4.22); N (5.32); P (6.21); S (12.53).

12-(2-Hydroxyphenyl)-9-sulfide-9-(4-methoxyphenyl)-8,12-dihydro-9H, 11H-benzo[5,6]-chromeno[2,3-d][1,3,2] thiazaphosphinin-11-imine (3e).

Yield (78%); crystallized from EtOH; mp 200 ^{o}C; IR (KBr) cm^{-1}: σ 3200 (NH), 3018 ($CH_{aromt.}$), 2910 ($CH_{aliph.}$), 646 (P=S); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 7.66-6.34 (m, 14H, $CH_{aromt.}$), 5.98 (s, 3H, 2NH, OH), 4.61(s, 3H, OCH_3), 3.60 (s, 1H, CH). Anal. Calcd. $C_{27}H_{21}N_2O_3PS_2$ (516.56): C (62.78); H (4.11); N (5.42); P (6.00); S (12.41). Found: C (62.44); H (4.22); N (5.32); P (6.21); S (12.53).

9-(4-Methoxyphenyl)-9,11-dithioxo-12-phenyl-8,12-dihydro-9H,11H-benzo [5,6]-chromeno[2,3-d][1,3,2] thiazaphosphinine (3f).

Yield (76%); crystallized from EtOH; mp 225 ^{o}C; IR (KBr) cm^{-1}: σ 3197 (NH), 3000 ($CH_{aromt.}$), 2900 ($CH_{aliph.}$), 650 (P=S); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 8.00-7.42 (m, 15H, $CH_{aromt.}$), 6.22 (s, 2H, 2NH), 4.87 (s, 3H, OCH_3), 3.67 (s, 1H, CH). MS, m/z (%): 517 (M^+) (5), 504 (6), 474 (1.7), 438 (2), 406 (6), 331 (4), 297 (100), 253 (7), 238 (17) 192 (24), 118 (44). Anal. Calcd. $C_{27}H_{20}NO_2PS_3$ (517.55): C (62.65); H (3.89); N (2.71); P (5.98); S (18.58). Found: C (62.75); H (3.69); N (2.93); P (5.88); S (18.56).

4-Imino-2-(4-methoxyphenyl)-2-sulfide -5-phenyl-1,5-dihydro-2H,4H-chromeno[2,3-d][1,3,2]thiazaphosphinin-8-ol (5a).

Yield (88%); crystallized from EtOH; mp142 ^{o}C; IR (KBr) cm^{-1}: σ 3176 (NH), 3043 ($CH_{aromt.}$), 696 (P=S); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 7.92-6.87 (m, 12H, $CH_{aromt.}$), 6.32 (s, 3H, 2NH, OH), 4.66 (s, 3H, OCH_3), 3.67(s, H, CH); MS, m/z (%): 466 (M^+) (19), 402 (22), 401 (30), 371 (21), 289 (23), 220 (21), 197 (100), 157 (27). Anal. Calcd. $C_{23}H_{19}N_2O_3PS_2$ (466.50): C (59.22); H (4.10); N (6.00); P (6.64); S(13.74). Found: C (59.42); H (4.22); N (6.22); P (6.30); S(13.54).

5-(4-Chlorophenyl)-4-imino-2-(4-methoxyphenyl)-2-sulfide-1,5-dihydro-2H,4H-chromeno[2,3-d][1,3,2] thiazaphosphinin-8-ol (5b).

Yield (85%); crystallized from EtOH; mp167 °C; IR (KBr) cm^{-1}: σ 3199 (NH), 3027 ($CH_{aromt.}$), 675 (P=S); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 7.55-6.37 (m, 11H, $CH_{aromt.}$), 6.47 (s, 3H, 2NH, OH), 4.35 (s, 3H, OCH_3), 3.88(s, H, CH). Anal. Calcd. $C_{23}H_{18}ClN_2O_3PS_2$ (500.95): C (55.15); H (3.62); Cl (7.08); N (5.59); P (6.18); S(12.80). Found: (55.25); H (3.42); Cl (7.18); N (5.53); P (6.18); S(12.85).

4-Imino-2,5-di(4-methoxyphenyl)-2-sulfide -1,5-dihydro-2H,4H-chromeno[2,3-d]-[1,3,2]thiazaphosphinin-8-ol (5c).

Yield (89%); crystallized from EtOH; mp181 °C; IR (KBr) cm^{-1}: σ 3170 (NH), 3000 ($CH_{aromt.}$), 644 (P=S); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 7.82-6.77 (m, 12H, $CH_{aromt.}$), 6.55 (s, 3H, 2NH, OH), 4.66 (s, 3H, OCH_3), 4.32 (s, 3H, OCH_3), 3.81(s, H, CH). MS, m/z (%): 497 (M^{+1}) (12), 481 (2), 464 (0.86), 432 (0.68), 325 (0.47), 276 (4), 202 (3.8), 188 (100), 170 (44), 124 (61). Anal. Calcd. $C_{24}H_{21}N_2O_4PS_2$ (496.53): C (58.06); H (4.26); N (5.64); P (6.24); S(12.91). Found: C (58.26); H (4.24); N (5.44); P (6.24); S(12.93).

8-Hydroxy-2-(4-methoxyphenyl)-2,4-dithioxo-5-phenyl-1,5-dihydro-2H,4H-chromeno-[2,3-d][1,3,2] thiazaphosphinine (5d).

Yield (89%); crystallized from EtOH; mp 205 °C; IR (KBr) cm^{-1}: σ 3200 (NH), 3010 ($CH_{aromt.}$), 608 (P=S); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 8.12-7.43 (m, 13H, $CH_{aromt.}$), 6.44 (s, 2H, NH, OH), 4.36 (s, 3H, OCH_3), 3.55(s, H, CH). MS, m/z (%): 483 (M^+) (4), 451 (2), 433 (2), 370 (2), 293 (3), 221 (12), 212 (19), 198 (17), 197 (100), 115 (23). Anal. Calcd. $C_{23}H_{18}NO_3PS_3$ (483.55): C (57.13); H (3.75); N (2.90); P (6.41); S(19.89). Found: C (57.33); H (3.95); N (2.55); P (6.51); S(19.74).

2,10-Di(4-methoxyphenyl)-2,10-disulfide-5,7-diphenyl-1,5,10,11-tetrahydro-2H,4H,7H,-8H-[1,3,2]thiaza phosphinino[5'',4'':5',6']pyrano[3',2':6,7] chromeno [2,3-d][1,3,2]thia-zaphosphinine-4,8-diimine (7a).

Yield (67%); crystallized from EtOH; mp 245 °C; IR (KBr) cm^{-1}: σ 3182 (NH), 3030 ($CH_{aromt.}$), 621 (P=S); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 9.23 (s, 4H, 4NH), 7.92-6.13 (m, 20H, $CH_{aromt.}$), 4.98 (s, 6H, $2OCH_3$), 3.78(s, 2H, 2CH). MS, m/z (%): 823 (M^{+1}) (41), 822 (M^+) (23), 807 (23), 791 (26), 761 (22), 728 (25), 698 (24), 667 (28), 590 (28), 514 (22), 364 (28), 315 (38), 285 (44), 263 (100), 235 (89), 180 (8), 158 (32). Anal. Calcd. $C_{40}H_{32}N_4O_4P_2S_4$ (822.90): C (58.38); H (3.92); N (6.81); P (7.53); S(15.58). Found: C (58.44); H (3.54); N (6.82); P (7.74); S(15.68).

5,7-di(4-chlorophenyl)-2,10-di(4-methoxyphenyl)-2,10-disulfide-1,5,10,11-tetrahydro-2H,4H,7H,8H-[1,3,2] thiazaphosphinino[5'',4'':5',6']pyrano[3',2':6,7] chromeno [2,3-d][1,3,2]thiazaphosphinine-4,8-diimine (7b).

Yield (75%); crystallized from EtOH; mp 200 °C; IR (KBr) cm^{-1}: σ 3210 (NH), 3030 ($CH_{aromt.}$), 621 (P=S); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 9.00 (s, 4H, 4NH), 8.12-7.00 (m, 18H, $CH_{aromt.}$), 4.28 (s, 6H, $2OCH_3$), 3.35(s, 2H, 2CH). MS, m/z (%): 892 (M^{+1}) (6), 891 (M^+) (7), 799 (9), 731 (9), 658 (8), 512 (10), 510 (41), 437 (15), 359 (3), 297 (24), 276 (96), 233 (25), 231 (72), 187 (100), 139 (40), 77 (41). Anal. Calcd. $C_{40}H_{30}Cl_2N_4O_4P_2S_4$ (891.79): C (53.87); H (3.39); Cl (7.97); N (6.28); P (6.95); S(14.38). Found: C (53.68); H (3.40); Cl (7.93); N (6.38); P (6.96); S(14.48).

2,5,7,10-tetra(4-methoxyphenyl)-2,10-disulfide -1,5,10,11-tetrahydro-2H,4H,7H,8H-[1,3,2] thiazaphosphinino[5'',4'':5',6']pyrano[3',2':6,7] chromeno[2,3-d][1,3,2]thiaza-phosphinine-4,8-diimine (7c).

Yield (67%); crystallized from EtOH; mp 165 °C; IR (KBr) cm^{-1}: σ 3154 (NH), 3043 ($CH_{aromt.}$), 625 (P=S); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 9.11 (s, 4H, 4NH), 7.92-6.53 (m, 18H, $CH_{aromt.}$), 4.76 (s, 6H, $2OCH_3$), 4.44 (s, 6H, $2OCH_3$), 3.39(s, 2H, 2CH). Anal. Calcd. $C_{42}H_{36}N_4O_6P_2S_4$ (882.95): C (57.13); H (4.11); N (6.35); P (7.02); S(14.52). Found: C (57.23); H (4.31); N (6.15); P (7.22); S(14.22).

2,10-di(4-methoxyphenyl)-5,7-diphenyl-2,4,8,10-tetrasulfide -1,5,10,11-tetrahydro-2H,4H,7H,8H-[1,3,2] thiazaphosphinino[5'',4'':5',6']pyrano[3',2':6,7] chromeno[2,3-d][1,3,2]thiazaphosphinine (7d).

Yield (50%); crystallized from EtOH; mp 150 °C; IR (KBr) cm^{-1}: σ 3452 (NH), 3000 ($CH_{aromt.}$), 611 (P=S); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 10.00 (s, 2H, 2NH), 8.00-7.23 (m, 20H, $CH_{aromt.}$), 3.88 (s, 6H, $2OCH_3$), 3.66(s, 2H, 2CH). MS, m/z (%): 856 (M^+) (7), 825 (8), 760 (14), 721 (11), 697 (10), 667 (7), 590 (9), 516 (2), 440 (1), 368 (100), 366 (29), 296 (5), 261 (81), 260 (29), 196 (37), 185 (10), 159 (28), 73 (56). Anal. Calcd. $C_{40}H_{30}N_2O_4P_2S_6$ (856.99): C (56.06); H (3.53); N (3.27); P (7.23); S(22.45). Found: C (56.17); H (3.33); N (3.35); P (7.33); S(22.36).

Pharmacology

Inhibition zone was used for testing the activity of the compounds against toxigenic bacteria and dermatophytes fungi based on the method previously described by Speer and Sussmuth 1987[42]. 50 µg of the appropriated compounds were dissolved in DMSO, evaporation of the solvent and the disc put on surface inoculated medium. The dishes were incubated at 28-37 ºC for 48 h to 15 days for bacteria and fungi, respectively. At the end of incubation period, the diameter of no growth was measured.

RESULTS AND DISCUSSION

Chemistry

2-Amino-chromenes are generally prepared by refluxing an activated phenol with arylidine derivatives[40,41]. The cyclization of the dimer *p*-methoxyphenylthiophosphine sulphide (Lawesson's Reagent, LR) with 2-aminobenzo[f]chromenes **2a-f** was carried out in a boiling acetonitrile solution to afford benzochromeno[2,3-d][1,3,2]thiazaphosphinine derivatives **3a-f** (Scheme 1).

The IR spectra of compounds **3a-e** showed the absence of the absorption bands corresponding to amino and cyano groups while appearing characteristic bands at average 3200, 3100, 650 cm^{-1} were corresponding to NH and P=S. ^{1}H-NMR showed the appearance of new signals between δ 6.23-5.97 ppm and 4.87 – 3.81ppm are characteristic of 2NH protons and three aliphatic protons (OCH_3), respectively. ^{1}H-NMR of compound **3f** showed the absence of the signals corresponding to ester group of the starting material. Mass spectra of compounds **3a, 3c** and **3f** showed the molecular peak ions at 500 (12%), 530 (65%) and 517 (5%), respectively.

In a similar condition, the chromene derivatives **4a-d** were allowed to react individually with Lawesson's Reagent to furnish chromeno[2,3-d][1,3,2] thiazaphosphinin-8-ol derivatives **5a-d** (Scheme 2).

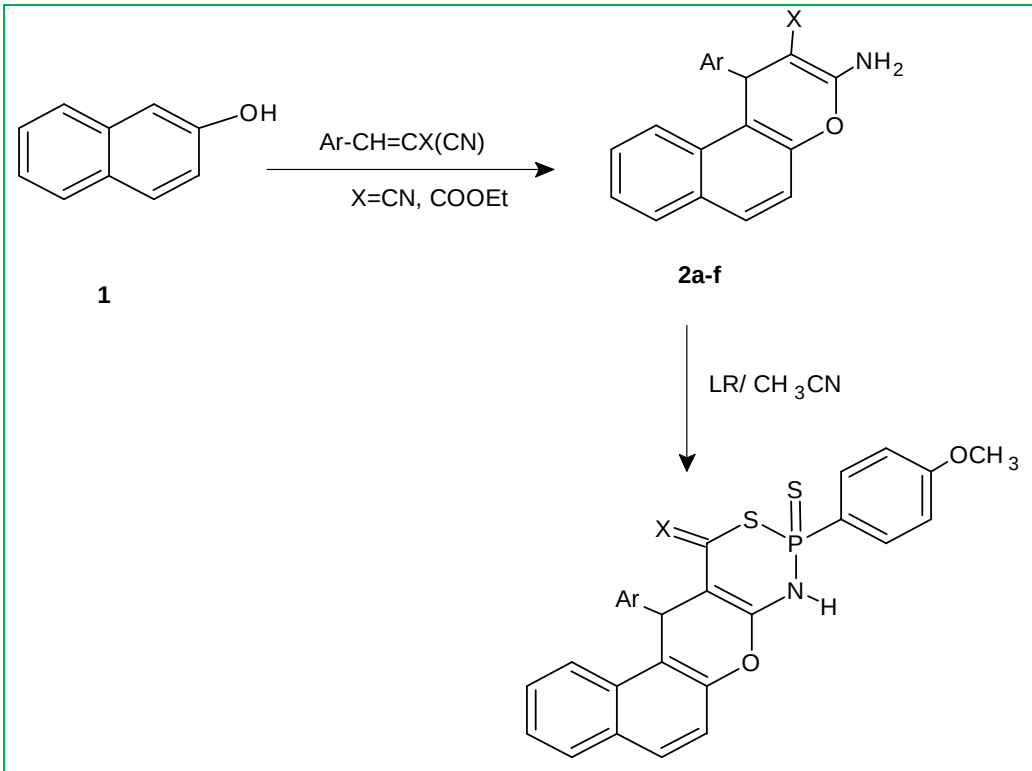
The reaction pathway of compound **5a** was assumed to proceed *via* the nucleophilic attack of the amino group on LR followed by addition of SH to the cyano group (Scheme 3).

The mechanism of compound **5d** was proposed to proceed *via* a nucleophilic attack on LR followed by ring closure and elimination of ethanol molecule which subsequent by thiation to produce 8-hydroxy-2-(4-methoxyphenyl)-2,4-dithioxo-5-phenyl-1,5-dihydro-2H, 4H-chromeno[2,3-d][1,3,2]thiazaphosphinine **5d** (Scheme 4).

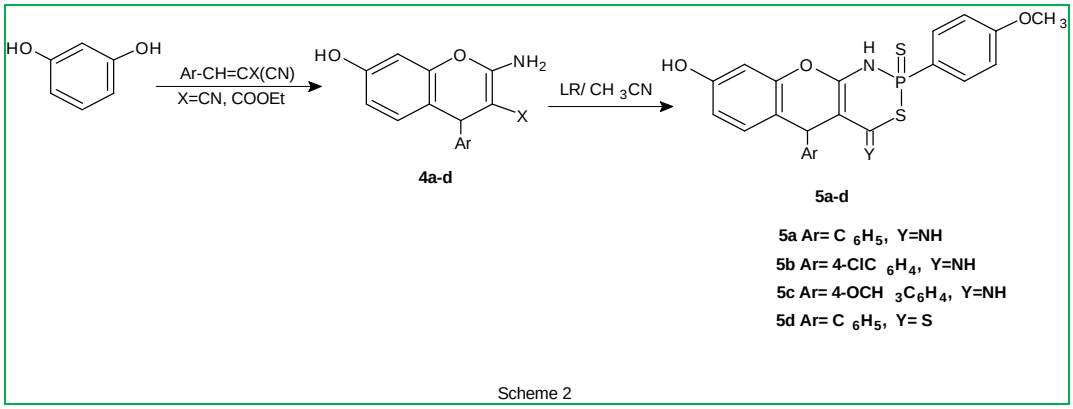
The structure of products **5a-d** was determined by elemental analysis and spectral data (see Experimental section).

Prompted by the aforementioned results, we have also investigated the reactivity of pyrano[3,2-g]chromene towards Lawesson's Reagent. Thus, the reaction of compounds **6a-d** with (LR) in 1:2 molar ratio gave the corresponding bisthiazaphosphinino[5'',4'':5',6']pyrano [3',2':6,7]chromene **7a-d** in high yield (Scheme 5).

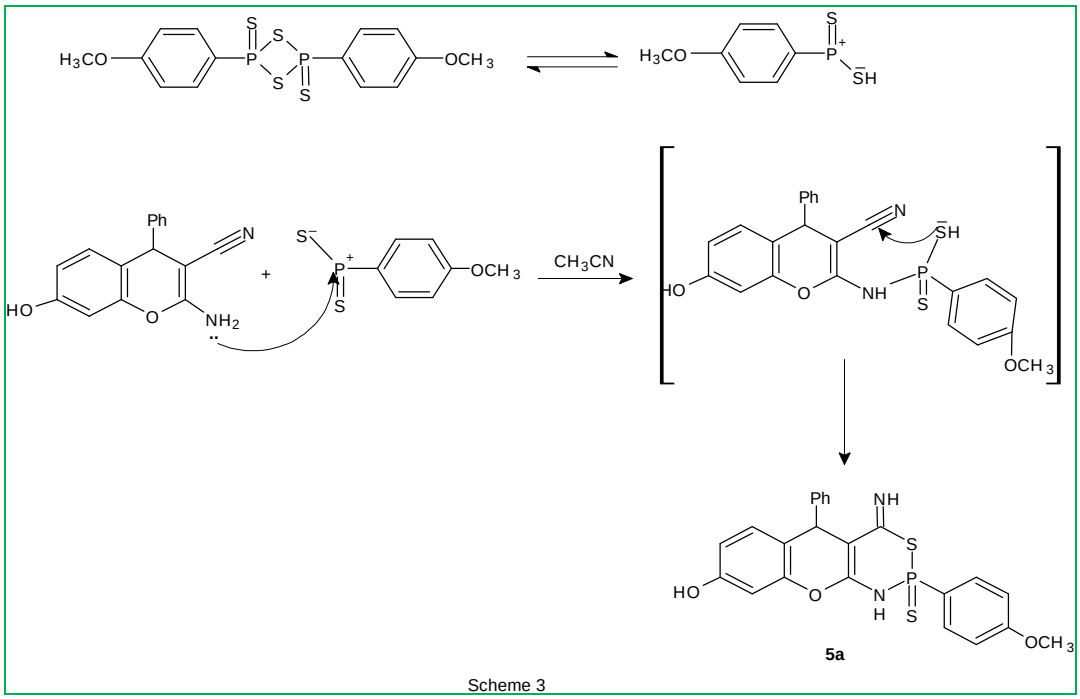
The structures of the latter products were deduced from their elemental analyses and spectral data. The ^{1}H-NMR spectrum of compound **7a**, for example, revealed the absence of the signal corresponding to amino group of the starting material and the appearance of new signals characteristic of protons corresponding to methoxy group. Mass spectra of compounds **7a**, **7b** and **7d** showed the molecular peak ions at 823 (41%), 892 (6%), 856 (7%), respectively.



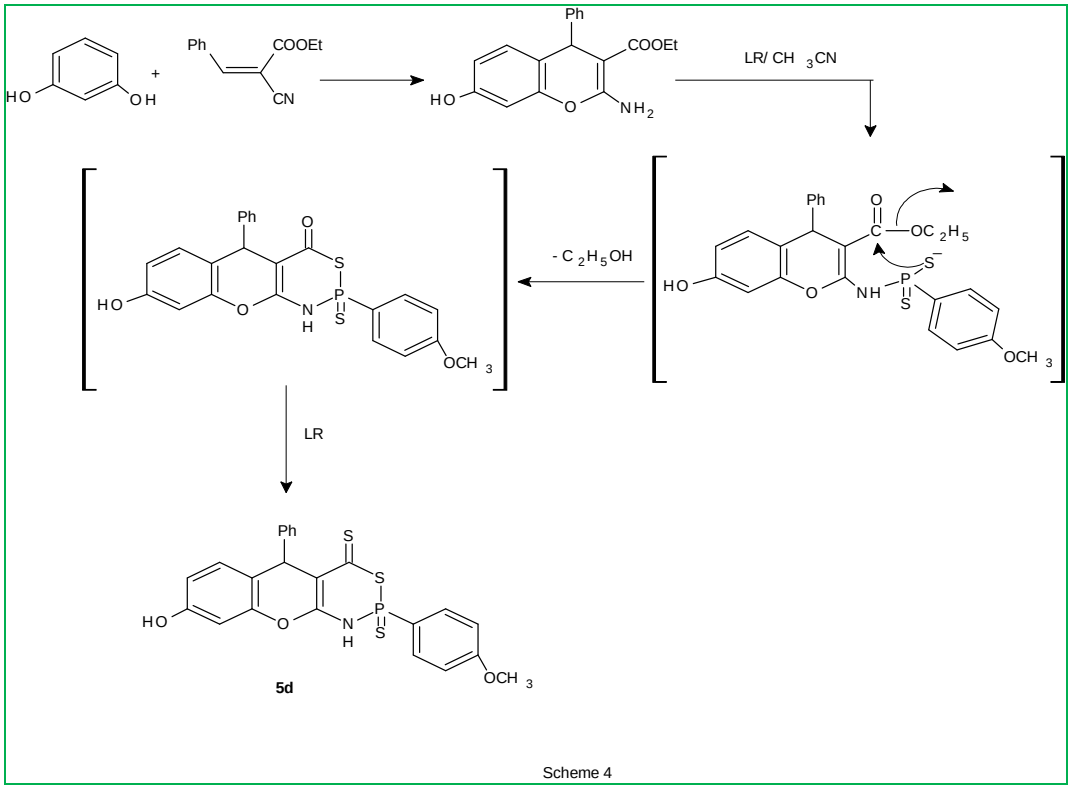
Scheme 1



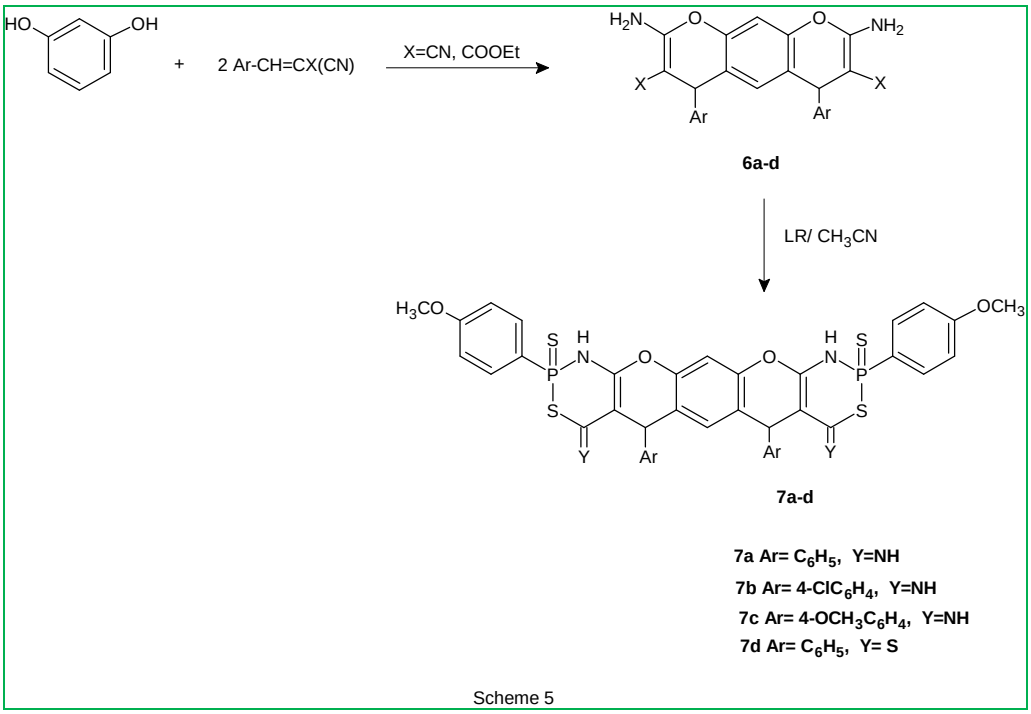
Scheme 2



Scheme 3



Scheme 4



Scheme 5

Table 1: Toxicity (brine shrimp larvae) test and activity of benzochromeno[2,3-d][1,3,2]thiazaphosphinine and its derivatives against bacterial and fungal strains, respectively.

Inhibition zone diameter (mm)							
Compd	Antibacteria activity				Antifungal activity		Brine Shrimp (animal)
	(Gram +ve)		(Gram –ve)				
	Bacillus cereus	*Staphylococcus albus*	*Psedomonas aureginosa*	*Escherichia coli*	*Trichophyton mentagrophytes*	*Trichophyton verrucosum*	
3a	15	16	13	11	10	10	H
3b	16	15	13	12	10	10	H
3c	17	15	14	11	09	10	H
3d	17	15	13	13	09	10	H
3e	16	16	11	13	09	10	H
5a	17	16	12	13	18	15	H
5b	18	15	12	12	13	16	H
5d	19	22	11	12	17	18	H
7a	28	20	25	20	19	11	H
7b	28	29	25	20	19	11	H
7c	28	30	25	20	17	18	H
7d	30	30	30	28	24	24	H
DMSO (control)	-	-	-	-	-	-	N

H= High toxicity, N= no toxicity, Concentration 50 ppm; Weakly active: less than 10 mm, Moderately active: 11-20 mm, Highly active: more than 20mm.

Pharmacology

Toxicity (Brine Shrimp Test)

The isolated compounds were tested for toxicity using brine shrimp test (*Artimia salina* L.); all screened compounds had high toxicity to the brine shrimp larvae.

Antibacterial Test

In vitro antimicrobial activity of the tested compounds summarized in Table **1** revealed the following: compounds **3a-e** and **5a**, **5b**, **5d** showed moderate activity 11-20 mm against the two types of bacteria *Bacillus cereus*, *Staphylococcus albus* (Gram positive) and *Escherichia coli*, *Psedomonas aureginosa* (Gram negative), while compounds **7a-d** were proved to be highly active 20-30 mm on the same types of bacteria.

Antifungal Test

All the synthesized products were evaluated *in vitro* for their antifungal activity (dermatophytes fungi) and

revealed that compound **7d** displayed highest activity against *Trichophyton mentagrophytes and Trichophyton verrucosum.* Compounds **5a**, **5b**, **5d**, **7a**, **7b** and **7c** have moderate activity against two fungal strains, while compounds **3a-e** showed weekly activity.

CONCLUSION

Lawesson's Reagent is employed to generate new phosphorous heterocyclic compounds based chromene scaffold structures. Thus, compounds benzochromeno[2,3-d][1,3,2]thiaza-phosphinines **3a-f**, chromeno[2,3-d][1,3,2]thiazaphosphinin-8-ol **5a-d** and bisthiazaphosphinino[5'',4'':5',6']pyrano[3',2':6,7]chrome ne **7a-d** were synthesized in a satisfactory yield. Most of such compounds exhibited a good inhibitory effect against various microbial strains and observed evidently that all compounds bearing thiazaphosphinine moiety are displayed active. So the synthesized compounds must carry out for using in medical treatments.

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