Egypt.J.Chem. **Vol. 62**, No. 10. pp. 1949 - 1962 (2019)

Egyptian Journal of Chemistry
http://ejchem.journals.ekb.eg/

Synthesis and Antimicrobial Evaluation of New 2-Methylquinazolin-4(3H)-one Phosphorothioates

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A SERIES of new compounds characterized by presence of quinazoline scaffold and phosphorothioate moiety in their molecular structure, was prepared through reacting Japanese reagent (JR, **1a**) and Lawesson reagent (LR, **1b**) with quinazoline-4-ones (**3a-e**) in boiling toluene. The expected quinazoline-4-thiones were also formed and well identified. Molecular docking studies were performed to determine the molecular affinity between the new products and the target protein. The starting quinazolines and ten of the new products were *in vitro* evaluated as antimicrobial agents using Cephradine and Fluconazole as reference drugs for antibacterial and antifungal assays, respectively. Of particularly, the dioxathiaphosphinane (**12**) and benzoxaphospholylidene (**17**) exhibited 15% potent inhibition that equals to Cephradine against *Escherichia coli* strains.

Keywords: Japanese and Lawesson reagents, Quinazolines, Phosphorothioates, Antimicrobial activity.

Introduction

The potentialities of 2,4-bis(phenylthio)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Japanese reagent, JR, **1a**) and its 2,4-bis-(4-methoxy)-analogue (Lawesson reagent, LR, **1b**) as thiating agents have been tested among diverse classes of carbonyl compounds [1-4]. At high temperature, each reagent exists in an equilibrium with the corresponding monomeric species **2a,b** (Fig. 1) which allows them to undergo [2+4] cycloaddition with certain carbonyl compounds to produce interesting four and six-membered phosphorus heterocycles incorporating the O-P-S- grouping [5-8].

1 **2**

1,2	a	b
R	SC_6H_5	$4\text{-}OCH_3C_6H_4$

Fig. 1. Japanese and Lawesson reagents are in equilibria with their more reactive dithiophosphine ylide structures, in solution

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Received 5/4/2019; Accepted 28/4/2019
DOI: 10.21608/ejchem.2019.11548.1736

On another side, compounds belonging to the quinazolin-4-one class are considered as important heterocyclic templates by virtue of their long history of application, particularly in the field of medicinal chemistry since they are known to exhibit anti-microbial [9-11], anti-tumor [12-15], anti-inflammatory [16,17] as well as anti-malarial activities [18]. Thus, and in pursue of our growing interest in the realm of organophosphorus chemistry of heterocycles [7,8], we have now studied the behaviour of the 1,3-dithiaphosphetanes **1a**,**b** towards quinazolin-4-ones **3a-e** and **4a,b** (Fig. 2) and the product evaluation as anti-microbial agents.

Experimental

Chemistry

Melting points were determined in open glass capillaries using an Electrothermal IA 9100 series digital melting point apparatus (Electrothermal, Essex, U.K.). IR spectra were recorded (KBr pellets) on a Perkin-Elmer 1650 FT-IR spectrophotometer. The NMR spectra were recorded in $CDCl_3$ on a Joel spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C). Chemical shifts were recorded in δ ppm relative to TMS as internal reference. The coupling constants (*J*) are given in Hertz (Hz). Mass spectra were recorded at 70 eV on a JEOL JMS/AX-500 spectrometer.

General procedure for the synthesis of compounds 5-18

A mixture of equimolar amounts of the appropriate reactants was dissolved in 30 ml dry toluene and refluxed until TLC showed the completion of the reaction (1-2 h). Toluene was evaporated under reduced pressure and the remaining crude product was subjected to column chromatography, using the appropriate eluent to afford the target products. The starting compounds **3a-e** [19-23], **4a,b** [24] Japanese reagent (**1a**) [25] and Lawesson reagent (**1b**) [26] were prepared according to literature procedures. Compounds **5a**, **5d**, and **5e** have been reported in the literature [27-29] and the spectroscopic data are identical to those of the previously prepared, ones.

O-{3-Hydroxy-2-methyl-4-[(2-methyl-4-oxoquinazolin-3(4H)-yl)oxy]-3,4-dihydroquinazolin-4-yl} S-phenyl hydrogen phosphorotrithioate (7)

Chromatographic purification: petroleum ether (60-80)-acetone (75/25, v/v). Colorless crystals, yield 30 %, m.p. 226 ^oC; IR (KBr): 3406 (OH), 2359 (SH) 692 (O-C), 661 (P=S), 518 (P-S) cm^{-1}; ^1H NMR δ: 2.46 (1s, 6H, $2CH_3$), 7.56-7.49 (m, 5H, Ar), 7.81-7.70 (m, 4H, Ar), 8.15-8.11 (m, 4H, Ar), 12.55 (s, 1H, OH), 10.50 (s, 1H, SH); ^{13}C NMR δ: 24.5, 23.9 ($2CH_3$), 92.51(d, $^2J_{CP}$ = 35.9 Hz, C-4), 115.9, 120.8, 126.1, 126.7, 128.1, 128.7, 134.2, 147.0, 147.6, 155.1 (C, Ar), 162.7 (C=O);

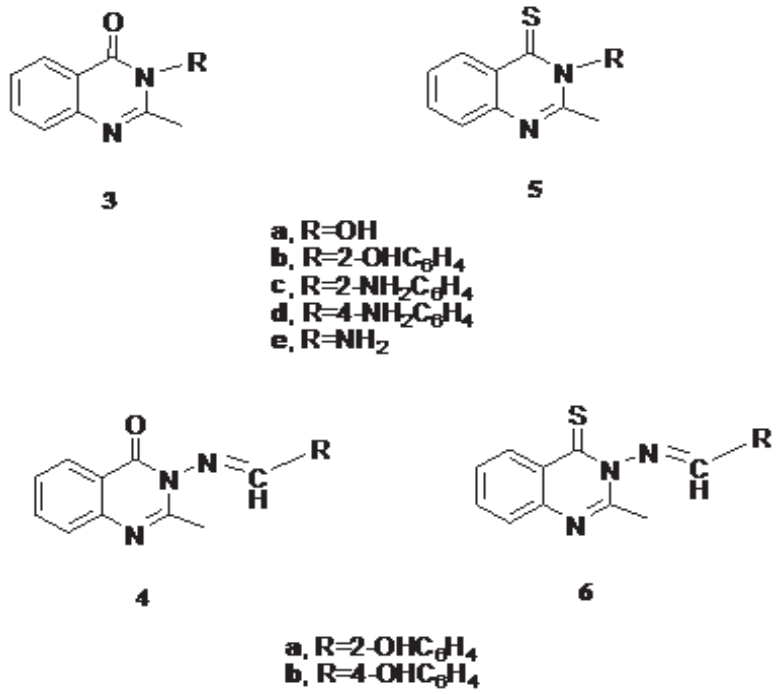


Fig. 2. Starting material: 3a-e and 4a, b; thionated products 5a-e, and 6a, b.

^{31}P NMR δ: -1.18; MS(EI): m/z 557 [M+H] (15 %); Anal. calcd for $C_{24}H_{21}N_4O_4PS_3$ (556.616): C, 51.79; H, 3.80, N 10.07; P, 5.56; S, 17.28 % ; Found: C, 51.79; H, 3.92; N, 10.17; P, 5.52; S, 17.10 %

O,O-Bis(2-methyl-4-thioxoquinazolin-3(4H)-yl) S-phenyl phosphorodithioate (8)

Chromatographic purification: petroleum ether (60-80)-acetone (85/15, v/v). Colorless crystals, yield 20 %, m.p. 256 °C; IR (KBr): 680 (P=S) cm^{-1}; ^{1}H NMR δ: 2.32 (s, 6H, CH_3), 6.79-7.00 (2d, 6H, J= 12 Hz, Ar), 7.47-7.39 (m, 2H, Ar), 7.77-7.63 (m, 4H, Ar), 8.23 (d, 1H, J= 12 Hz, Ar) ;^{13}C NMR δ: 24.2 ($2CH_3$), 115.9, 120.9, 126.1, 126.7, 128.1, 128.7, 134.2, 147.0, 147.3, 155.1 (C, Ar), 191.7 (C=S); ^{31}P NMR δ: -0.75; MS(EI): m/z 554 [M$^+$] (10 %); Anal. calcd for $C_{24}H_{19}N_4O_2PS_4$ (554.667): C, 51.97; H, 3.45; N, 10.10; P, 5.58; S, 23.12 %; Found: C, 51.97; H, 3.53; N, 10.15; P, 5.57; S, 23.15 %.

2-(4-Methoxyphenyl)-2'-methyl-3'H-spiro [1,3,2-oxathiaphos phetane-4,4'-quinazolin]-3'-ol 2-sulfide (9)

Chromatographic purification: petroleum ether (60-80)-acetone (85/15, v/v). Colorless crystals yield 35 %, m.p. 259 °C ; IR (KBr): 3400 (OH), 1627 (C=C), 664 (P=S) cm^{-1} ; ^{1}H NMR δ: 3.00 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.94-7.00 (d, 2H, J= 12 Hz, Ar), 7.71-7.83 (m, 4H, Ar), 7.97-7.99 (d, 1H, J= 8Hz, Ar), 8.35-8.29 (d, 1H, J= 8Hz, Ar), 9.99-9.98 (br, 1H, OH); ^{13}C NMR δ: 24.3 (CH_3), 53.9 (OCH_3), 91.8 (d, $^2J_{CP}$ = 30 Hz, C-4), 115.7, 120.9, 123.1, 126.4, 127.1, 128.1, 129.0, 147.6, 155.1, 162.7 (C, Ar); ^{31}P NMR δ:50.59; MS(EI): m/z 378 [M$^+$] (70 %); Anal. calcd for $C_{16}H_{15}N_2O_3PS_2$ (378.405): C, 50.78; H, 4.00; N, 7.40; P, 8.19; S, 16.95 % ; Found: C, 50.69; H, 4.15; N, 7.48; P, 8.11; S, 16.90 %.

2-(4-Methoxyphenyl)-2'-methyl-3'H-spiro[1,3,2-dithiaphosphetane-4,4'-quinazolin]-3'-ol 2-sulfide (10)

Chromatographic purification: petroleum ether (60-80)-acetone (80/20, v/v). Colorless crystals, yield 55 %, m.p. 275 °C ; IR (KBr): 3401 (OH), 1627 (C=C), 668 (P=S) cm^{-1} ; ^{1}H NMR δ: 3.07 (s, 3H, CH_3), 3.96 (s, OCH_3), 7.05-7.00 (d, 2H, J= 8 Hz, Ar), 7.90-7.76 (m, 4H, Ar), 8.09-8.05 (m, 1H, Ar), 8.42-8.39 (d, 1H, J= 8 Hz, Ar), 10.26-10.29 (br, 1H, OH); ^{13}C NMR δ: 24.3 (CH_3), 55.3 (OCH_3), 67.35 (d, $^2J_{CP}$ = 36 Hz, C-4), 116.2, 120.8, 126.1, 127.1, 128.1, 129.0, 134.2, 147.6, 155.1, 162.7 (C, Ar); ^{31}P NMR δ: 52.76; MS(EI): m/z 395 [M+H] (15 %); Anal. calcd for $C_{16}H_{15}N_2O_2PS_3$ (394.471): C, 48.72; H, 3.83; N, 7.10; P, 7.85; S, 24.39 %; Found: C, 48.67; H, 3.75; N, 7.22; P, 7.80; S, 24.44 %.

3-(2-Hydroxyphenyl)-2-methylquinazoline-4(3H)-thione (5b)

Chromatographic purification: petroleum ether (60-80)-ethyl acetate (90/10, v/v). Yellow crystals, yield 60 %, m.p. 270 °C ; IR (KBr): 3470 (OH), 1152 (C=S), 1630 (C=C) cm^{-1} ; ^{1}H NMR δ: 2.61 (s, 3H, CH_3), 7.78-7.79 (m, 2H, Ar), 7.85-7.84 (m, 1H, Ar), 8.10-8.08 (m, 3H, Ar), 8.42-8.40 (m, 2H, Ar), 11.49 (s, 1H, OH) ; ^{13}C NMR δ: 17.9 (CH_3), 110.8, 113.0, 116.3, 119.2, 119.8, 127.1, 130.3, 130.6, 131.6, 137.5, 155.5 (C, Ar), 185.5 (C=S); MS(EI): m/z 269 [M+H] (85 %); Anal. calcd for $C_{15}H_{12}N_2OS$ (268.333):C, 67.14; H, 4.51; N, 10.44; S, 11.95 %; Found: C, 67.28; H, 4.32; N, 10.32; S, 11.82 %

O-[2-(2-Methyl-4-thioxoquinazolin-3(4H)-yl) phenyl] S-phenyl hydrogen phosphorotrithioate (11)

Chromatographic purification: petroleum ether (60-80)-ethyl acetate (30/70, v/v). Colorless crystals, yield 25 %, m.p. 285 °C; IR (KBr): 2375 (SH),1627 (C=C) cm^{-1} ; ^{1}H NMR δ: 2.68 (s, H, CH_3), 6.79-6.77 (m, 3H, Ar), 7.56-7.58 (m, 3H, Ar), 7.77-7.71 (m, 5H, Ar), 8.24-8.21 (m, 2H, Ar), 12.20 (S, 1H, SH); ^{13}C NMR δ: 29.2 (CH_3), 114.7, 115.5, 120.8, 123.1, 124.8, 127.4, 131.3, 132.3, 134.9, 135.2, 161.1 (C, Ar), 155.1 (d, $^2J_{CP}$ = 30.0 Hz, C-O-P), 191.1 (C=S); MS (EI): m/z 472 [M$^+$] (45 %); Anal. calcd for $C_{21}H_{17}N_2OPS_4$ (472.606): C, 53.37; H, 3.63; N, 5.93; P, 6.55; S, 27.14 %; Found: C, 53.21; H, 3.49; N, 5.86; P, 6.60; S, 27.18 %

3-(2-Aminophenyl)-2-methylquinazoline-4(3H)-thione (5c)

Chromatographic purification: petroleum ether (60-80)-ethyl acetate (90/10, v/v). Yellow crystals, yield 45 %, m.p. 180 °C; IR (KBr): 3250 (NH_2), 1150 (C=S) cm^{-1} ; ^{1}H NMR δ: 2.57 (s, 3H, CH_3), 4.23-4.19 (br, 2H, NH_2), 7.48-7.45 (m, 2H, Ar), 7.76-7.66 (d, 4H, Ar), 8.27-8.26 (m, 2H, Ar); ^{13}C NMR δ: 17.9 (CH_3), 110.1, 113.0, 116.0, 118.9, 119.8, 127.1, 130.0, 131.3, 132.3, 137.2, 155.5 (C, Ar), 185 (C=S); MS (EI): m/z 267 [M$^+$] (80 %); Anal. calcd for $C_{15}H_{13}N_3S$ (267.348): C, 67.39; H, 4.90; N, 15.72; S, 11.99 % ; Found: C, 67.26; H, 4.82; N, 15.64; S, 11.80 %

3,3''-Bis(2-aminophenyl)-2,2''-dimethyl-2'-(phenylthio)-3H,3''H-dispiro[quinazoli

ne-4,4'[1,5,3,2]dioxathiaphosphinane-6',4''-quinazoline]2'-sulfide (12)

Chromatographic purification: petroleum ether (60-80)-acetone (65/35, v/v). Colorless crystals, yield 30 %, m.p. 265 °C; IR (KBr): 3248 (NH_2), 670 (P=S) cm^{-1} ; ^1H NMR δ: 2.68, 2.83 (2s, 6H, $2CH_3$), 4.10 (br, 4H, $2NH_2$), 6.89-6.91 (m, 5H, Ar), 7.52-7.56 (m, 3H, Ar), 7.71-7.82 (m, 10H, Ar), 8.20-8.24 (m, 3H, Ar); ^{13}C NMR δ: 24.5, 23.3 ($2CH_3$), 104.55 (d, $^2J_{CP}$ = 37 Hz, C-O), 115.3, 116.2, 120.8, 126.4, 127.1, 128.1, 128.7, 134.2, 135.2, 136.5, 147.0, 154.2, 155.1, 163.0, 164.6 (C, Ar); ^{31}P NMR δ: 105.73; MS(EI): m/z 706 [M^+] (8 %); Anal. calcd for $C_{36}H_{31}N_6O_2PS_3$ (706.839): C, 61.17; H, 4.42; N, 11.89; P, 4.38; S, 13.61 %; Found: C, 61.23; H, 4.30; N, 11.76; P, 4.29; S, 13.58 %

O-(3-(2-Aminophenyl)-2-methyl-4-((2-(2-methyl-4-thioxoquinazolin-3(4H)-yl) phenyl)amino)-3,4-dihydroquinazolin-4-yl) S-phenyl S-hydrogen phosphorotrithioate (13)

Chromatographic purification: petroleum ether (60-80)-acetone (30/70, v/v). Colorless crystals, yield 60 %, m.p. 267 °C ; IR (KBr): 3200 (NH_2), 2370 (SH), 650 (P=S) cm^{-1} ; ^1H NMR δ: 2.68, 2.83 (2s, 6H, $2CH_3$), 4.02 (br, 2H, NH_2), 6.80-6.75 (m, 1H, Ar), 6.94-6.91 (m, 5H, Ar), 7.22 (s, 1H, Ar), 7.56-7.50 (m, 2H, Ar), 7.71-7.84 (m, 10H, Ar), 8.20-8.24 (m, 2H, Ar), 7.36 (s, 1H, NH), 9.76 (s, 1H, SH); ^{13}C NMR δ: 22.9, 24.2 ($2CH_3$), 101.0 (d, $^2J_{CP}$ = 66.9 Hz, C-4) , 115.9, 120.5, 126.1, 127.4, 128.1, 128.7, 134.2, 136.5, 147.0, 147.3, 155.1, 155.5, 162.7 (C, Ar), 191.7(C=S); ^{31}P NMR δ: -1.80 ; MS (EI): m/z 722 [M^+] (13 %); Anal. calcd for $C_{36}H_{31}N_6OPS_4$ (722.904): C, 59.81; H, 4.32; N, 11.63; P, 4.28; S, 17.74 % ; Found: C, 59.72; H, 4.40; N, 11.70; P, 4.30; S, 17.65 %

4-[2'-Methyl-2-(phenylsulfanyl)-2-sulfido-3'H-spiro[1,3,2-oxathiaphosphetane-4,4'-quinazolin]-3'-yl]aniline (14)

Chromatographic purification: petroleum ether (60-80)-acetone (85/15, v/v). Colorless crystals, yield 60 %, m.p. 241 °C; IR (KBr): 3260 (NH_2), 660 (P=S) cm^{-1} ; ^1H NMR δ: 2.54 (s, 3H, CH_3), 4.35-4.37 (br, 2H, NH_2), 6.69-7.10 (m, 6H, Ar), 7.15-7.19 (m, 7H, Ar); ^{13}C NMR δ:17.9 (CH_3), 92.5 (d, $^2J_{CP}$ = 30.0Hz, C-4), 110.4, 113.3, 116.0, 119.2, 119.8, 126.7, 130.3, 130.6, 131.6, 137.9, 155.5, 160.0, 160.7 (C, Ar); ^{31}P NMR δ: 57.11 ; MS (EI): m/z 456 [M+H] (15 %); Anal. calcd for $C_{21}H_{18}N_3OPS_3$ (455.555): C,55.37; H,3.98; N, 9.22; P, 6.80; S, 21,12 %; Found: C, 55.42; H, 3.89; N, 9.18; P, 6.82; S, 21.02 %

O-(3-(4-Aminophenyl)-2-methyl-4-((4-(2-methyl-4-oxoquinazolin-3(4H)-yl) phenyl) amino)-3,4-dihydroquinazolin-4-yl) S-phenyl S-hydrogen phosphorotrithioate (15)

Chromatographic purification: petroleum ether (60-80)-acetone (85/15, v/v). Colorless crystals, yield 60 %, m.p. 256 °C ; IR (KBr): 3200 (NH_2), 2373 (SH), 1627 (C=C), 650 (P=S) cm^{-1}; ^1H NMR δ: 2.68, 2.83 (2s, 6H, $2CH_3$), 4.02-4.06 (br, 2H, NH_2), 6.91-6.89 (m, 5H, Ar), 8.21-7.82 (m, 3H, Ar), 7.50-5.56 (m, 3H, Ar), 7.82-7.71 (m, 10H, Ar), 5.20 (s, 1H, NH), 9.67 (s, 1H, SH); ^{13}C NMR δ: 24.2, 24.0 ($2CH_3$), 102.6 (d, $^2J_{CP}$ = 30.0 Hz, C-4), 115.9, 120.8, 126.4, 126.7, 128.1, 128.7, 133.9, 134.9, 147.0, 155.1 (C, Ar), 162.7 (C=O); ^{31}P NMR δ:0.34; MS (EI): m/z 671 [M-H_2S] (80 %); Anal. calcd for $C_{36}H_{31}N_6O_2PS_3$ (706.839): C, 61.17; H, 4.42; N,11.89; P, 4.38; S, 13.61 % ; Found: C, 61.30; H, 4.36; N, 11.80; P, 4.31; S, 13.54 %

2,2''-Dimethyl-3H,3''H-dispiro[quinazoline-4,2'-[1,3]dithietane-4',4''-quinazoline]-3,3''-diamine (16)

Chromatographic purification: petroleum ether (60-80)-acetone (85/15, v/v). Colorless crystals, yield 60 %, m.p. 185 °C; IR (KBr): 3410 (NH_2), 1617 (C=C) cm^{-1}; ^1H NMR δ: 2.61 (s, 6H, $2CH_3$), 7.50-7.52 (m, 2H, Ar), 7.77-7.74 (m, 4H, Ar), 8.70-8.71 (m, 2H, Ar), 11.49-12.50 (br, 4H, $2NH_2$); ^{13}C NMR: 21.9 ($2CH_3$), 96.4, 127.4, 127.7, 128.4, 128.4, 135.6, 144.7, 150.9 (C, Ar); MS(EI): m/z 382 [M^+] (20 %); Anal. calcd for $C_{18}H_{18}N_6S_2$ (382.506): C, 56.52; H, 4.74; N, 21.97; S, 16.77 %; Found: C, 56.45; H, 4.67; N, 21.90; S, 16.71 %.

3-[(2-Hydroxybenzylidene)amino]-2-methylquinazoline-4(3H)-thione (6a)

Chromatographic purification: petroleum ether (60-80)-acetone (65/35, v/v). Yellow crystals, yield 55 %, m.p. 230 °C ; IR (KBr): 3450 (OH), 1627 (C=C) cm^{-1} ; ^1H NMR δ: 2.73 (s, H, CH_3), 7.09-7.02 (m, 2H, Ar), 7.41-7.40 (d, 1H, Ar), 7.49-7.48 (d, 1H, Ar), 7.55-7.53 (m, 2H, Ar), 7.81-7.79 (t, 1H, J= 1.2 Hz, Ar), 8.33-8.31 (d, 1H, J= 8 Hz, Ar), 9.03 (s, 1H, =CH), 10.71 (s, 1H, OH); MS (EI): m/z 295 [M^+] (80 %); Anal. calcd for $C_{16}H_{13}N_3OS$ (295.359): C, 65.06; H, 4.44; N, 14.23; S, 10.86 % ; Found: C, 65.16; H, 4.34; N, 14.20; S,10.82 %.

3-{[(3E)-2-(4-methoxyphenyl)-2-sulfido-1,2-benzoxaphosphol-3(2H)-ylidene]amino}-2-methylquinazoline-4(3H)-thione (17)

Chromatographic purification: petroleum

ether (60-80)-acetone (65/35, v/v). Yellow crystals, yield 55 %, m.p. 230 °C ; IR (KBr): 1495 (C=N), 1246 (C-OCH3), 655 (P=S) cm^{-1}; ^{1}H NMR δ: 2.77 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 6.69-6.73 (m, 2H, Ar), 7.26-7.19 (m, 4H, Ar); 7.74-7.82 (m, 5H, Ar), 8.28-8.30 (m, 1H, Ar), ^{13}C NMR δ: 17.9 (CH_3), 53.6 (OCH_3), 113.3, 116.3, 118.9, 119.8, 126.7, 130.3, 130.6, 132.0, 137.5, 154.8, 155.1, 155.5 (C, Ar), 185.5 (C=S); ^{31}P NMR δ: +22.2; MS (EI): m/z 463 [M^+] (10 %); Anal. calcd for $C_{23}H_{18}N_3O_2PS_2$ (463.511); C, 59.60; H, 3.91; N, 9.07; P, 6.68; S, 13.84 %; Found: C, 59.65; H, 3.83; N, 9.16; P, 6.60; S, 13.81 %

3-[(4-Hydroxybenzylidene)amino]-2-methylquinazoline-4(3H)-thione (6b)

Chromatographic purification: petroleum ether (60-80)-acetone (65/35, v/v). Yellow crystals, yield 55 %, m.p. 272 °C; IR (KBr): 3510 (OH), 1617 (C=C) cm^{-1}; ^{1}H NMR δ: 2.74 (s, H, CH_3), 7.10-7.03 (m, 1H, Ar), 7.43-7.41 (m, 2H, Ar), 7.54-7.52 (m, 2H, Ar), 7.81-7.79 (m, 2H, Ar), 8.33-8.34 (m, 1H, Ar), 9.04 (s, 1H, =CH), 10.67 (s, 1H, OH); MS (EI): m/z 295 [M^+] (80 %); Anal. calcd for $C_{16}H_{13}N_3OS$ (295.358): C, 65.06; H, 4.44; N, 14.23; S, 10.86 % ; Found: C, 65.16; H, 4.34; N, 14.20; S, 10.82 %.

(E)-O-4-((2-methyl-4-oxoquinazolin-3(4H)-ylimino) methyl)phenyl S-hydrogen 4-methoxyphenylphosphonodithioate (18)

Chromatographic purification: acetone-methanol (95/5, v/v). Colorless crystals, yield 40 %, m.p. 287 °C; IR (KBr): 2320 (SH), 1720 (C=O), 645 (P=S) cm^{-1}; ^{1}H NMR: 2.68 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.92-6.88 (m, 3H, Ar), 7.54, 7.52 (m, 2H, Ar), 7.79-7.73 (m, 5H, Ar), 8.26-8.21 (m, 2H, Ar), 8.63 (s, 1H, =CH), 12.00-12.02 (br, 1H, SH); ^{13}C NMR δ: 29.48 (CH_3), 54.20 (OCH_3), 115.0, 115.9, 120.5, 123.1, 124.4, 127.7, 128.7, 135.2, 135.5, 144.0, 155.5, 158.0, 160.3, 162.3 (C, Ar), 169.1 (C=O); ^{31}P NMR δ: +94.9; MS (EI): m/z 481 [M^+] (60 %); Anal. calcd for $C_{23}H_{20}N_3O_3PS_2$ (481.527): C, 57.37; H, 4.19; N, 8.73; P, 6.43; S, 13.32 %; Found: C, 57.26; H, 4.09; N, 8.61; P, 6.28; S, 13.40 %.

Biology

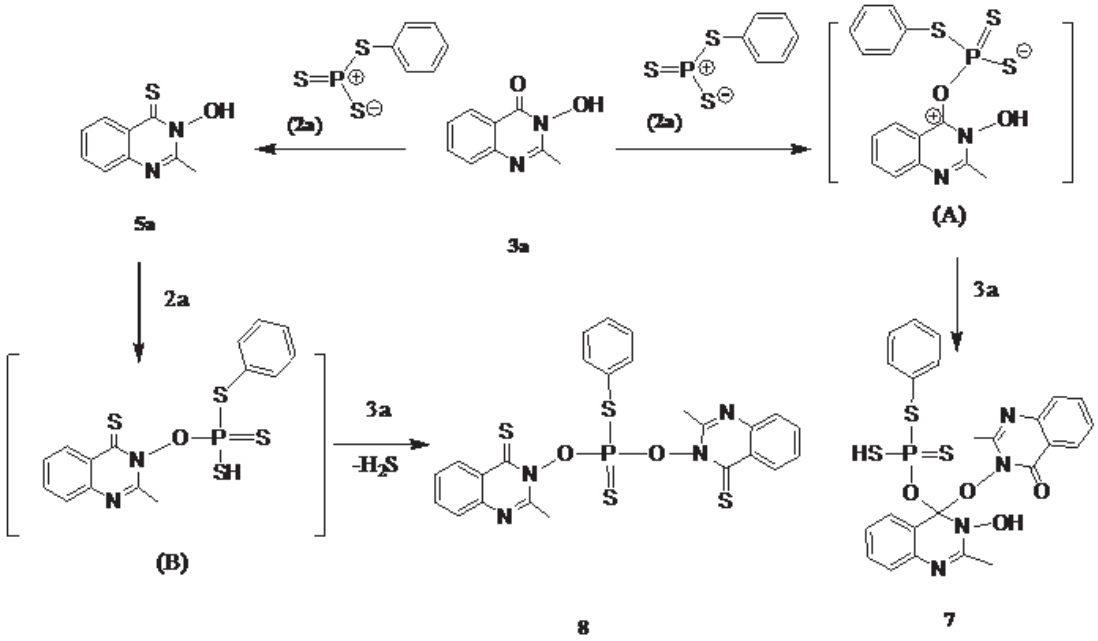
The antibacterial and antifungal activities were carried out in the Department of Microbial Chemistry, National Research Centre, using the diffusion plate method. A filter paper sterilized disc saturated with a measured quantity (25 µl) of the sample (1 mg/ml) is placed on a plate (9 cm diameter) containing a solid bacterial medium (nutrient agar) or a fungal medium (potato dextrose agar) which has been seeded with the spore suspension of the test organism. After incubation at 37 °C for 24 h for bacteria (in case of fungi, at 25 °C for 72 h), the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism (% inhibition = sample inhibition zone (cm)/plate diameter x 100). All measurements were done in DMSO as a solvent which has zero inhibition activity. The antimicrobial activity of the tested compounds were examined with Gram-positive bacteria *(Bacillus cereus* and *Staphylococcus aureus* ATCC 653), Gram-negative bacteria *(Escherichia coli* NRRN 3008 and *Pseudomonas aeruginose* ATCC 10145) and *fungus (Candida albicans* EMCC105). The obtained results are compared with the reference antibiotic Cephradine and Fluconazale that were purchased from Egyptian markets.

Results and Discussion

Chemistry

The Japanese reagent **(JR, 2a)** reacted with 3-hydroxy-2-methylquinazolin-4(3*H*)-one **3a** in refluxing toluene to give a mixture of the expected quinazoline thione **5a,** phosphorotrithioate **7** and the phosphorodithioate derivative **8** which were separated and purified by column chromatography. Compatible microanalytical and spectral analyses were gained for these products (cf. Experimental). The IR spectrum of compound **7** (KBr, cm^{-1}) revealed absorption bands at *v* 3406 (OH, free), 3259 (SH), 661 (P=S) and at 518 cm^{-1} (P-O-C) [30]. The ^{13}C NMR spectrum of **7** showed the phosphorotrithioate, P-O-C-O- carbon [31], at δc = 92.51 ppm; ^{2}Jcp = 35.9 Hz. Moreover, its ^{31}P NMR spectrum showed a negative shift ($\delta p_{=}$ -1.18 ppm) confirming thus a phosphorotrithioate structure [32]. The formation mechanism for compounds **7** and **8** is outlined in scheme 1.

Moreover**,** 2-(4-methoxyphenyl)-2'-methyl-3'H-spiro[1,3,2-oxathiaphosphetane-4,4'-quinazolin]-3'-ol 2-sulfide **9** and 2-(4-methoxyphenyl)-2'-methyl-3'*H*-spiro[1,3,2-dithiaphosphetane-4,4'-quinazolin]-3'-ol 2-sulfide **10** were produced through reaction of Lawesson reagent (LR, **2b)** with quinazolinone **3a** (Scheme 2). Spiro-structures of these compounds are supported by ^{1}H, ^{13}C and ^{31}P NMR spectral data. Compounds **9** and **10** are characterized by presence of signals at $\delta p_{=}$ 50.59 and 52.76 ppm,



Scheme 1. The proposed reaction mechanism for the synthesis of phosphorotrithioate (7) and phosphorodithioate (8)

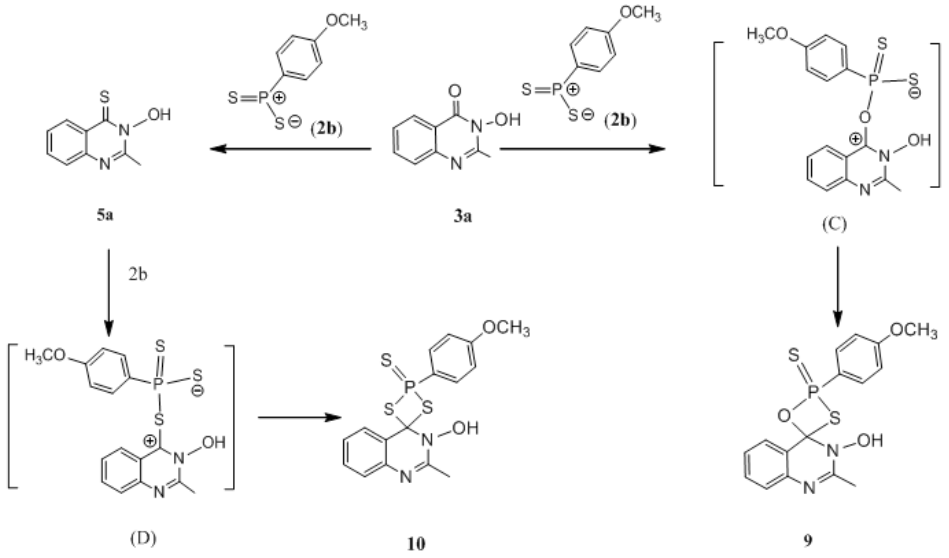
respectively in their ^{31}P NMR spectra, confirming the spiro structure [33]. Formation of compounds, **9** and **10** is assumed to proceed *via* electrophilic attack of the monomeric form of LR, **2b** on the carbonyl function in **3a** or the thiocarbonyl function of its thione **5e**, respectively, followed by ring closure to give oxathiaphosphetane **9** and dithiaphosphetane **10** (Scheme 2).

On the other hand, when JR**,** **1a** (its monomeric species **2a**) was allowed to react with 3-(2-hydroxyphenyl)-2-methylquinazolin-4(3H)-one **3b** in boiling toluene, it afforded a mixture of 3-(2-hydroxyphenyl)-2-methylquinazoline-4(3H)-thione **5b** and *O*-[2-(2-methyl-4-thioxoquinazolin-3(4*H*)-yl)phenyl] *S*-phenyl hydrogen phosphorotrithioate **11** (Scheme 3). Meanwhile, ^{13}C NMR spectrum of **11** exhibited signals at δc = 191.1 and δ_C = 29.5 ppm, which are assigned to carbons of C=S and CH_3 groups, respectively. Moreover, its EI/MS spectrum showed the molecular ion peak at m/z 472 (M^+, $C_{21}H_{17}N_2OPS_4$, 75%).

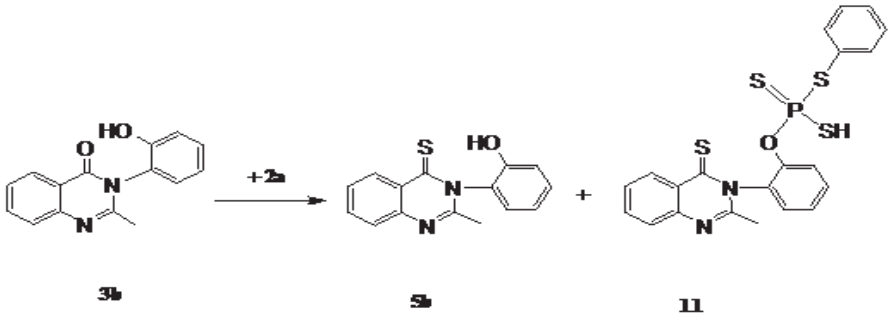
Furthermore, Japanese reagent **2a** reacted with the substituted 3-(2-aminophenyl)-2-methylquinazoline-4(3H)-thione **3c** to produce the 3-(2-aminophenyl)-2-methylquinazoline-4(3*H*)-thione **5c** and the dipolar intermediate (**E**) which in turn reacted with another molecule of the quinazoline **3c** and/or quinazoline thione **5c**, generating 3,3''-bis(2-aminophenyl)-2,2''-dimethyl-2'-(phenylthio)-3*H*,3''*H*-dispiro[quinazoline-4,4'-[1,5,3,2]dioxathiaphosphinane-6',4''-quinazoline]2'-sulfide **12** that possess δ_P = 105.7 [34] and *O*-(3-(2-aminophenyl)-2-methyl-4-((2-(2-methyl-4-thioxoquinazolin-3(4H)-yl)phenyl) amino)-3,4 dihydroquina zolin-4-yl) S-phenyl S-hydrogen phosphorotrithioate **13**. (Scheme 4).

Meanwhile, 3(4-aminophenyl)-2-methyl-quinazolin-4(3*H*)-one **3d** reacted with **2a** in boiling toluene to yield the corresponding thione **5d** together with oxathiaphosphetane **14** and the phosphorotrithioate **15**. The ^{13}C NMR spectrum of compound **14** exhibited signals at δc = 17.9 and δc 92.5 = ppm, corresponding to (CH_3) and (O-C-S) carbon atoms, respectively. ^{31}P NMR spectrum showed δp = 57.11 ppm that confirms the spiro-structure of **14** [33]. The structure of phosphorotrithioate (**15**) was proven from its microanalyses, IR, 1H, ^{13}C NMR, and mass spectra. The IR spectrum of compound **15** exhibited of SH band at *v* 2373 and NH_2 band at *v* 3200. Moreover, 3-Amino-2-methyl- quinazolin-4(3*H*)-one **3e** reacted also with **2b** in boiling toluene to give yellow crystals of 3-amino-2-methyl-quinazolin-4(3*H*)-thione **5e** and the dimeric product **16** (Scheme 5).

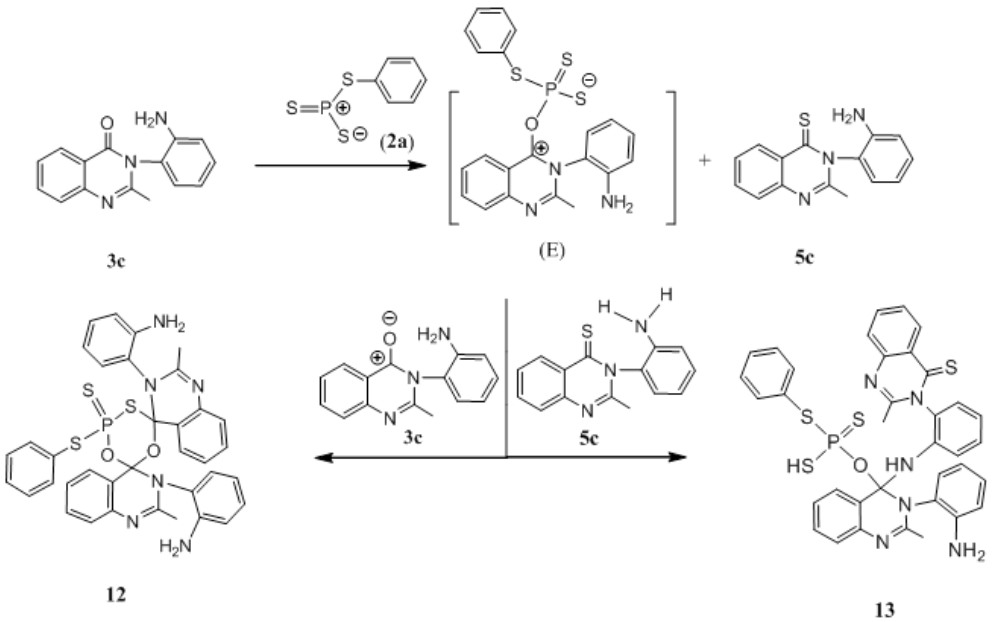
The Schiff bases **4a,b** reacted with LR, **2b** yielding 3-{[(3E)-2-(4-methoxyphenyl)-



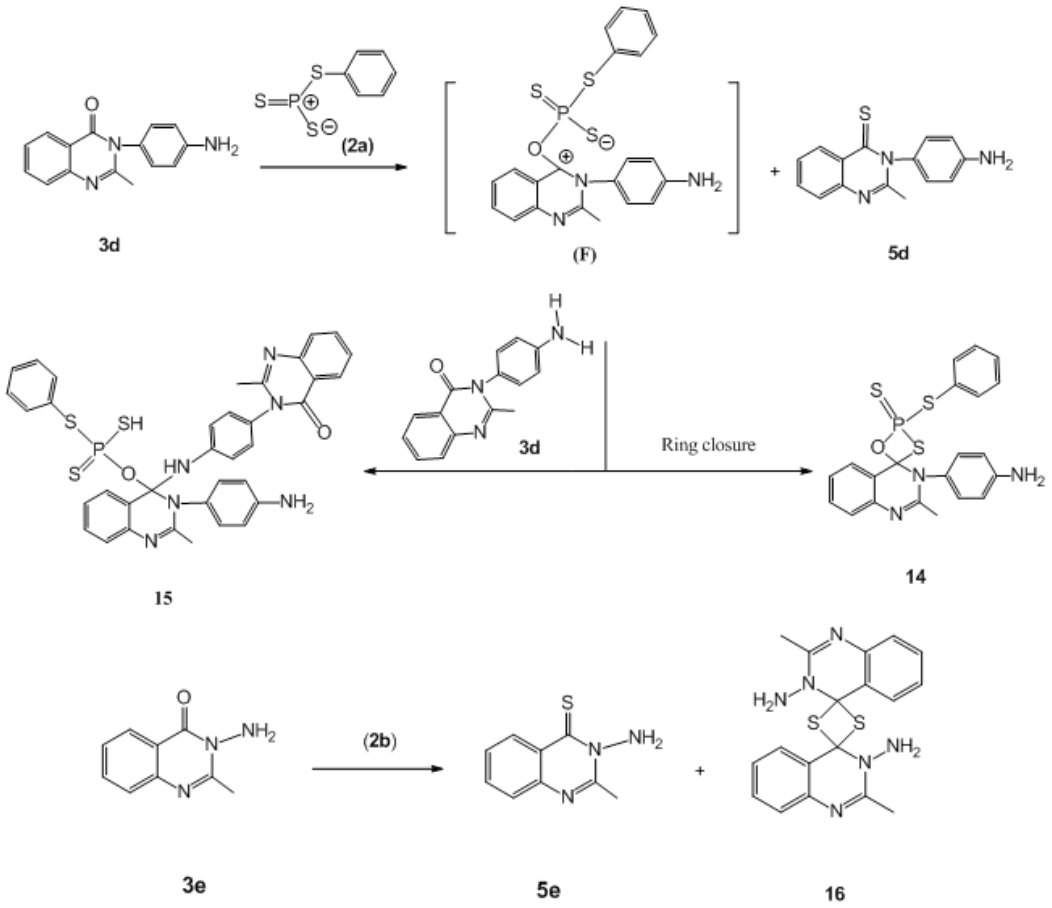
Scheme 2. The proposed mechanism for synthesis oxathiaphosphetane (9) and dithiaphosphetane (10)



Scheme 3. Synthesis quinazoline thione (5b) and phosphorotrithioate 11



Scheme 4. The proposed reaction mechanism for synthesis of quinazoline thione (5c), dioxathiaphosphinane (12) and phosphorotrithioate (13)

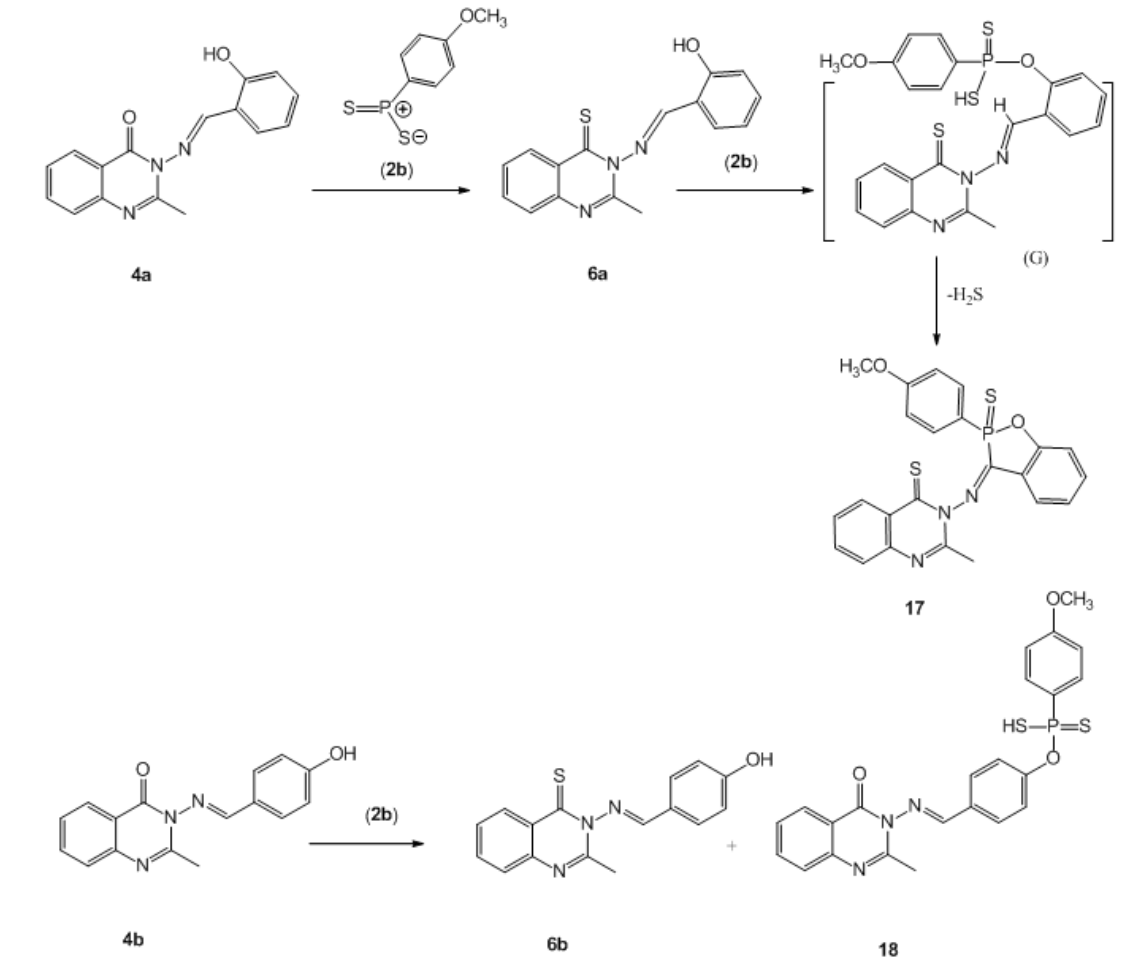


Scheme 5. Synthesis of oxathiaphosphetane (14), phosphorotrithioate (15) and ditheitane (16)

2-sulfido-1,2-benzoxaphosphol-3(2H)-ylidene] amino}-2-methylquinazoline-4(3H)-thione **17** and (*E*)-*O*-4-((2-methyl-4-oxoquinazolin-3(4H)-ylimino) methyl)phenyl S-hydrogen 4-methoxyphenylphosphonodithioate **18** in addition to the thionated products **6a,b** (Scheme 6). The ^{31}P NMR spectrum of benzoxaphospholylidene, **17** recorded a signal at δp = +22.2 ppm [35] and its ^{13}C NMR spectrum exhibited δc = 185.5 ppm (C=S). Regarding compound **18**, ^{31}P NMR spectrum showed a positive shift at δp =+94.9 ppm which is consistent with the assigned phosphonodithioate phosphorus atom [36].

Docking studies

Docking studies were performed to assess the molecular affinity between the tested compounds and the target protein. Determination of the consistent receptor was based on previous studies [37]. The crystallographic structure of the protein (PDBs) was obtained from the protein data bank. Macromolecule file (PDB code: 2opo and 3pte, Fig. 3a, b respectively) was modified using the ADT (Auto Dock Tools) package. Docking studies were performed on compounds **7, 9, 12, 14, 15, and 18** to assess their affinity to the binding proteins of the cell wall. All docking experiments were performed by the auto-dock tool. The current docking results showed that compounds **12** and **14** have the highest affinity as they recorded values of -4.3 and -4.7 kcal/mol, respectively. Meanwhile, compounds **7, 9, 15** and **18** have the lowest binding affinity which is congruent with the inhibition clear zone values. The docking studies show that there are interactions between compound **12** and **14** which have the highest binding affinity due to their interactions with basic amino acid residues through hydrogen bonds (Fig. 4a, b). The presence of asparagine (Asn81) and lysine (Lys80) suggest stabilization of the protein-ligand complex. The compound binding is near the active site of the protein which suggests its potential effect. Therefore, compounds **12** and **14** may have the most potent antimicrobial activity.



Scheme 6. The proposed reaction mechanism for synthesis benzoxaphospholylidene (17) and phosphonodithioate (18) from the reaction of quinazolinone (4a,b) with Lawesson reagent (2b)

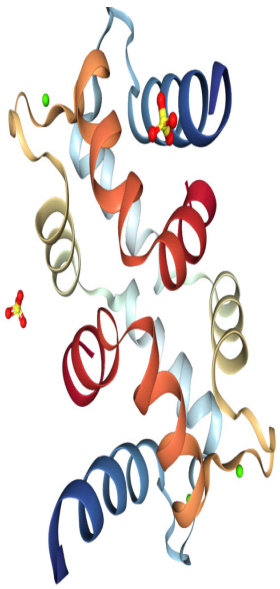


Fig. 3a. Three-dimensional structure of cell wall proteins (PDB ID: 2opo)

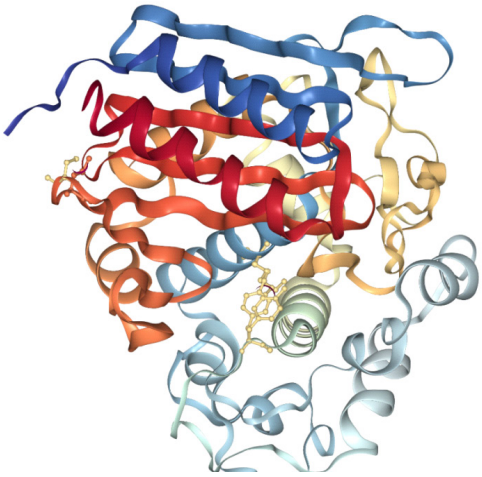


Fig. 3b. Three-dimensional structure of cell wall proteins (PDB ID: 3pte)

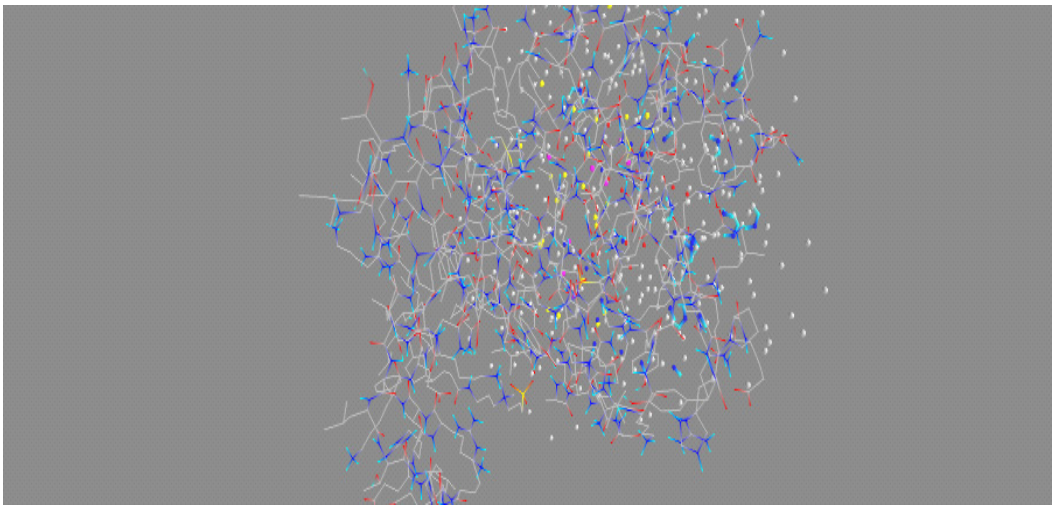


Fig. 4a. Molecular docking of compound 12 and cell wall proteins.

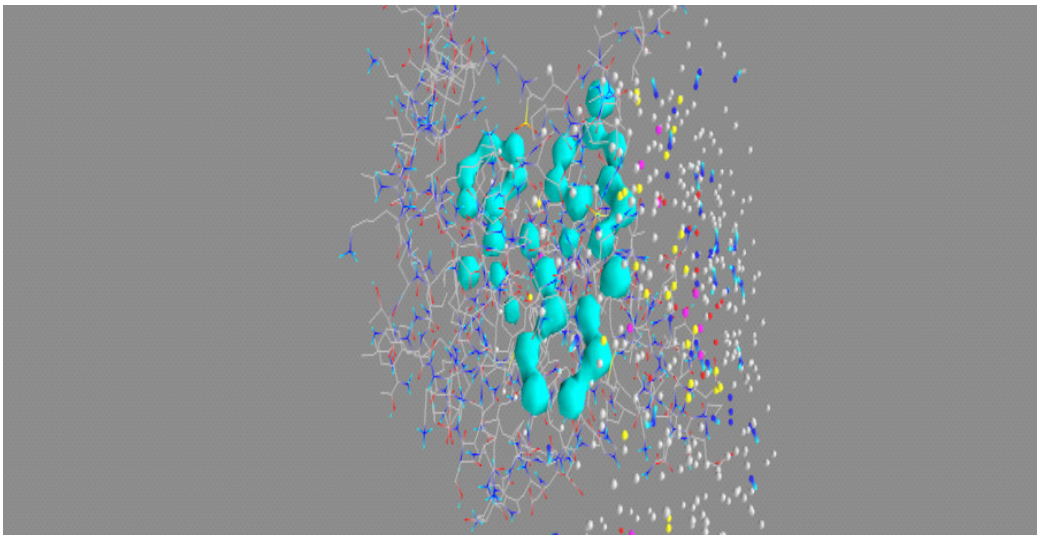


Fig. 4b. Molecular docking of compound 14 and cell wall proteins.

Biological Activity

The *in vitro* antimicrobial screening of 16 compounds was carried out against different Gram-positive (*Bacillus cereus* and *staphylococcus aureus* ATCC 6538), Gram-negative (*Escherichia coli* NRRN 3008 and *pseudomonas aeruginose* ATCC 10145) bacteria, as well as against the *Candida Albicans* fungi, compared to Cephradine and Fluconazole as references for antibacterial and antifungal activities, respectively (Table 1).

As depicted from Table 1, compounds **4a**, **12** and **14** revealed broader spectrum of activity against all the tested organisms as compared to those of other compounds. Concerning Gram-positive bacteria, compounds **5d**, **12** and **14** were the most active as *Bacillus Cereus* inhibitors, showing 15% inhibition, whereas **3a**, **4a**, **5d** and **17** showed a remarkable inhibition in case of *Staphylococcus Aureus* strains, with 14% inhibition (for **3a** and **5a**) and 15% (for **4a** and **17**), compared to the reference drug, Cephradine (30%). Regarding Gram-negative bacteria, compounds **5d** and **16** demonstrated high activities among the tested samples, exhibiting 15% inhibition against strains of *Pseudomonas Aeruginosas*, versus to 20% inhibition of Cephradine. Interestingly, compounds **12** and **17** displayed a significant inhibition against *Escherichia Coli* strains with 15%, which is the

TABLE 1. The obtained results revealed that the tested compounds had different antimicrobial responses

Microorganism	Gram Stain Reaction	Inhibition Clear Zone (mm)						
		Compound No					Reference antibiotic	
		3	a3	d3 5d	c3	e	Cephradine	Fluconazole
Bacillus cereus	Positive	7	8	0	13	15	30	-
Escherichia coli	Negative	14	12	11	0	0	15	-
Pseudomonas aeruginosa	Negative	0	0	0	10	15	20	-
Staphylococcus aureus	Positive	14	0	0	10	14	30	-
Candida albicans	Yeast	0	0	0	12	12	-	35

Microorganism	Gram Stain Reaction	Inhibition Clear Zone (mm)								
		Compound No							Reference antibiotic	
		5	a11	9 a17	12	7			Cephradine	Fluconazole
Bacillus cereus	Positive	11	11	15	0	0	0	0	30	-
Escherichia coli	Negative	0	0	15	12	12	13	15	15	-
Pseudomonas aeruginosa	Negative	8	0	12	10	9	0	0	20	-
Staphylococcus aureus	Positive	8	8	13	0	10	0	15	30	-
Candida albicans	Yeast	15	12	12	0	12	0	10	-	35

Microorganism	Gram Stain Reaction	Inhibition Clear Zone (mm)						
		Compound No					Reference antibiotic	
		4	b4	14	16	a	Cephradine	Fluconazole
Bacillus cereus	Positive	10	12	15	10		30	-
Escherichia coli	Negative	11	0	12	12		15	-
Pseudomonas aeruginosa	Negative	0	15	10	12		20	-
Staphylococcus aureus	Positive	10	0	12	15		30	-
Candida albicans	Yeast	8	15	15	12		-	35

same as Cephradine (15%). On the other hand, compounds **5a**, **14** and **16** showed activity against the fungus, *Candida Albicans* with 15% inhibition, but still less than the reference drug, Fluconazole (35%). Based on the above mentioned data, it seems that the examined dioxathiaphosphinane (**12**) and benzoxaphospholylidene (**17**) exhibit potent antibacterial activity deserving thus further studies [38-41].

Conclusion

Actually, the present study assures that the Japanese and Lawesson reagents react with quinozolin-4-ones (**3a-e** and **4a,b)** both in the dimeric form (**1a,b**) to give the respective quinazolin-4-thiones (**5a-e** and **6a,b**) and in the monomeric dipolar forms (**2a,b**) to produce new series of phosphorothiated quinazoline derivatives (**7, 8, 11, 13, 15, 17** and **18**) and/or spiro-oxathiaphosphetane (**9,14**), dithiaphosphetane (**10**), dioxathiaphosphinane **(12)** and dithietane (**16**) quinazolines. These results explore new approaches for utilizing the Japanese and Lawesson reagents in the synthesis of four and six-membered phosphorus heterocycles derived form quinazolines. Moreover, docking experiment have shown that some of the new products are promising to be utilized as antimicrobial candidates. The biological screening demonstrated that, dioxathiaphosphinane (**12**) and benzoxaphospholylidene (**17**) show a remarkable activity equals to that of the reference drug, Cephridine, *in vitro*, which can serve as promising candidates for further biological evaluations.

Associated content

^{1}H, ^{13}C and ^{31}PNMR, Mass Spectra of the new compounds

Acknowledgments

We are indebted to National Research Centre, Egypt for the financial support (NRC grant 110-90-112).

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تحضير مشتقات ٢ -مثيل الكينازولينون فوسفوروثيوات وتقيمها كمضادات للميكروبات

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تم تحضير العديد من المركبات المحتويه على مجموعات الكينازولين والفوسفودای ثيوات بالإضافة لمركبات الثيوكينازولين المتوقعه من خلال تفاعل بعض الكواشف الفوسفورية مع مشتقات الكينازولينون فى مذيب الطولوين ودرجه حرارة ١٢٠ درجه مئويه. كذلك تم اجراء النمذجه الجزيئيه لمعرفه مدى الإرتباط بين المركبات الجديدة والبروتين المستهدف. تم اجراء التقيم البيولوجى لبعض المركبات الجديدة كمضادات ميكروبيه مشتخدماً عقار السيفرادين (كمضاد للبكتيريا) والفلوكونازول (كمضاد للفطريات) كأدويه مرجعيه. أوضحت النتائج ان مشتقات الداي أوكساثيافوسفينان ١٢ والبنزأوكسافوسفوليليدين ١٧ ذات نشاط فعال مساوٍ لعقار السيفرادين (١٥٪) كمثبطات لنمو سلالات بكتيريا الإشريكيه القولونيه.