Synthesis of New Fluorine/Phosphorus Substituted 6-(2’-Amino Phenyl)-3-Thioxo-1,2,4-Triazin-5(2H, 4H)One and Their Related Alkylated Systems as Molluscicidal Agent as against the Snails Responsible for Bilharziasis Diseases

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Abstract

New fluorine substituted 6-(5’-fluoro-2’-triphenylphosphiniminophenyl) 3-thioxo-1,2,4-triazin-5(2H, 4H) one (2) was obtained via Wittig’s reaction of the corresponding 6-(5’-fluoro-2’-amino-phenyl)-3-thioxo-1,2,4-triazinone (1). Behavior of compound 2 towards alkylating agents and/or oxidizing agents was studied were, N-hydroxyl (3), Mannich base (4,5), S-alkyl (6,7,8) and thiazolo [3,2-b][1,2,4] triazinones (10-14) and or 3-disulfide (18), 3-sulfonic acid 19 and 1,2,4-triazin-3,5-Dionne (20) derivatives obtained. Structures of the new products are established by elemental and spectral data. The new targets obtained screened as Molluscicidal agents against Biomphalaria Alexandrina snails responsible for Bilharziasis diseases, in compare with Baylucide as standard drug.

Keywords

Fluorine, Phosphorus, Sulfur-1,2,4-Triazine, Characteristic Properties, Molluscicidal Activity

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1. Introduction

The incorporation of fluorine atoms into a heterocyclic nitrogen molecule frequently provides properties of pharmacological interest as compared to their non-fluorinated analogs [1]-[5]. Also, bonded phosphorus atoms with S, O, N and C-atoms of heterocyclic systems enhance their important properties as herbicides, pesticides and insecticides [6]-[11]. On the other hand, 3-thio-1,2,4-triazin-5-one derivatives and their N- and S-alkyl derivatives have gained considerable attention due to their well as medicinal utility such as anti-HIV, anti AIDS and anticancer agents [12]-[16]. Literature reveals that no reports of a molecular scaffold containing these important cores. With this based upon these observations. The present work aims to synthesis and chemical reactivity of 1,2,4-triazinone bearing, fluorine, phosphorus and sulfur atoms through alkylation reactions and the new systems as Molluscicidal agents against Biomophalaria Alexandrina snails by removal from the wastewater (Clean water).

2. Experimental

Melting points were determined with an electro-thermal Bibly Stuart Scientific Melting point SMPI (UK). A Perkin Elmer (Lambda EZ-210) double beam spectrophotometer (190 - 1100 nm) used for recording the electronic spectra. A Perkin Elmer model RXI-FT-IR 55,529 cm⁻¹ used for recording the IR spectra (EtOH as solvents). A Brucker advance DFX 400 MHz using TMS as an internal standard for recording the ¹H¹³C NMR spectra in deuterated DMSO (δ in ppm). AGC-MS-QP 1000 Ex model is used for recording the mass spectra. Hexafluorobenzene was used as external standard for ¹⁹F NMR at 8425 MHz and ³¹P (in CDCl₃, 101.25 MHz) [17]. Elemental analysis was performed on Micro Analytical Center of National Reaches Center-Dokki, Cairo, Egypt. Compound 1 was prepared according the reported method [14] and compound 15 as procedure published [18].

6-(5'-Fluor phenyl)2' amino-3-thio-1,2,4-triazine-5(2H, 4H)one (1)

Equimolar mixture of 5-fluoroisatin (in 100 ml NaOH, 5%) and thiosemicarbazide (in 10 ml H₂O) reflux for 2 h, then cold and poured onto ice-HCl. The solid result was filtered off and crystallized from EtOH as yellow crystals to give 1. Yield (80%), m.p. 263 °C - 265 °C. Analytical data, Found C = 44.91, H = 2.90, F = 7.58, N = 23.40, S = 13.29%; Calculated for C₂₉H₂₄FN₄PO₃S (558) C = 62.36, H = 4.30, F = 3.40, N = 10.03, S = 5.73%. M/Z (558, M + H₂O, 5%), base peak (68, 100%), 148 (21), 136 (18), 110 (30), 96 (50), 82 (58), 70 (78); UV: (λ max EtOH) 280 nm. IR νₐₜ = 3424 (NH₂) 3258, 3169 (NH, NH), 1685 (C =O), 1618 (NH₂), 1545 (C=O), 1263 (C-F): 858, 818 (aryl CH) 685 (C-F) 1H NMR (DMSO) = 14.56, 12.78 (each 1H, s, 2NH), 8.21, 7.76, 7.66, 7.65, 7.64, 7.484, 7.840, 7.47, 7.464, 7.460, 7.45, 7.398, 7.391, 7.38, 7.37, 7.29, 7.28, 7.27, 7.02, 7.01, 7.009, 7.005, 6.994, 6.990, 6.866, 6.859, 6.852, 6.845, (18H of aromatic protons). ¹³C NMR = δ 179.47 (C=S), 162 (C=O), 159 - 157 (spin coupling C-F), 138.54 (C=N), 131.82, 121.8, 121.51 (aromatic carbons), 78.14, 77.71 (C₅-C₆ 1,2,4-triazine). Compound 1 was prepared according to the reference [17] and compound 15 as procedure published [18].

6-[5'-Fluoro-2' (triphenylphosphiniminophenyl)-3-thio-1,2,4-triazine-5(2H, 4H)one (2)

A mixture of 1 (0.01 mol) and phosphine (0.01 mol) in acetonitrile (20 ml), THF (20 ml) reflux for 2 h then cold. The solid produced and crystallized from EtOH to give 2 as yellow crystals. Yield (80%), m.p. 263 °C - 265 °C. Analytical data, Found C = 64.60, H = 3.96, F = 3.70, N = 11.01, S = 6.33%; Calculated for C₂₉H₂₄FN₄PO₃S (558): C = 62.36, H = 4.30, F = 3.40, N = 10.03, S = 5.73%. UV: (λ max EtOH) 310 nm. IR νₐₜ = 3335 (b, 2OH) 2974, 2889 (2CH₂), 1646 (C=O), 1382 (P=N), 1240 (C-F), 1086 (C-S), 1046 (P-N), 879 (aryl CH), 650 (C-F). ¹H NMR (DMSO): 14.66, 12.78 (each 1H, s, 2NH), 8.21, 7.76, 7.66, 7.65, 7.64, 7.484, 7.840, 7.47, 7.464, 7.460, 7.45, 7.398, 7.391, 7.38, 7.37, 7.29, 7.28, 7.27, 7.02, 7.01, 7.009, 7.005, 6.994, 6.990, 6.866, 6.859, 6.852, 6.845, (18H of aromatic protons). ¹³C NMR = δ 179.47 (C=S), 163.0 (C=O), 138.62 (C-F), 131 (C=N), 118.94 - 104.97 (aromatic carbons), 78.76, 77.21 (C₅-C₆ of 1,2,4-triazine).

2,4-Di(hydroxymethyl)-6-(5'-fluoro-2' (triphenylphosphiniminophenyl)-3-thio-1,2,4-triazine-5(2H, 4H)one (3)

A mixture of 2 (0.01 mol) and formaldehyde (0.02 mol), in methanol (50 ml) reflux for 2 h, cold. The solid obtained filtered off and crystallized from MeOH to give 2 as pale yellow crystals. Yield = (65%) m.p. 280 °C - 282 °C. Analytical data: Found C = 61.92, H = 4.21, F = 5.23, N = 9.93, S = 5.43% Calculated for C₂₉H₂₄FN₄PO₅S₈ (1158): C = 62.36, H = 4.30, F = 3.40, N = 10.03, S = 5.73%. UV: (λ max EtOH) = 363 nm. IR νₐₜ = 3346 (b, 2OH) 2974, 2889 (2CH₂), 1646 (C=O), 1382 (P=N), 1240 (C-F), 1086 (C=S), 1046 (P-N), 879 (aryl CH), 755 (C-F). ¹H NMR (DMSO) = δ 8.34 - 6.84 (18 aromatic protons), 4.8, 4.4 (each s, 2H, alcoholic 2OH) 2.62, 2.58 (each s, 4H, 2CH₂). ¹³C NMR (DMSO) = δ 179.86 - 179.68 (C=S), 163.07 (C=O), 159.62, 158.03 (C-F), (C-N), 138.60 (C=N), 132.121 - 107.94 (aromatic carbons), 77.75 77.32 (C₅-C₆ of 1,2,4-triazine), 40.57 -
A mixture of 2 (0.01 mol), piperidine (0.02 mol) and formaldehyde (0.02 mol) in methanol (50 ml) reflux for 2 h, cold. The solid produced filtered off and crystallized from MeOH to give 4 as yellow crystals. Yield = (60%) m.p. 179°C - 180°C. Analytical data found C = 67.41, H = 5.83, F = 2.55, N = 11.97, S = 4.33%. Calculated for C_{39}H_{42}F_{7}N_{6}OPS (692): C = 67.63, H = 12.13, F = 2.74, N = 12.13, S = 4.62%. IR ν cm⁻¹ = 3062 (aromatic CH), 2936, 2840 (aliphatic CH₂), 1721 (C=O), 1538 (C≡N), 1468 (deform CH₂), 1389 (P=N), 1248 (C-F), 1184 (C=S), 1049 (P-N), 885, 815, 754 (aryl CH), 709 (C-F). ¹H NMR (DMSO) = δ 8.23 - 6.80 (18H, aromatic), 2.95, 2.92, 2.89 and 2.58 (CH₂ of piperidine, N-CH₂-N). ¹³C NMR (DMSO) δ 172 (C=S), 154 (C=O), 147.25 (C-F), 137.54 (C=N), 116.10 - 108 (aromatic carbons), 77.80, 77.39 (C₅-C₆ of 1,2,4-triazine), 40 - 58, 40.47, 40.33, 40.19, 40.05 (CH₃ of piperidine) 39.91 - 39.63 (N-CH₂-N).

1,1-Di-[6-(5'-Fluoro-2'-triphenylphosphiniminophenyl)-5-oxo-1,2,4-triazine-3-yl]thioacetic acid (6)

Equimolar mixture of 2 and monochloroacetic acid in DMF (20 ml) warm for 30 min, then poured onto ice. The solid yielded filtered off and crystallized from EtOH to give 6 as faint yellow crystals. Yield (80%), m.p. 187°C - 188°C. Analytical data: Found: C = 62.42, H = 3.81, F = 3.20, N = 9.85, S = 5.57% ; Calculated for C_{29}H_{29}F_{7}N_{6}OPS (556). C = 62.58, H = 3.95, F = 3.41, N = 10.07, S = 5.75. IR ν cm⁻¹ = 3327 (b, OH, NH), 2973, 2884 (CH₂), 1659 (b, 2 C=O), 1440 (deform CH₂), 1380 (P=N), 1250 (C-F), 1087 (C-S), 1045 (P-N) 880 (Ar CH), 810 (Ar CH). ¹H NMR (DMSO) δ 10.31 (s, 1H, NH), 8.06, 8.0, 7.98 - 7.97, 7.96 - 8.74, 7.73 & 7.72, 7.721, 7.14, 7.08, 7.67 & 7.66, 7.65, 7.63, 7.53 - 7.51, 7.48 - 7.35 & 7.34, 6.997, 6.992, 6.838 - 6.824 (18 CH, aromatic) & 4.74 (s, 1H, OH of COOH). ¹³C NMR (DMSO) δ 168.29 (C=O), 156.40 (C-O), 157.16 (C=O), 142.13 (C-F) 131.35 (C=O), 130.04 - 102.25 (aromatic carbons), 72.43, 72.22 (C₅-C₆ of 1,2,4-triazine), 34.95 - 34.81 (CH₂ carbon).

1,1-Di-[6-(5'-Fluoro-2'-triphenylphosphiniminophenyl)-5-oxo-1,2,4-triazine-3-yl]dimercaetoxyacetic acid (7)

A mixture of 2 (0.02 mol) and 1.1-dichloroacetic acid (0.01 mol) in DMF (20 ml) reflux for 30 min, cold then poured into ice. The resulted solid filtered off and crystallized from dioxin to give 7 as faint yellow crystals, yield (60%) m.p. 238°C - 240°C. Analytical data: Found: C = 63.45, H = 3.49, F = 3.39, N = 10.39, S = 5.88% ; Calculated for C_{39}H_{42}F_{7}N_{6}OPS_{2} (1052) C = 63.87, H = 3.80, F = 3.61, N = 10.64, S = 6.08%. IR ν cm⁻¹ = 3425, 3259, 3170 (OH, NH, NH), 1865, 1680 (C=O), 1618 (C≡N), 1476, 1452 (aliphatic CH), 1360 (P=N), 1252 (C-F), 1193 (C-S), 1045 (P-N), 903, 859, 818, 758 (aryl CH) 685 (C-F). ¹H NMR (DMSO) δ 12.79, 12.78 (each s, 2NH), 10.75 (s, 1H, OH), 8.21 - 6.84 (18 CH, aromatic), 2.82 - 2.59 (s, 1H, CH) ¹³C NMR: δ 179.72 (C=S), 168.29 (C=O), 156.40 (C-O), 157.16 (C=O), 142.13 (C-F) 131.35 (C=O), 130.04 - 102.25 (aromatic carbons), 72.43, 72.22 (C₅-C₆ of 1,2,4-triazine), 34.95 - 34.81 (CH₂ carbon).
A mixture of 2 (0.03 mol) and 1,1,1-trichloroacetic acid (0.01 mol) in DMF (20 ml) warm for 30 min then cold and poured on to ice. The produced solid filtered off and crystallized from EtOH to give 8 as reddish crystals. Yield (60%); m.p. 189°C - 190°C. Analytical data: Found C = 63.89, H = 3.45, F = 3.55, N = 10.67, S = 5.83%. Calculated for C_{29}H_{21}FN_{5}OPS (537): C = 64.80, H = 3.91, F = 3.53, N = 13.03, S = 5.95%. M/Z = 537 (2%), 370 (2), 226 (2), 168 (100), 140 (60), 114 (30), 62 (18). 

6'-Fluoro-2'-triphenylphosphiniminophenyl)-5-oxo-1,2,4-triazine-3,7-dione (9)

Equimolar mixture of 2 and monochloroacetic acid in DMF (20 ml) reflux for 2 h then cold and poured onto ice. The solid obtained filtered off and crystallized from dioxan to give 9 as brown ppt, Yield (60%) m.p. 224°C. Compound 6 (0.50 mg) heat above its melting point (60°C higher) for 10 min, cold then treat with MeOH. The solid produced filtered off and crystallized from dioxan to give 9 as brown ppt. Yield (58%), m.p. 225°C - 227°C. Analytical data: Found C = 64.40, H = 3.51, F = 3.35, N = 10.51, S = 5.49%. Calculated for C_{29}H_{21}FN_{5}OPS (537): C = 64.68, H = 3.71 F = 3.53, N = 10.40. S = 5.94%. UV (λ_{max} EthOH) 352 nm. IR ν cm^{-1} = 3204 (b- OH), 1694 (C=O), 1623 (C=O), 1563, 1475 (CH2), 1380 (P=N), 1299 (C-F), 1148 (S=C), 816, (aryl CH), 711 (C-F). 1H NMR (DMSO) = δ 10.79 (s, 1H, Phenolic OH), 8.23 (s, 1H, CH of thiazole), 7.95 - 7.47, 7.35, 7.35 , 6.98, 6.80 (aromatic CH). 13C NMR (DMSO) = δ 167.21 (C=O), 147.47, (C=O), 136.64 (C-F), 132.97 (C=N), 131.92 - 128.54, 118.80 - 118.14, 113.79 - 113.73 (aromatic carbons), 111.04 - 110.99 (-CH=), 77.80, 77.38 (C_{5}-C_{6} of 1,2,4-triazine).

3-Amino-6'(5'-fluoro-2'-triphenylphosphiniminophenyl)-thiazolo[3,2-b][1,2,4]triazine-7-one (11)

A mixture of 2 (0.01 mol) and chloroacetanitride (0.01 mol) in DMF (20 ml) warm for 10 min then cold and poured onto ice. The result solid filtered off and crystallized from dioxan to give 10 as faint Yellow crystals. Yield (70%); m.p. 214°C - 215°C. Analytical data: Found C = 64.39, H = 3.58, F = 3.11, N = 12.85, S = 5.75%. Calculated for C_{29}H_{21}FN_{5}OPS (537): C = 64.80, H = 3.91, F = 3.53, N = 13.03. S = 5.95%. M/Z = 537 (5%) 281 (20), 207 (60), 149 (20), 113 (30), 85 (100), 58 (100). IR λ cm^{-1} = 3424, 3167 (NH, S=CH=C=NH) 2100 - 2085 (C=C=O), 1716 (C=O), 1624 (C=O), 1481 (CH2), 1370 (P=N), 967, 839, 762 (aryl CH), 700 (C=O). 1H NMR (DMSO) = δ 13.90, (s, 1H, NH), 12.76 (s, 1H, NH=CH2), 8.22 - 6.81 (aromatic CH), 4.69 (1H, NH=CH2) 2.59 (2H, CH2). 13C NMR (DMSO) = δ 158.11 (C=O), 147.0 (C-F), 132 (C=N), 131.86 - 128.44 (aromatic carbons), 120.4 (C≡N), 77.96, 77.53 (C_{5}-C_{6} of 1,2,4-triazine), 40.13 (C≡N), 33.63 (CH3).

3-(4'-Fluoro benzoyl)amino-6'(5'-fluoro-2'-triphenylphosphiniminophenyl)-thiazolo[3,2-b][1,2,4]triazine-7-one (12)

Equimolar mixture of 11 and 4-fluorobenzoyl chloride in DMF (20 ml) warm for 10 min then cold and poured onto ice. The resulted solid filtered off and crystallized from EtOH to give 12 as deep-Yellowish crystals. Yield (75%); m.p. 205°C - 207°C. Analytical data: Found C = 65.19 H = 3.41, F = 5.49, N = 10.51, S = 4.59%. Calculated for C_{29}H_{21}FN_{5}OPS (537), C = 64.80, H = 3.91, F = 3.53, N = 13.03, S = 5.95%. M/Z, 537 (2%), 370 (2), 226 (2), 168 (100), 140 (60), 114 (30), 62 (18), 70 (18). IR ν cm^{-1} = 3348, 16430 (C=O), 1383 (P=N), 1250 (C-F), 1086 (C-S), 1045 (P-N), 878 (aryl CH). 1H NMR (DMSO) = δ 8.11 (s, 1H, CH=CH2), 7.72 - 7.011 (b-CH), 6.98 - 6.80 (aromatic CH), 3.99 - 3.84 (2H-NH2). 13C NMR (DMSO) = δ 162.54 (C=O), 132.16 (C-F), 132.00 (C=N), 131.99 (C=S), 131.66 - 131.64 (C=CH2), 128.61 - 120.55 (aromatic carbons), 77.59, 77.38 (C_{5}-C_{6} of 1,2,4-triazine), 40.51 (N=C=N).
7.64, 7.44 - 7.42, 7.28, 7.27 (aromatic CH). $^{13}$C NMR = (DMSO): $\delta$ 167.53 (C=O), 162.54 (C=O) 138.59 (C-F) 132.25 (C-N), 132.19 (C=N), 129.33 - 127.27, 117.78 - 115.17, 112.15, 12.09, 110.52, 108.12, 107.95 (aromatic carbons), 77.64, 77.43 (C$_2$-C$_6$ of 1,2,4-triazine).

**Schiff base (13)**

Equimolar amounts of 11 and 4-fluorobenzaldehyde in absolute ethanol (20 ml) reflux for 30 min then cooled. The solid thus obtained filtered off and crystallized from EtOH to give 13 as Yellow ppt. Yield (70%); m.p. 248°C - 250°C. Analytical data: Found C = 66.85, H = 4.31, F = 4.44, S = 3.36%, Calculated for C$_{46}$H$_{34}$F$_2$N$_7$O$_2$PS$_2$ (849); C = 66.91, H = 4.00, F = 4.70, S = 5.13%, Calculated for C$_{45}$H$_{36}$F$_2$N$_7$O$_2$PS (807); C = 66.94 (S-CH=N), 40.57, 39.76 (2 CH$_3$).

**6-(5'-Fluoro-2'-triphenyl phosphiniminophenyl)-3-oxo-3-phenyl-thiazolo[3,2-b][1,2,4]triazine-7-one (14)**

A mixture of 2 (0.01 mol) and phenacylbromide (0.01 mol) in ethanolic KOH, (20 ml, 5%) reflux for 2 h, cold then poured onto ice-HCl. The solid produced filtered off and crystallized from dioxan to give 14 as deep-yellowish crystals. Yield (80%); m.p. 238-240°C. Analytical data: Found C = 64.88, H = 3.85, F = 4.38, N = 11.40, S = 7.45%, Calculated for C$_{46}$H$_{34}$F$_2$N$_7$O$_2$PS$_2$ (849); C = 65.01, H = 4.00, F = 4.47, N = 11.24, S = 7.53%; M/Z (849, 0.0%), 370 (2), 329 (40), 290 (100), 158 (2), 128 (100), 96 (100), 65 (100). UV: (C=O) 323 nm. IR vcm$^{-1}$ = 3332 (NH), 2973, 2868 (aliphatic CH), 1636 (C = O), 1488 (CH$_2$), 1381 (P=N), 1234 (C-S), 1205 (P=N), 880, 850 (aryl CH). $^1$H NMR (DMSO) $\delta$ 3.55, N = 10.89, S = 6.22%.

**Diaarylthioether (16)**

A mixture of 2 (0.01 mol) and Schiff base 15 (0.01 mol) in dry C$_6$H$_6$ (100/ml) reflux for 4 h, cold then powered onto ice. The resultant solid filtered off and crystallized dioxan to give 16 as Yellowish crystals. Yield (75%); m.p. 254°C - 255°C. Analytical data: Found C = 69.88, H = 3.59, F = 3.01 N, 9.00, S = 5.13%, Calculated for C$_{46}$H$_{34}$F$_2$N$_7$O$_2$PS$_2$ (849); C = 65.01, H = 4.00, F = 4.47, N = 11.24, S = 7.53%; M/Z (849, 0.0%), 370 (2), 329 (40), 290 (100), 158 (2), 128 (100), 96 (100), 65 (100). UV: (C=O) 323 nm. IR vcm$^{-1}$ = 3332 (NH), 2973, 2868 (aliphatic CH), 1636 (C = O), 160.63, 155.18 (C-F), 151.9 (C=S), 134.64, 134.25, 134.23 (C=N), 129.487 - 115.492 (aromatic carbons), 77.72, 77.50 (C$_2$-C$_6$ of 1,2,4-triazine), 67.00 (S=CH=NH), 39.95 - 39.81, 39.67 - 39.55 (2 CH$_3$).

**2,3-Diaryl-2,3-dihydro-4-thioxo-7-(5'-fluoro-2'-triphenylphosphiniminophenyl) -1,3,5-thiazolo[3,2-b][1,2,4]triazine-8-one (17)**

A mixture of 16 (0.01 mol) and Schiff base 15 (0.01 mol) in MeOH (20 ml) reflux for 4 h, cold then powered onto ice. The resultant solid filtered off and crystallized from dioxan to give 17 as yellowish crystals. Yield (75%); m.p. 254°C - 255°C. Analytical data: Found C = 69.88, H = 3.59, F = 3.01 N, 9.00, S = 5.13%, Calculated for C$_{46}$H$_{34}$F$_2$N$_7$O$_2$PS$_2$ (849); C = 65.01, H = 4.00, F = 4.47, N = 11.24, S = 7.53%; M/Z (849, 0.0%), 370 (2), 329 (40), 290 (100), 158 (2), 128 (100), 96 (100), 65 (100). UV: (C=O) 323 nm. IR vcm$^{-1}$ = 3332 (NH), 2973, 2868 (aliphatic CH), 1636 (C = O), 160.63, 155.18 (C-F), 151.9 (C=S), 134.64, 134.25, 134.23 (C=N), 129.487 - 115.492 (aromatic carbons), 77.72, 77.50 (C$_2$-C$_6$ of 1,2,4-triazine), 67.00 (S=CH=NH), 39.95 - 39.81, 39.67 - 39.55 (2 CH$_3$).

**Di-Heteroaryldisulfide (18)**

Compound 2 (0.05 gm) and FeCl$_3$ (0.5 gm) in MeOH (20 ml) reflux for 3 h, then filtered. The solid produced filtered off and crystallized from dioxan to give 18 as deep-yellowish crystals. Yield (80%), m.p. 238°C - 240°C. Analytical data: Found C = 64.88, H = 3.85, F = 4.38, N = 11.40, S = 7.45%, Calculated for C$_{46}$H$_{34}$F$_2$N$_7$O$_2$PS$_2$ (849); C = 65.01, H = 4.00, F = 4.47, N = 11.24, S = 7.53%; M/Z (849, 0.0%), 370 (2), 329 (40), 290 (100), 158 (2), 128 (100), 96 (100), 65 (100). UV: (C=O) 323 nm. IR vcm$^{-1}$ = 3332 (aliphatic CH), 1634 (C=O), 1614. 1593 (C=N) 1475, 1425 (C-F), 1318 (P=N), 1264 (C-F), 1199 (C=S), 1130 (C-S), 1052 (P-N), 985, 899, 854, 814, 732 (aryl CH). $^{13}$C NMR (DMSO) = $\delta$ 179.70 (C=S), 163.07 (C=O), 155.08 (C-F), 138.62 (C=N), 132.23, 132.12 (C=aromatic carbons), 129.43 - 115.44, 112.09 - 107.96 (aromatic carbons), 77.71, 77.28 (C$_2$-C$_6$ of 1,2,4-triazine). 67.94 (S=CH=NH), 40.57, 39.72 (CH$_2$).
A recent work on the synthesis and chemistry of bioactive sulfur bearing 1,2,4-triazine moiety was reported [16] [19]. In continuation of this attitude the present investigation reports the synthesis of fluorine and phosphorus-substituted 6-amino-phenyl-3-thioxo-1,2,4-triazin-5-(2H, 4H) one (1) and study that behavior towards various alkylating agents. Treatment of 5-fluoroisatin with thiosemicarbazide in alkaline medium [14] [15] produced 6-(2'-amino-5'-fluorophenyl-3-thioxo-1,2,4-triazin-5-(2H'4H) one (1). Warm compound 1 with triphenylphosphine in acetonitrile produced the yield 2 (Scheme 1).

In the imino [yield, 2] a negative charge of nitrogen is bonded to positive charge of phosphorus stabilized by partial overlap of the filled N-P orbital. This stabilization increase due to the charge on the $\alpha$-carbon atom is spread by 1,2,4-triazine resonance. Abdel-Rahman [14] [15] reported that N-alkyl of 3-thioxo-1,2,4-triazinones exhibited a wide biological spectrum anti HIV and anticancer properties. Similarly, hydroxyl methylation of compound 2 by boil with formaldehyde-methanol produced 2,4-di(hydroxymethyl)-6-(5'fluoro-2'-triphenylphosphinomethyl)-3-thiasso-1,2,4-triazin-5-one (3). Also, reflux of compound 2 with secondary and primary amines such as piperidine, 4-fluoroaniline and 4-amino-antipyrine in the presence of formaldehyde methanol, furnished the Mannich bases 4 and 5 (Scheme 2).

Formation of 3 and 4 was may be as (Figure 1).
Scheme 2. Formation of compounds 3 - 5.

Figure 1. Formation of compounds 3 & 5a.
Due to a higher nucleophilicity of sulfur atoms, the direct displacement of an acidic proton of mercapto group by a simple electrophile can be easily occur via treatment of compound 2 with haloacetic acids. Thus treatment of compound 2 with halo aliphatic acids such as mono/di/trichloroacetic acids in DMF afforded the substituted thiaacetic acids 6-8 (Scheme 3).

The multicomponent reaction (MCR) was considered as powerful synthetic tool for preparing target molecules of biological relevance in an efficient manner. Thus, treatment of compound 2 with active methylene reagents as chloroacetanitriile in warm DMF [20] produced 3-cyanomethyl thiad-4-iminophosphorane-1,2,4-triazin-5-(2H)one (10). The latter compound 10 use for the synthesis of thiazolo [3,2-b][1,2,4]triazinones (11-13) systems (Scheme 4). Acidic hydrolysis of 10 by warm with diluted HCl for short time (10 min) yielded the compound 6. Boil compound 6 with DMF along time afforded 6-iminophosphorane-2,3-dihydroro-thiazolo [3,2-b] [1,2,4] triazine-3,7-dione (9) (Scheme 4).

Heat compound 10 on heating with DMF a long time (2 hours), produced 3-aminothiazolo-1,2,4-triazine 11. Presence of an amino group in structure 11 was deduced from treat with 4-fluorobenzoylchloride (DMF) and/or with 4-fluorobenzaldehyde (EtOH) yield the anilido 12 and/or Schiff's base 13 (Scheme 4). Treatment of compound 2 with α, β-bifunctional oxygen-halogen reagents as phenacyl bromide in ethanolic KOH, yielded 3-phenyl-6-iminophosphorane-thiazolo [3,2-b][1,2,4]triazin-7-one (14) (Scheme 5). The nitrogen-sulfur containing fused heterobicyclic structures have demonstrated a high degree of binding affinity when they serve as Ligands for various biological receptors [12] [13]. Thus addition of Mercator group (as nucleophilic) of compound 2 to an Schiff's base 15 in boil dry dioxan yielded the thioether 16, which upon ring closure reaction by reflux with CS₂ in DMF furnished 2,3-diyral-2,3-dihydro-7-iminophosphorane-4-thioxo-1,3,5-thiadiazino[3,2-b] [1,2,4]triazin-8-one (17) (Scheme 5).

Abdel-Rahman et al. [21]-[25] reported that thioethers, sulfide and sulfonic acid bearing a 1,2,4-triazine moieties. Exhibited a very interesting medicinal activity as anti-HIV and anticancer agents. Recently, Slawinski et al. [25] synthesized 2-mercaptothenesulfonamide bearing a 1,2,4-trinzines exhibited a significant activity against cell lines of colon cancer, renal cancer, and melanoma, as well as good selectivity toward non-small cell lung cancer. Similarly, oxidation of compound 2 via treatment with FeCl₃ in boiling methanol and/or with H₂O₂ in ethanol by stirred at room temperature furnished the disulfide 18 and/or 3-sulfonic-1,2,4-triazinone 19. Finally, treatment of 2 with ethanolic KMnO₄ at room temperature [21] led to the direct formation of 6-(5′-fluoro-2-triphenylphosphiniminophenyl)-1,2,4-triazin-3,5(2H, 4H)dione (20) (Scheme 5).

Scheme 3. Formation of compounds 6 - 8.
3.2. Elucidation the Former Structures

3.2.1. UV Spectra

The electronic conjugated molecule of compound 2 exhibited $\lambda_{\text{max}}$ at 310 nm while that of compounds 3 (363), 5a (364), 8 (359) and 16 (323) nm. A higher absorption bands of new acyclic systems than that of 2 confirm that N- and S-substitution were formed. On the other hand, the absorption bands of fused heterobicycle compounds 9 (352), 17 (347) and 10 (321) nm is higher than the start 2 (310) nm. This is attributing to extension of hetero-conjugation of heterobicyclic systems through a type of cyclization.

3.2.2. IR Spectra

The new compounds obtained recorded the absorption bands at 1380 - 1390, 1250 - 1230 cm\(^{-1}\) due to presence of both P=N and C-F functional groups. Compounds 3-5 showed a lack of band at 3200 - 3100 cm\(^{-1}\) for NH=OH of 1,2,4-triazinones, while that of compounds 6-8 and 10 recorded the absorption band at 3343 and 1643 cm\(^{-1}\) attributed to presence of 4NH & 5C=O of 1,2,4-triazinone. Only compounds 9-14 showed a lack of the absorption bands at 1200 - 1100 cm\(^{-1}\) for C=S, which confirm that heterocyclization. In addition to the compounds 6-9 & 18, 20 exhibited a two absorption bands at $\nu$ 1700 and 1665 cm\(^{-1}\) due to the presence of two carbonyl groups. Also, IR absorption spectra of compounds 3-8, 9-10 and 16 recorded the absorption bands at $\nu$ 2975 and 2885 cm\(^{-1}\) attributed to aliphatic functional groups [1] [14] [15] [26].

3.2.3. NMR Spectral Study

1) $^1$H NMR spectrum of 1 showed a resonated signals at $\delta$ 14.6, 12.6 and 10.9 ppm for 3NH with $\delta$ 8.6 - 0.80, 7.69 - 7.64, 7.41 - 7.31 ppm for three aromatic protons, while that of 3 exhibited a signals at $\delta$ 5.24 and 4.98 ppm attributed to presence of $^4$NH & $^5$C=O of 1,2,4-triazinone. Only compounds 9-14 showed a lack of the absorption bands at 1200 - 1100 cm\(^{-1}\) for C=S, which confirm that heterocyclization. In addition to the compounds 6-9 & 18, 20 exhibited a two absorption bands at $\nu$ 1700 and 1665 cm\(^{-1}\) due to the presence of two carbonyl groups. Also, IR absorption spectra of compounds 3-8, 9-10 and 16 recorded the absorption bands at $\nu$ 2975 and 2885 cm\(^{-1}\) attributed to aliphatic functional groups [1] [14] [15] [26].
11 exhibited only signals at $\delta$ 8.01 and 3.99 ppm for = CH thiazole and amino-protons. Moreover $^1$H NMR spectrum of 16 showed a signal at $\delta$ 12.76 and 10.75 ppm for two NH of 1,2,4-triazine while a lacks of these (2NH) protons of 17, with presence of CH proton of thiadiazine moiety at $\delta$ 9.68 ppm. $^1$H NMR spectra of compounds 18 recorded the presence of $\delta$ at 14.55 and 12.79 ppm attributed to 2NH of 1,2,4-triazine protons, while that of 19 exhibited a signals at $\delta$ 12.8 and 10.7 ppm for NH and CH (SO$_2$-OH) protons, with signals of aromatic protons. Finally, compound 20 exhibited $\delta$ at 12.73 and 10.82 ppm attributed to NH and OH protons.

2) 13C NMR spectra of all the synthesized compounds showed a resonated signals at $\delta$ 180, 165 - 163, 140 - 138, 135 - 121 and 112 ppm attributed to C=S, C=O, C=N, aromatic and C-F carbons. Also, 13C NMR spectra of compounds 3-6, 9 and 10 recorded signals at $\delta$ 39 - 33 ppm for CH$_2$ carbons. Only the compound 10 showed an additional signal at $\delta$ 112 ppm for C≡N carbon. Finally, 13C NMR spectra of the entire compound exhibited a resonated signals at 77 - 75 ppm for C5-C6 of 1,2,4-triazine [27] (Figure 2).

3) $^{19}$F NMR spectral study recorded a signal at $\delta$ -126 to -125 ppm.

4) $^{31}$P NMR spectral study exhibited a signal at $\delta$ 30 - 29 ppm attributed to P=N [17].

3.2.4. Mass Fragmentation Study

Mass fragmentation pattern study of some selective synthesized compounds indicated that fused heterobiycyclic systems 11 have a more base peak, while that of acyclic structures 1 and 16 have only base peak which indicate that their less stability. A higher stability of fused heterobicyclic systems is due to the delocalization of net charge over all the active centers (Figure 3 to Figure 5).

4. Molluscicidal Activity

Based upon the earlier work by Abdel-Rahman et al. [7] [16] on the synthesis of phosphono substituted-1,2,4-
triazine derivative and their molluscicidal activities against Biomphalaria Alexandrina Snails responsible for Bilharziasis diseases, the prepared compounds were tested as killing of that snails (shell in diameter 5 - 8). The intermediate host of sohistosomamausoni in Giza Govern state that was not treated with mollusicides. The snails were adapted to laboratory conditions for two weeks before being used in toxicity tests to be sure that the snails are strong and healthy. Snails were kept in plastic aquaria filled with dechlorinated tap water at room temperature (25°C - 27°C). Stock solution (500 μg ml⁻¹) of the tested compounds were synthesized in the least volume of ethanol and completed of the least volume of ethanol and completed to the required volume with dechlorinated tap water on the basis of weight volume. A series of more diluted solutions were then prepared following the instructions given by WHO organization [28] [29]. The result given in (Table 1) revealed that the high activity towards snails in the following sequences:

18 > 2 > 20 > 3 > 8 and 9 > 10 > 6 > 17 >> 5a and 5b > 7 > 14 at 100 ppm in compared with Baylucide as
Figure 4. Mass fragmentation pattern of compound 1.

Figure 5. Mass fragmentation pattern of compound 16.
Table 1. The molluscicidal activity of the synthesized systems (2 - 20) mortality of snails various concentration (ppm).

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>25 ppm</th>
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Reference standard, Baylucide 100 100

standard reference. In general, the strong effect of the compounds 2, 3, 8, 18 and 20 is due to presence both the S-S, S-H and O-H functional groups which agree with bio-oxidation-reduction processes. The moderate effect of the compounds 5a, 6, 9, 10 and 17 is attributed to thioether and cyclic sulfur nitrogen systems. Finally, the lethal effect of the compounds 4, 5b, 7, 11 and 14 may be to absence of SH and/or OH of Mannich base and for thiazolotriazine systems which led to the inhibition of delocalization electron-density over all the center of systems. Also, presence of hetero-elements (F, P, S, O) and N elements in incorporated with 1,2,4-triazines led to increases of electron-negativity, over all the molecular structure and enhance the electrostatic force and hydrophobic properties [17] [18] [31]-[33]. Thus, total electron-barrier of molecular distribution of the evaluated systems synthesized led to highly inhibition of the enzymatic effect on the living processes for the tested snails by causing break of a vital cyclic of that snails, and enhance the possibility killing of these snails. QSAR study of the obtained resulted from (Table 1), and based on the introduction of P, S and F in the synthesized 1,2,4-triazines, in compared with the mortality of tested snails, indicated that, increases of P and S percent % led to increase of mortality, while, increase of F percentage % led to decrease of mortality of snails. Also, very high electronegative of fluorine atom can modify the electronic distribution in the molecule affecting its absorption distribution and metabolism. In conclusion, 3-thioxo-1,2,4-triazine-5-ones bearing an P, S and F elements and their related S-alkyl derivatives, enhance the mortality of snails, which cause Bilharziasis Diseases than that their non-fluorinated and non-phosphinated systems. Also, increases of P and S percentage % led to higher mortality of the tested snails, in hope to obtain more clean water from waste water.
5. Conclusion

New fluorine substituted 6-(5’-fluoro-2’-triphenylphosphiniminophenyl) 3-thioxo-1,2,4-triazin-5 (2H, 4H) one (2) was obtained via Wittig’s reaction of the corresponding 6-(5’-fluoro-2’-aminophenyl)3-thioxo-1,2,4-triazinone (1). 3-thioxo-1,2,4-triazine-5-ones bearing an P, S and F elements and their related S-alkyl derivatives, enhance the mortality of snails, which cause Bilharziasis Diseases than that their non-fluorinated and non-phosphinated systems. Also, increases of P and S percentage % led to higher mortality of the tested snails, in hope to obtain more clean water from waste water.

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