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Synthesis of Some More New Fluorinated 1,2,4-triazino[3,4-b][1,3,4]Thiadiazolonesand Their Molluscicidal Against Selective Snails - Part I

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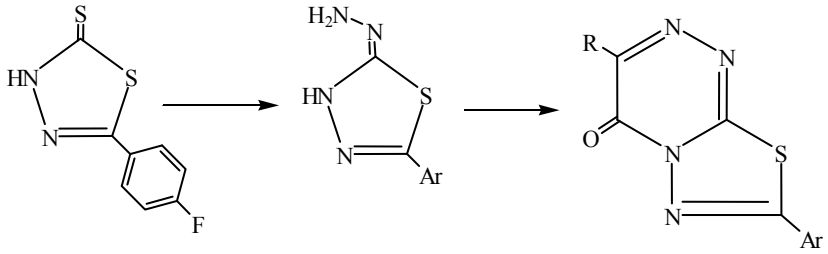
Abstract: Some more new fluorinated 1,2,4-triasino[3,4-b][1,3,4]thiadiazolones (6-9 and 11-16) have been synthesized from cyclocondensation of 5-hydrazino-2-(4'-fluorophenyl)-1,3,4-thiadiazole with bifunctional oxygen and halogen compounds. Structures of the products have been deduced from their elemental, chemical and spectral data (UV, IR, $^{1}H/^{13}C$ NMR (nuclear magnetic resonance) and mass). All the new compounds evaluated as molluscicidal against towards snails which responsible for Bilharziasis diseases.



Key words: Fluorine, 1,2,4-triasino[3,4-b]thiadiazolones, molluscicidal activities.

1. Introduction

Functionally 1,2,4-triazines possess important pharmacological, medical agents, as anti HIV [1], antitumor [2], anti-inflammatory [3] and as molluscicidal agents [4], as well as in agriculture field as heribicides [5], Cellobise activity [6] and forms a type of more oxidation states of metal-complexes [7, 8].

On the other hand, 1,3,4-thiadiazoles are one of the privileged structure fragments in medicinal chemistry having broad spectrum ofpharma-cologicalactivities, such as anti-inflammatory [9], antitumor [10], anticancer [11], analgesic [9], antioxidant [12], molluscicidal [13], antiproliferative [14] and as potent anticancer agent induces growth inhibition followed by apoptosis in He p G_2 cells [15]. Abdel-Rahman et al. [16], synthesized a series of 1,2,4-triazino[3,4-b] [1,3,4]thiadiazolones as anticancer and anti HIV drugs [1]. Thus, in the design of some more new effective drugs, the development of multi-heterocyclic systems through to combination of different pharmacophores in one frame as 1,2,4-triazine and 1,3,4-thiadiazole moieties may lead to new fluorinated organic compounds with interesting biological properties. Thus in the present work prompted by these observations, the synthesis of fluorine substituted 1,2,4-triazino-1,3,4-thiadiazolones and their molluscicidal activity are aimed at.

2. Experiments

Melting points of the products were determined on Stuart SMP_3 (UK) and uncorrected. UV absorption spectra (λ_{max} nm) were recorded in DMF on Shimadzu UV and visable 310 IPC-spectro-photometer. A Perkins Elmer Model RXI-FT IR system 55529 was

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used for recording IR spectra of the prepared compounds γ cm^{-1}. A Brucker advanced DPX 400 MHz model using TMS as internal standard was used for recording the ^{1}H and ^{13}C NMR spectra of the compounds on deuterated ($CDCl_3$, d_6, δ ppm). Mass spectrum was measured on GCMS Q 1000 Ex at 70 eV. Elemental microanalysis was performed by the microanalytical at Cairo-University, Egypt. Compounds 1 [4] and 10 [6] were prepared according the published methods.

2.1 Preparation of Hydrazone (2)

A mixture of 1 (0.01 mol) [4] and 4-fluorobenzaldehyde (0.01 mol) in ethanol (50 mL) with drops of glacial acetic acid, refluxed for 1h, cooled. The solid obtained filtered off and crystallized from acetone to give 2 as pall yellow crystals, yield 85%, m.p. 155-157 °C, IR (γ cm^{-1}): 3,100 (NH), 1,601 (C=N), 1,224 (C-F), 1,154 (C-S), 820 (p-substituted phenyl, 617 (deformation C-F). ^{1}HNMR ($DCCl_3$-d_6): δ (ppm): 8.60 (s, 1H, NH), 7.84 (s, 1H, CH=N), 7.71-7.50, 7.49-7.24, 7.15-7.02 (each s, 4H, aromatic H). 5.0 (s,1H, SH). ^{13}C NMR($DCCl_3$-d_6): δ (ppm): 165.90, 160.84 (2 C=S), 130.58-130.34 (aromatic carbons), 116.14-115.92 (C=N). CHNSF analysis for $C_8H_7N_2S_2F$ (214), Calcd: C, 44.85; H, 3.27; N, 13.08; S, 29.90; F, 8.87%. Found: C, 44.51; H, 3.00; N, 12.80; S, 29.50; F, 8.59%.

2.1.1 Synthesis of 2,3,4,5-tetrahydro-2-(4'-fluorophenyl)-1,3,4-thiadiazol-5-thion (3)

A compound 2 (0.5 g) was refluxed with dry benzene (50 mL) for 8 h, cooled. The soled thus obtained filtered off and crystallized from benzene to give 3 as pall yellow crystals, yield 70%, m.p. 177-179 °C. IR (γ cm^{-1}): 2,300-2,250 (NH-NH), 1601 cm^{-1} (C=C), 1,226 (C-F), 826 (p-substituted phenyl), 618 (C-F). ^{1}HNMR ($DCCl_3$–d_6) δ (ppm): 8.60 (s, 1H, NH), 7.84 (s, 1H, NH), 7.83-7.80 ppm, 7.34, 7.27-7.10 (each s, CH and aromatic protons). ^{13}C NMR ($DCCl_3$-d_6) δ (ppm): 165.32, 130.58-130.34, 116.14-115.92, 77.34. CHNSF analysis for $C_8H_7N_2S_2F$ (214), Calcd: C, 44.85; H, 3.27; N, 13.08; S, 29.90; F, 8.87%. Found: C, 44.66; H, 3.21; N, 12.79; S, 29.55; F, 8.69%.

2.1.2 Synthesis of 2-(4'-fluorophenyl)-1,3,4-thiadiazol-5-(4H)-thion(4)

A mixture of 3 (0.5 g) and sulfur (0.2 g) in dry benzene (50 mL) was refluxed for 4 h, cooled. The solid produced filtered off and crystallized from benzene to give 4 as orange crystals, yield 82%, m.p. 210-212 °C. IR (γ cm^{-1}): 3,200 (NH), 3,050 (aromatic CH), 1,600 (C=N), 1,329 (NCSN), 1,228 (C-F), 1,156 (C-S), 1,055 (C-S-C), 830 (p-substituted phenyl), 627 (C-F). ^{1}HNMR ($DCCL_3$-d_6) δ (ppm): 11.70 (s, 1H, NH), 7.97-7.74, 7.69-7.58, 7.49-7.41, 7.25-7.03 (each s, 4H, aromatic CH). ^{13}C NMR ($DCCl_3$-d_6) δ (ppm): 180 (C=S), 140 (C=N), 130-129 (aromatic carbons). CHNSF analysis for $C_8H_5N_2S_2F$ (212), Calcd: C, 45.28; H, 2.35; N, 13.20; S, 30.18; F, 8.87%. Found: C, 44.89; H, 2.20; N, 12.88; S, 29.95; F, 8.70%.

2.1.3 Synthesis of 2-(4'-fluorophenyl)-5-hydrazino-1,3,4-thiadiazole (5)

A mixture of 4 (5 g) and hydrazine hydrate (7mL) in ethanol (100 mL) was refluxed for 8 h, cooled. The solid thus obtained filtered off and crystallized from ethanol to give 5 as faint yellow crystals; yield 75%, m.p. 188-190 ^{o}C. IR (γ cm^{-1}): 3,420, 3,111 (NH_2, NH), 1,673 (deformation NH_2), 1,501 (C=N), 1,350 (cyclic NCSN), 1,210 (C-F), 1,042 (C-S-C), 810 (p-substituted phenyl), 639 (C-F). ^{1}HNMR ($DCCl_3$-d_6) δ (ppm): 8.55 (s, 1H, NH) 7.68-7.46, 7.01-6.96 (4H, aromatic protons), 2.98 (s, 2H, NH_2). ^{13}C NMR ($DCCl_3$-d_6) δ (ppm): 130.58, 130.49, 130.37, 130.34, 116.14, 115.93. UV (DMF): λ_{max} 355 nm. CHNSF analysis for $C_8H_7N_4SF$ (210), Calcd: C, 45.71; H, 3.33; N, 26.65; S, 15.23; F, 9.0%. Found: C, 45.55; H, 3.05; N, 26.49; S, 15.01; F, 8.89%.

2.1.4 Synthesis of 3-methyl-7-(4'-fluorophenyl)-1,2,4-triazino[3,4 b][1,3,4]Thiadiazol-4-one (6)

A mixture of 5 (0.01 mol) and sodium pyruvate (0.01 mol) in aqueous sodium hydroxide (5%, 100 mL)

was refluxed for 2 h, cooled then neutralized using HCl. The solid formed filtered off and crystallized from THF to give 6 as faint yellow crystals, yield 68%, m.p. 171-172 °C. IR (γ cm^{-1}): 2,921 (CH_3), 1,631 (C=O), 1,600 (C=N), 1,507 (C=N), 1225 (C-F), 1,154 (C-S), 825 (p-substituted phenyl), 617 (C-F).^{1}HNMR ($DCCl_3$-d_6) δ (ppm): 7.84-7.80, 7.24, 7.15-7.10, (s,s,m,4H aromatic), 1.57(s,3H, CH_3). ^{13}C NMR ($DCCl_3$-d_6) δ (ppm): 160.85 (C=O), 130.58-130.34 (aromatic group), 116.14, 115.93, 77.35-76.71, 25-22 (methl group). CHNSF analysis for $C_{11}H_7N_4SFO$ (262), Calcd: C, 50.38; H, 2.67; N, 21.37; S, 12.21; F, 7.25%. Found: C, 50.13; H, 2.55; N, 21.11; S, 12.09; F, 7.13%.

2.1.5 Synthesis of 3-phenyl-7-(4'-fluorophenyl)-4,5-dihydro-1,2,4Triazino[3,4b][1,3,4]Thiadiazole (7)

Equimolar amounts of 5 and phenacyl bromide in ethanol KOH (5%, 50 mL) was refluxed for 2 h, cooled then neutralized with HCl. The solid produced filtered off and crystallized from dioxan to give 7 as pall yellow, yield 60 %; m.p. 199-200 ^{o}C. IR (γ cm^1): 3060, 2,880 (aromatics aliphatic CH), 1,600 (C=N), 1,492, 1,447 (deformation CH_2), 1,345 (cyclic NCSN), 1,230 (C-F), 1156 (C-S), 761(p-substituted phenyl), 693(C-F). ^{1}HNMR ($DCCl_3$-d_6) δ (ppm): 8.16, 7.99, 7.73, 7.57, 7.45, 7.39, 7.24, 6.98, 6.8 (9H, aromatic), 4.48-4.35 (m, 2H, CH_2). ^{13}C NMR ($DCCl_3$-d_6) δ (ppm): 128.60, 77.34, 77.22, 77.02, 76.30, 44.22. CHNSF analysis for $C_{16}H_{11}N_4SF$ (310), Calcd: C, 61.93; H, 3.54; N, 18.06; S, 10.32; F, 6.12%. Found: C, 61.69; H, 3.33; N, 17.85; S, 9.98; F, 6.01%.

2.1.6 Synthesis of 3-(2'-amino-5'-fluorophenyl)-7-(4'-fluorophenyl)-1,2,4-triazin[3,4b][1,3,4]Thiadiazole-4-one (8)

A mixture of 5 (0.01 mol) and 5-fluoroisatin (0.01 mol, in warm 5% aqueous NaOH) was refluxed for 2 h, cooled then neutralized with AcOH. The solid thus obtained filtered off and crystallized from EtOH to give 8 as a yellow crystal, yield 58%, m.p. 176-178 °C. UV (DMF), λ_{max} 303nm. IR (γ cm^{-1}): 3,264 and 1,631 (NH_2), 1,681 (C=O), 1,601, 1,507 (C=N), 1,320 (cyclic NCSN), 1,225 (C-F), 1,156 (C-S), 826 (p-substituted phenyl), 618 (C-F). ^{1}HNMR ($DCCl_3$-d_6) δ (ppm): 8.61-7.84, 7.84-7.83, 7.82-7.81, 7.818-7.812, 7.24, 7.15, 7.14, 7.13, 7.115, 7.110 (aromatic CH), 3.5 (s, 2H, NH_2). ^{13}C NMR ($DCCl_3$-d_6) δ (ppm): 165, 163, 160, 130.58, 130.49, 130.37, 116.15, 115.93, 77.34, 77.03, 76.71. M/Z: (Int.%): 357 (57% M^+ H_2O) 244 (1.0), 206 (15.0), 178 (100), 134 (45), 95 (25.0). CHNSF analysis for $C_{16}H_9N_5SF_2O$ (357), Calcd: C, 53.78; H, 2.52; N, 19.60; S, 8.63; F, 10.64%. Found: C, 53.58; H, 2.32; N, 19.55; S, 8.33; F, 10.43%.

2.1.7 Synthesis of 7-(4'-fluorophenyl)-1H-1,2,4-triazino[3,4-b][1,3,4]thiadiazole-3,4-dione(9)

Equimolar mixture of 5 and diethyl oxalated in THF (100 mL) was refluxed for 4h, cooled. The solid produsedfiltered off and crystallized from MeOH to give 9 as yellowish crystals; yield 60%, m.p. 167-168 °C. UV (DMF): λ_{max} 354 nm. IR (γ cm^{-1}): 3,300-3,107 (b, OH-NH), 1,673 (C=O), 1,644 (C=N), 1,500 (C=C), 1,330 (cyclic NCSN), 1,278 (C-F), 1,133(C-S), 763 (p-substituted phenyl), 623 (C-F). ^{1}HNMR ($DCCl_3$-d_6) δ (ppm): 11.33 (s, 1H, NH), 8.83-7.94, 7.66-7.63, 7.52-7.51, 7.03-6.99 (4H, aromatic CH). ^{13}C NMR ($DCCl_3$-d_6) δ (ppm): 163, 158, 142, 130, 116, 115, 77, 76. CHNSF analysis for $C_{10}H_5N_5SFO_2$ (264), Calcd: C, 45.45; H, 1.89; N, 21.21; S, 12.12; F, 7.19%. Found: C, 45.11; H, 1.58, N, 20.98, S, 11.89; F, 6.91%.

2.1.8 Synthesis of Trans3-(4'-bromostyryl)-7-(4'-fluorophenyl)-1,2,4-triazino[3,4b][1,3,4]Thiadiazol-4-one (11)

A mixture of 10 (0.01 mol) and 5 (0.01 mol) in glacial acetic acid (50 mL) was refluxed for 3h, cooled then poured onto ice. The yielded solid filtered off and crystallized from EtOH to give 11 as yellow crystals, yield 55%, m.p. 173-175 °C. UV (DMF): λ_{max} 400 nm. IR (γ cm^{-1}): 2,900 (aliphatic CH), 1,660 (C=O), 1,625 (C=N), 1,484 (deformation aliphatic CH), 1,340 (cyclic NCSN), 1,244 (C-F), 808 (p-substituted

phenyl), 749 (C-Br), 545 (C-F). ^{1}HNMR ($DCCl_3$-d_6) δ (ppm): 8.57, 8.0 (α, β- CH=CH coupling). 7.9-7.4 (4H, aromatic CH), 7.38-644 (4H, aromatic CH), 5.68-5.06, 4.8-4.21 (each m, 2H, CH=CH protons). ^{13}C NMR ($DCCl_3$-d_6) δ (ppm): 161.17 (C=O), 132.14 (C=C), 129.95 (aromatic carbons), 77.34, 77.23, 77.02, 76.71. M/Z: (Int.%): 448 (50% M^+ H_2O), 203 (100), 180 (8.25), 156 (15.0), 153 (5.0), 95 (3.0). CHNSFBr analysis for $C_{18}H_{10}N_4SFBrO$ (429), Calcd: C, 50.34; H, 2.33; N, 13.05; S, 7.45; F, 4.42%, Found: C, 50.11; H, 2.12; N, 12.85; S, 7.33; F, 4.25%.

2.1.9 Synthesis of 2,3,4,5-tetrahydro-7-(4'-fluorophenyl)-1,2,4-triazino[3,b][1,3,4]Thiadiazole-4-one (12)

A mixture of 5 (0.01 mol) and mono-chloroacetic acid (0.01 mol) in DMF (50 mL) was refluxed for 2 h, cooled then poured onto ice. The solid produced filtered off and crystallized from dioxan to give 12 as pall yellow crystals, yield 65%, m.p. 180-182 ^oC. IR (γ cm^{-1}): 3,197 (NH), 1,680 (C=O), 3542 (OH), 1,603 (C=N), 1,583 (C=C), 1,487 (deformation CH_2), 1,383 (NCSN), 1,204 (C-F), 1,180 (C-S), 818 (p-substituted phenyl), 687 (C-F). ^{1}HNMR ($DCCl_3$-d_6) δ (ppm): 8.60(s, 1H, NH), 7.84-7.81, 7.24-7.107 (each m, 4H, aromatic protons), 1.60 (s, 2H, CH_2). ^{13}C NMR ($DCCl_3$-d_6) δ (ppm): 160.84, 130.58, 130.50, 130.36, 130.33, 116.15, 115.93, 77.34, 77.23, 77.02, 76.71, 50.01. CHNSF analysis for $C_{10}H_7N_4SFO$ (250), Calcd: C, 48.0; H, 2.80; N, 22.4; S, 12.8; F, 7.60%. Found: C, 47.79; H, 2.55; N, 21.98; S. 12.60; F, 7.42%.

2.1.10 Synthesis of 7-(4'-fluorophenyl)-1,2,4-triazino[3,4-b][1,3,4]Thiadia zole-4-one (13)

An equimolar mixture of 5 and 1,1-dichloroacetic acid in DMF (50 mL) was refluxed for 2h, cooled then poured onto ice. The solid obtained filtered off and crystallized from EtOH to give 13 as faint yellow, yield 40%, m.p. 148-150 °C. IR (γ cm^{-1}): 3,020 (Aromatic CH), 1,700 (C=O), 1,610 (C=N), 1,330 (NCSN), 1,230 (C-F), 820 (p-substituted phenyl). ^{1}HNMR ($DCCl_3$-d_6) δ (ppm): 8.57 (s, 1H, cyclic CH of 1,2,4-triazine), 7.70-7.69, 7.589-7.584, 7.57-7.5, 7.49-7.24 (aromatic protons). CHNSF analysis for $C_{10}H_5N_4SFO$ (248), Calcd: C, 48.38; H, 2.01; N, 22.58; S, 12.90; F, 7.66%. Found: C, 48.11; H, 1.88; N, 22.21; S, 12.69; F, 7.51%.

2.1.11 Synthesis of 4-amino-6-(4'-bromophenyl)-3-thioxo-1,2,4-triazin-5-(2H)-one (14)

A mixture of thiocarbohydrazide (0.01 mol) and compound 10 (0.01mol) in DMF (50 mL) was refluxed for 3 h, cooled then poured onto ice. The yielded solid filtered off and crystallized from EtOH to give 14 as orange crystals, yield 80%, m.p. 245-247 °C. IR (γ cm^{-1}): 3,208 (NH_2), 3,120 (NH), 1663 (C=O), 1,625 (deformation NH_2), 1,585 (C=N), 1,485, 1,431 (deformation -CH=CH-), 1,245 (C-F), 1,176 (C-S), 808, 749 (p-substituted phenyl), 716 (C-Br), 632 (C-F). ^{1}HNMR ($DCCl_3$-d_6) δ (ppm): 8.49 (s, 1H, NH), 7.64, 7.62, 7.51, 7.41, 7.42, 7.40, 7.37, 7.30 (m, 8H, aromatic CH), 6.32 (2H, CH=CH-, coupling), 2.63 (s, 2H, NH_2). CHNSBr analysis for $C_{11}H_9N_4SBrO$ (325), Calcd: C, 40.61; H, 2.76; N, 17.23; S, 9.25%. Found: C, 40.43; H, 2.55; N, 17.01; S, 9.0%.

2.1.12 Synthesis of Schiff Base (15)

A mixture of 14 (0.01mol) and 4-fluorobenzaldehyde (0.01 mol) in ethanol (50 mL) with drops of conc. HCl (0.5 mL) was refluxed for 1h, cooled then poured onto ice-$NaHCO_3$. The solid obtained filtered off and crystallized from EtOH to give 15 as orange-yellowish crystals, yield 85%; m.p. 236-238 °C. IR (γ cm^{-1}): 3,180 (NH), 2,924 (aliphatic CH), 1,626 (C=O), 1,587 (C=N), 1,484, 1,400 (deformation -CH=CH-), 1,227 (C-F), 858, 809 (p-substituted phenyl), 780 (C-Br), 562 (C-F). ^{1}HNMR ($DCCl_3$-d_6) δ (ppm): 8.60 (s, 1H, NH), 8.5 (s, 1H, CH=N), 7.84-7.81, 7.7-7.6, 7.58-7.56, 7.24, 7.15-7.13, 7.10 (8H, aromatic CH), 6.98, 6.22 (each s, 2H, -CH=CH-). ^{13}C NMR ($DCCl_3$-d_6) δ (ppm): 161.17, 132.93, 132.34, 129.95, 77.36, 77.22, 76.70. CHNSF analysis for $C_{18}H_{12}N_4SFBrO$ (431), Calcd: C, 50.11;

H, 2.78; N, 12.99; S, 7.42; F, 4.90%. Found: C, 49.85; H, 2.55; N, 12.71; S, 7.19; F, 4.65%.

2.1.13 Synthesis of (4'-bromostyryl)-7-(4'-fluorophenyl)-6,7-dihydro-1,2, 4-triazino[3,4b] [1,3,4]Thiadiazole-4-one (16)

Compounds 15 (0.5 g) in dry C_6H_6 (100 mL) was refluxed for 6h, cooled. The solid produced filtered off and crystallized from C_6H_6 to give 16asdeep orange crystals, yield 89%, m.p. 228-230 °C. IR (γ cm^{-1}): 3,206 (NH), 2,920, 2,850 (aliphatic CH), 1,661 (C=O), 1,623 (C=N), 1,339 (cyclic NCSN), 1235 (C-F), 1,126 (C-S) 849,808 (p-substituted phenyl), 763 (C-Br), 647 (C-F). ^{1}HNMR ($DCCl_3$-d_6) δ (ppm): 8.53 (s, 1H, NH), 7.84 (s, 1H, CH of thiadiazole), 7.80-7.03 (8H, aromatic protons), 6.43 (2H, CH=CH). CHNSF analysis for $C_{18}H_{12}N_4SFBrO$ (431), Calcd: C, 50.11; H, 2.78; N, 12.99; S, 7.42; F, 4.40%. Found: C, 49.88; H, 2.55; N, 12.80; S, 7.09; F, 4.15%.

2.1.14 Synthesis of Trans-3-(4'-bromostyryl)-7-(4'-fluorophenyl)-1,2,4-tri azino[3,4-b][1,3,4]Thiadiazol-4-one (11)

Compound 16 (0.5 g) and sulfur (0.2 g) in dry C_6H_6 (100 mL) was refluxed for 6 h, cooled. The solid obtained filtered off and crystallized from ethanol to give 11. Melting point of 11 from 5 and/or 11 from 16 gave 175°C -176 °C. Mixed melting point gave 174°C -175 °C.

2.2 Biological Activity —The Molluscicidal Evaluation

In the past decades, the problem of human, plants and animals is present of very clean water. One from the diseases is bilharziasis which caused by snails in wastewater. 1,2,4-Triazine derivatives are used as molluscicidal agents [4-19]. In addition 1,3,4-thiadiazoles also showedmolluscicidal activities [13]. Thus, the main aim of the present work is combination between two heterocyclic moiety and evaluation as molluscicidal agents towards a type of snails responsible for Bilharziasis diseases, in hope to enhance their biocidal effects.

The prepared compounds were tested as killing of those snails (shell 5-8 mm). The intermediate host of sohistosomamausoni Giza city-egypt was not treated with molluscicides. 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 kept in plastic aguar filled with dechlorinated tap-water at room temperature. Stock soln (500 mg/mL) of the tested compounds were synthesized in the least volum 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 activity towards snails according the instructions given by WHO organization [20, 21]. The biocidal results reported in Table 1.

From the results obtained (Table 1), the authors conclude that:

Generally, all the new synthesized compounds showed a moderate activity.

Only the compound 16, 15, 14 and 9 exhibited a higher molluscicidal activity in compare with the standard Baylucide, which is may be due to presence of fluorinated 1,3,4-thiadiazolo-as-triazine (16). Schiff's base (15), N-amino-3-mercapto-1,3,4-triazinone (14) and 1,3,4-thia-diazolo-as-triazin-dione (9).

Number of compounds 8, 11 and 7 displayed a good effect while 6, 12 and 13 recorded a poor activity.

It is clear that, presence of both NH_2, NH, SH and OH functional groups, in addition of fluorine atom led to enhance the total electronegativities and also increase the charges on the effectives centers. This direction of electron-density, afforded to higher mortality of tested snails.

3. Results and Discussion

3.1 Synthesize of 1,2,4-triazino[3,4-b][1,3,4]Thiadiazlolone

The nucleophilic attack of NH_2 group to the πe acceptor carbons atoms provides a direct and

convenient method for functionalization of 1,2,4-triazines. Thus, 5-hydrazino-2-(4'-fluorophenyl)-1,3,4-thiadiazole (5) was used as starting material for building a targets, which obtained from condensation of dithioicformic acid hydrazide (1) [17] with 4-fluorobenzaldehyde in boiling ethanol-acetic acid to give the hydrazone 2. Cycloaddition reaction of 2 by refluxing with dry benzene produced the perhydro-1,3,4-thiadiazole 3 (Fig. 1). IR of 2 recorded a lack's of NH_2 with appearance of NH-NH hydrazo band of 3.

Aromaticity of 3 via warming with sulfur-dry benzene afforded 2-(4'-fluorophenyl)-1,3,4-thiadiazol-5(4H)one (4). Asimple nucleophilic substitution of SH group by $NHNH_2$ group of 4 was tack place from hydrazinolysis to give the start 5 (Scheme 1). Formation of 5 from 1 may be as shown in the Fig. 1.

Former structure of 5 was confirmed from both elemental and spectral measurements. IR spectrum showed an absorption bands in γ 3,420-3,111 cm^{-1} (hydrazino NH-NH_2), 3,100-3,090 cm^{-1} (aromatic CH) and 1,210 cm^{-1} (C-F). UV absorption spectra (DMF) recorded λ_{max} at 355 nm attribute the presence of n-π* and n-σ* electronic transition. ^{1}HNMR (DMSO-d_6) exhibited a resonated signals at δ 8.55 and 2.98 ppm for NH and NH_2 protons with δ 7.78-7.46 ppm characterized to aromatic protons. ^{13}C NMR give only a resonated signals of aromatic carbons and C=N at δ 130.50-130.34 ppm and 116.17, 115.93 ppm which deduced that structure.

The main aim of the present work is synthesize of new fluorinated 1,2,4-triazino-1,3,4-thiadia-zolones as biocidal probes. Thus, cyclocondensation of 5 with sodium pyruvate (aq. NaOH), phenacyl bromide (alco. KOH), 5-fluoroisatin (aq. NaOH) and/or diethyloxalate (THF) [18] furnished 3-methyl-7-(4'-fluorophenyl)-1,2,4-triazino[3,4-b][1,3,4]thiadiazol-4-one(6), 3-phenyl-7-(4'-fluorophenyl)-4,5-dihydro-1,2,4-triazino[3,4-b][1,3,4]thiadiazol-4-one (7) 3-(2'-amino-5'-fluorophenyl)-7-(4'-fluorophenyl)-1,2,4-triazino[3,4-b][1,3,4]thiadiazol-4-one (8) and/or 7-(4'-fluorophenyl)-2H-1,2,4-triazino[3,4b][1,3,4]thiadiazol-3,4-dione (9)

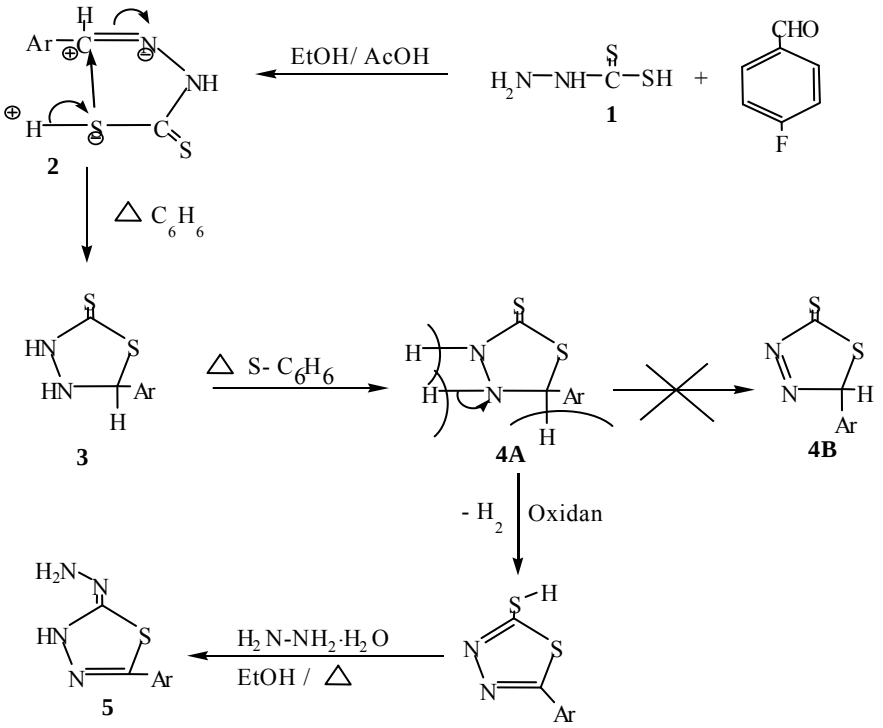
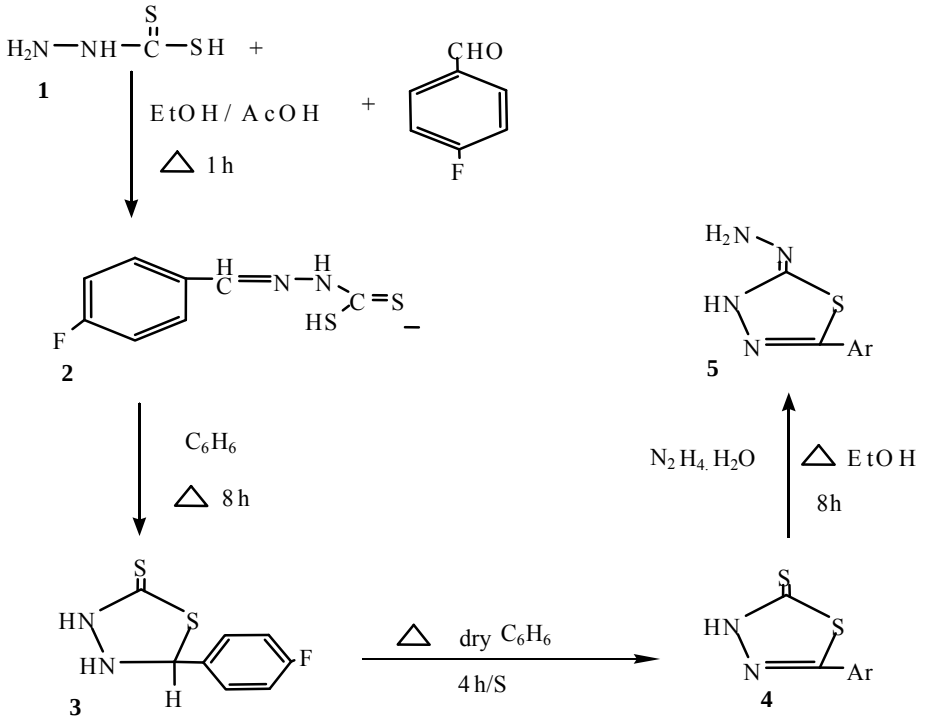


Fig. 1 Formation of compound 5 from 1.



Scheme 1 Formation of 2-5.

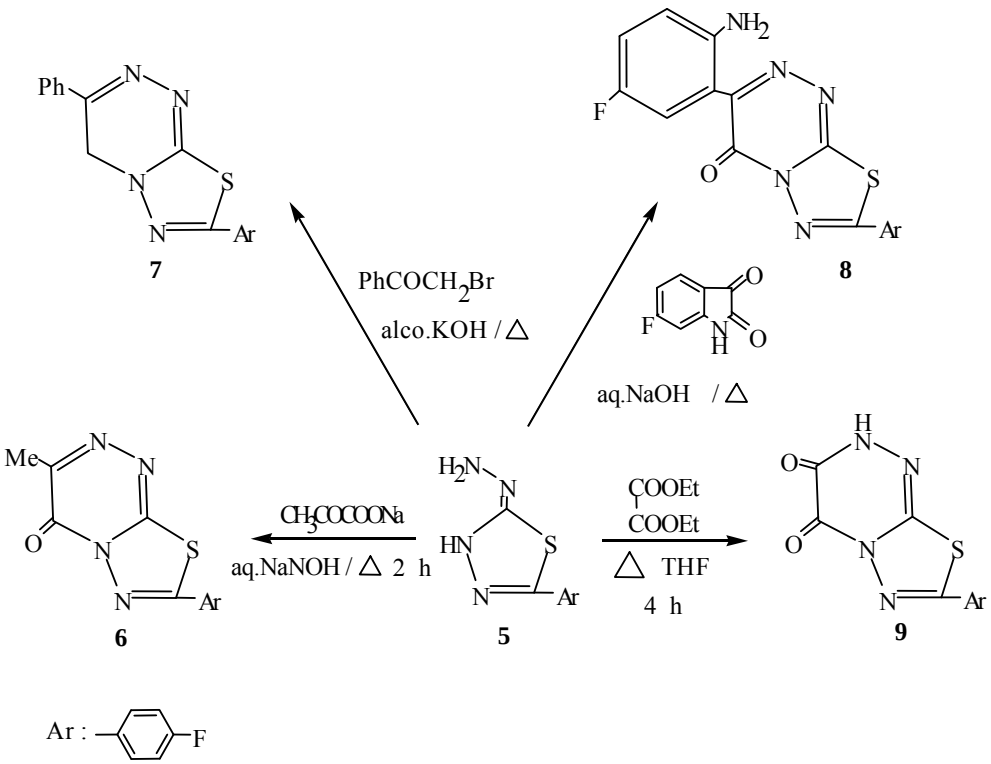
respectively (Scheme 2). Formation of 8 may be as shown in Fig.2.

Presence of hydrogen bond in the tautomeric forms AB having an N…H-O hydrogen bond is energetically more favorable in the former structural 9 (Scheme 3). Structure of compounds 6 and 8was elucidated from correct elemental analysis and their spectral data.

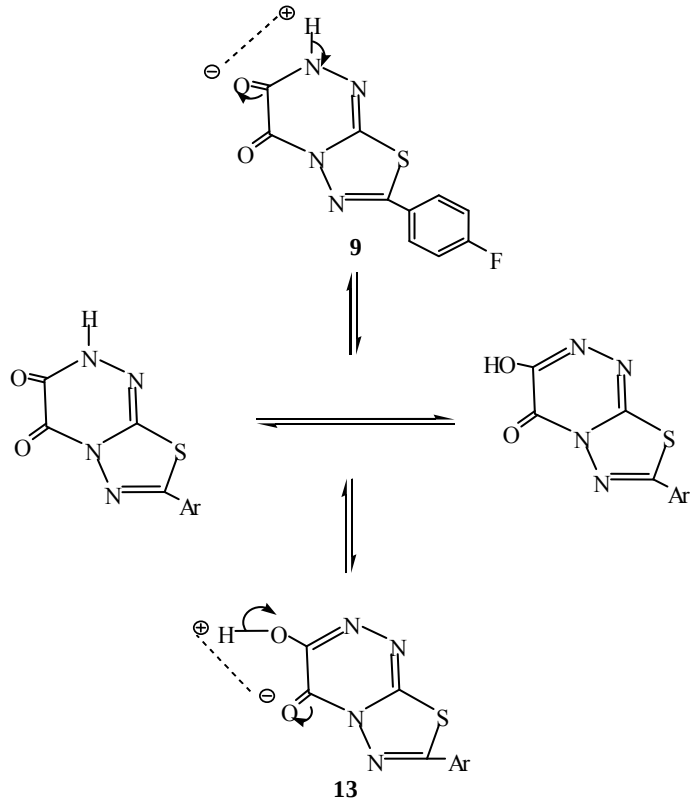
UV absorption spectra of 8 recorded λ_{max} at 303 nm, while IR of 6 and 8 exhibite γ at 1,681 cm^{-1} attribute C=O group, in addition γ at 3,264 and 1,631 cm^{-1} for NH_2 of 8. ^{1}HNMR spectrum of 8 showed δ at 8.61, 7.84-7.11 ppm for aromatic protons with δ at 3.58 ppm to NH_2 protons. ^{13}C NMR of 8 recorded a resonated signals at δ 165, 163, 160 and 130 ppm characterized for C=O, NCS, C=N and aromatic carbons. Also, mass study of 8 showed m/z at 357 (57%, M^+H_2O) with a base peak at 178 of C_9H_5NSF (Fig. 3).

Similary, cyclocondensation of compound 5 with trans-4-(4'-bromophenyl)-2-oxo-but-3-enoic acid (10) [6] in refluxing glacial acetic acid yielded 3-(4'-bromostyryl)-7-(4'-fluorophenyl)-1,2,4-triazino [3,4-b][1,3,4]thiadiazol-4-one (11) (Scheme 4). Formation of 11 may be as shown in the Fig. 4. In this reaction the compound 11A was isolatedand not 11B, which deduced from treated 11 with K_2CO_3 solution, were did not give acidity test. Thus, OH group of carboxylic tack part in a carboxylic group tack part in the cyclization step via loss H_2O.

Structure of compound 11 was established from both elemental and spectral analysis. UV absorption spectrum (DMF) recorded λ_{max} at 400 nm, which higher than that of 5. The additive value of UV is may be due to the extention heteroconjugation from 1,3,4-thiadiazole to 1,2,4-triazine and that styryl moiety. IR spectrum showed a frequency bands at γ 1682 and 1603 cm^{-1} for C=O and styryl groups, with lack's of OH functional group. ^{1}HNMR spectra exhibited a δ at 8.57 and 8.0 ppm which indicate the presence of α-and β-CH=CH spin-spin coupling with δ at 7.7-7.4 ppm for aromatic protons. Mass fragmentation pattern of compound 11 record a molecular ion peak at m/e 448 (50% M^+H_2O) with additional base peak at 203 as $C_{10}H_4N_4SFO$ (Fig. 5).



Scheme 2 Formation of 6-9.



Scheme 3 The tautomeric strucral formula of 9.

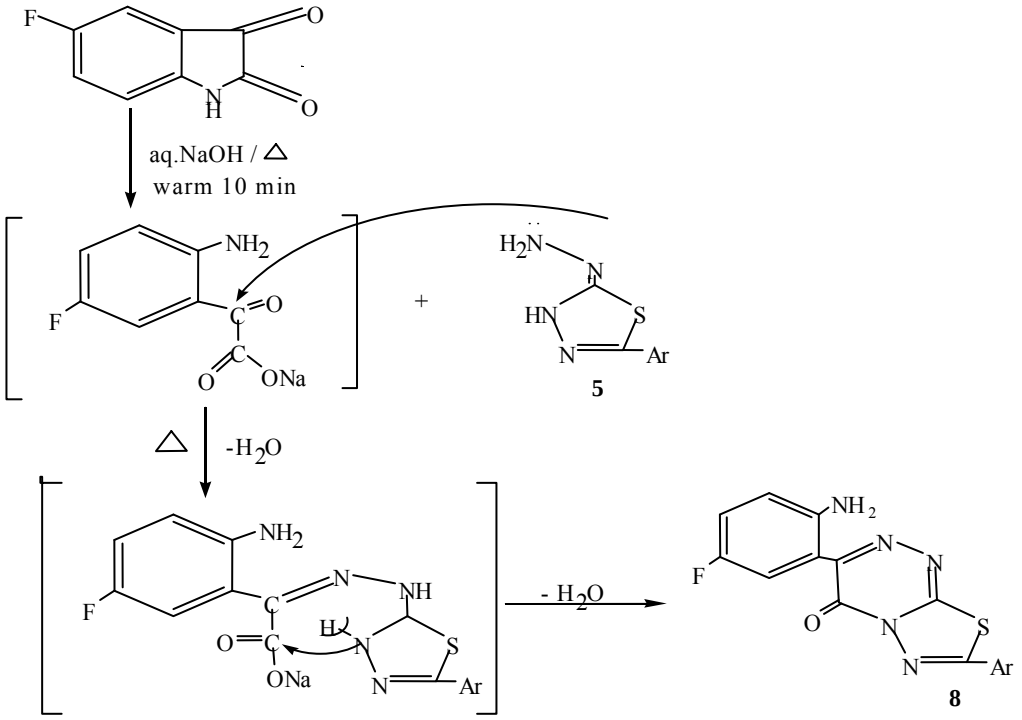


Fig. 2 Formation of compound 8 from 5.

A recent investigation [1, 2], which combines these two biological rings together to give a compact and planner system of 1,2,4-triazino-1,3,4-thidiazolones in hope to enhance that biocidal properties. Thus, alkylation of 5-hydrazino-thiadiazole 5 using both monochloro-acetic acid and/or 1,1-dichloroacetic acid in boiling DMF (via SN^2 reaction) produced 2,3-dihydro-7-(4'-fluorophenyl)-1,2,4-triazino[3,4b][1, 3,4]thiadiazol-4-one (13) respectively (Scheme 4).

Former structure of 12 was established from IR spectra were showed γ at 1,682 and 3,197 cm^{-1} for C=O and NH groups of 1,2,4-triazine moiety.

Another procedure for the synthetic of the 1,2,4-triazino[3,4b][1,3,4]Thiadiazolone (11) was deduced from cyclocondensation of compound 10 with thiocarbohydrazide in refluxing DMF to give 4-amino-6-(4'-bromostyryl)-3-thioxo-1,2,4-triazin-5-(2H)-one (14) [6]. Condensation of 14 with 4-fluorobenzaldehyde in warm ethanol-conc HCl produced the Schiff base 15. Cycloaddition of 15 by refluxing with benzene yielded 6,7-dihydro-3,7-disubstituted 1,2,4-triazino[3,4-b][1,3,4]thiadiazol-4-one (16). Finally aromatization of 16 via simple oxidation reaction by reflux with sulfur-dry benzene furnished the target 11 (Scheme 5). Melting point and mixed melting point from two routes, gave no-depression which confirm that structure.

Structure of 15 was established from elemental and spectral data. IR spectrum recorded a lack's of NH_2 group, while ^{1}HNMR spectrum gave us a good indication about that structure. A resonated signals at δ 8.6 ppm, 8.57 ppm for NH and azomethine, 6.98 ppm and 6.22 ppm for styryl protons, were observed, in additional a signal for styryl and heteroaromaticprotons. Also, structure of 16 was deduced from that IR which recorded γ at 3,206 cm^{-1} (NH), 1,661 cm^{-1} (C=O). ^{1}HNMR showed δ at 8.53 ppm and 7.84 ppm for NH and CH of thiadiazole ring.

4. Conclusions

The study reports the successful synthesis of some new fluorinated 5-hydrazino-1,3,4-thiadiazole andconversion into the corresponding fluorinated

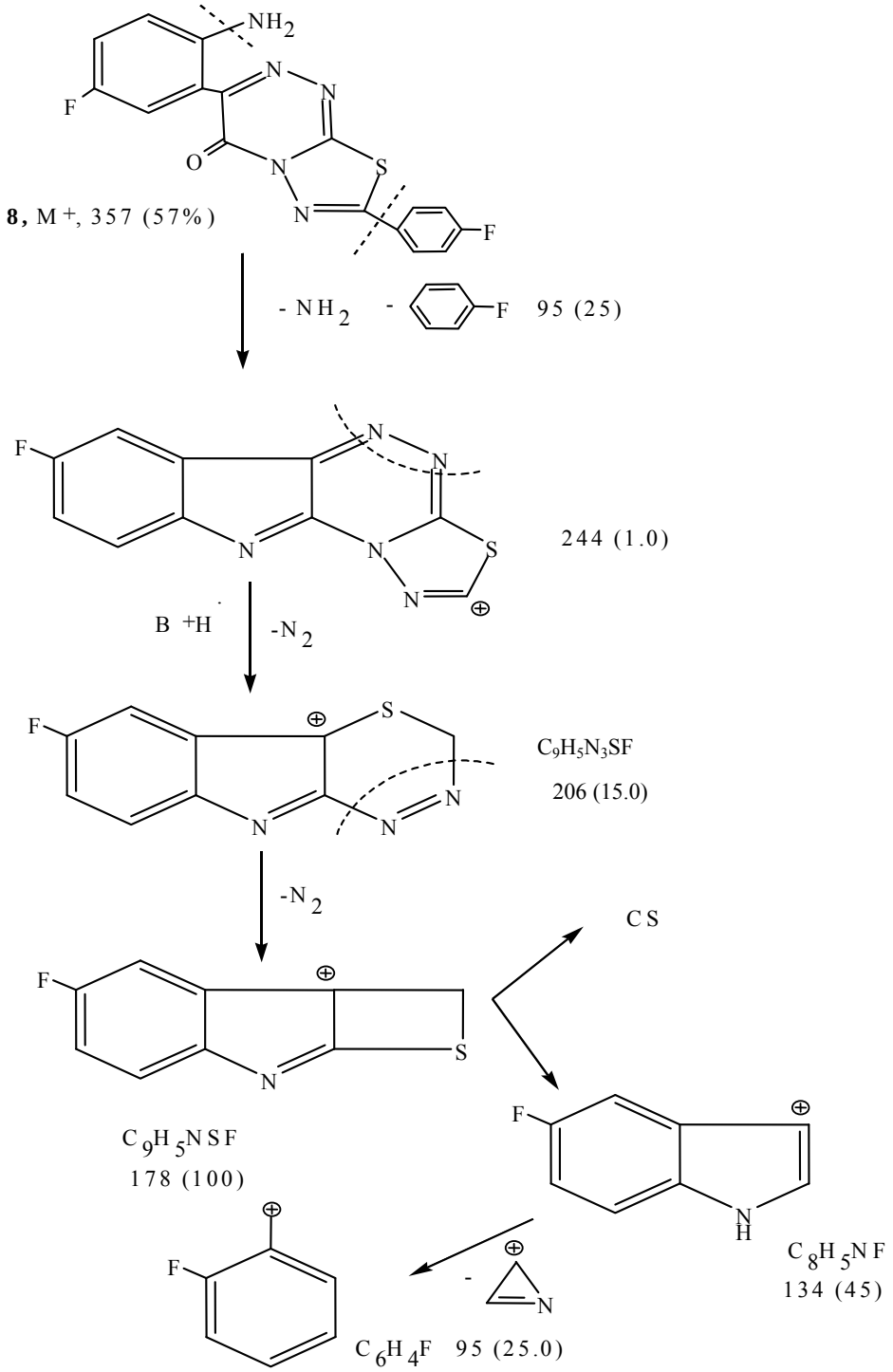
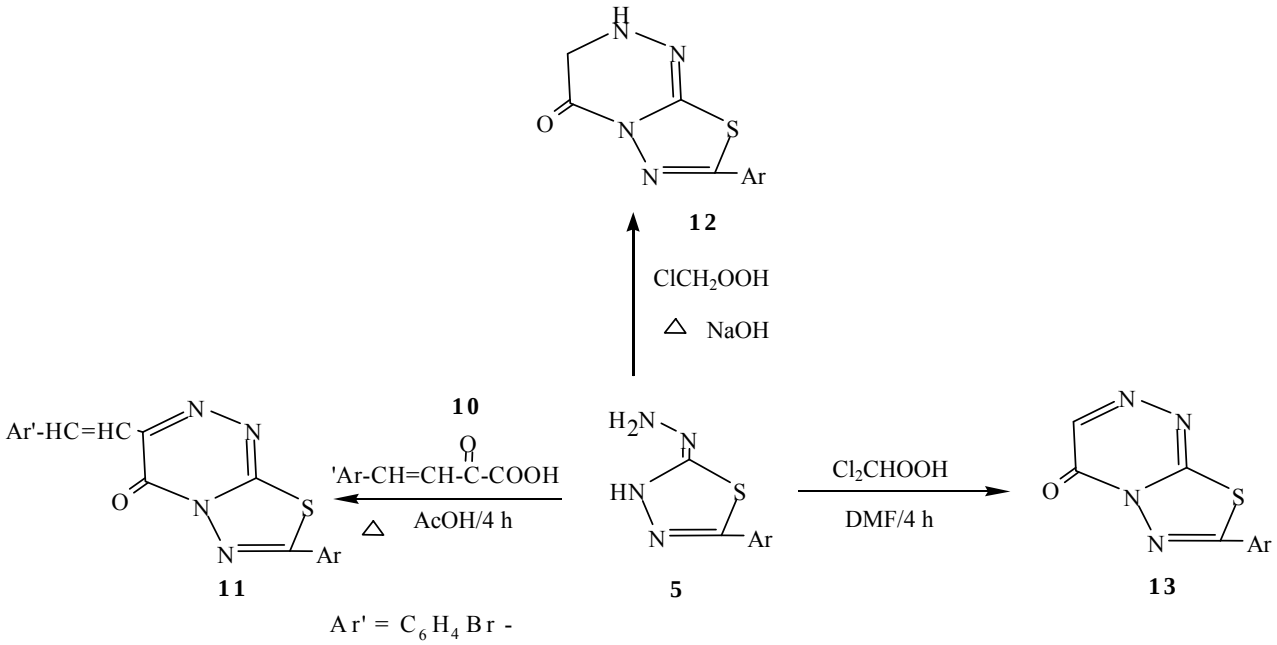
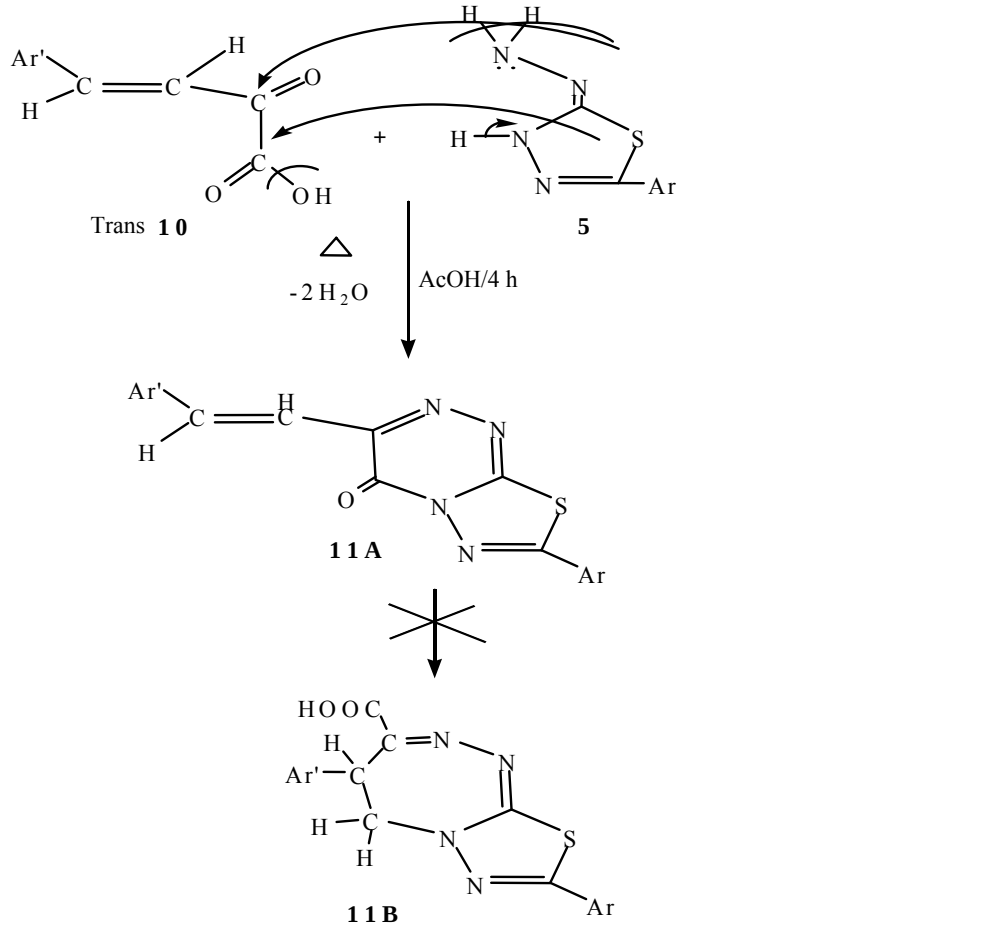


Fig. 3 Mass fragmentation pattern of compound 8.



Scheme 4 Formation of 11-13.



Scheme 5 Formation of 14-16.

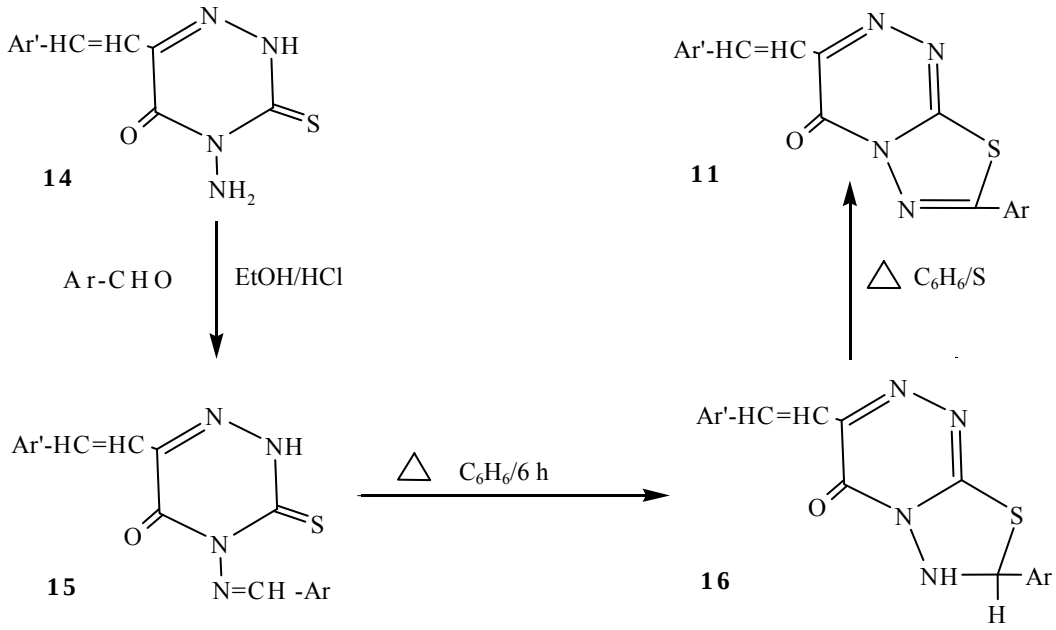


Fig. 4 Formation of compound 11 from 5.

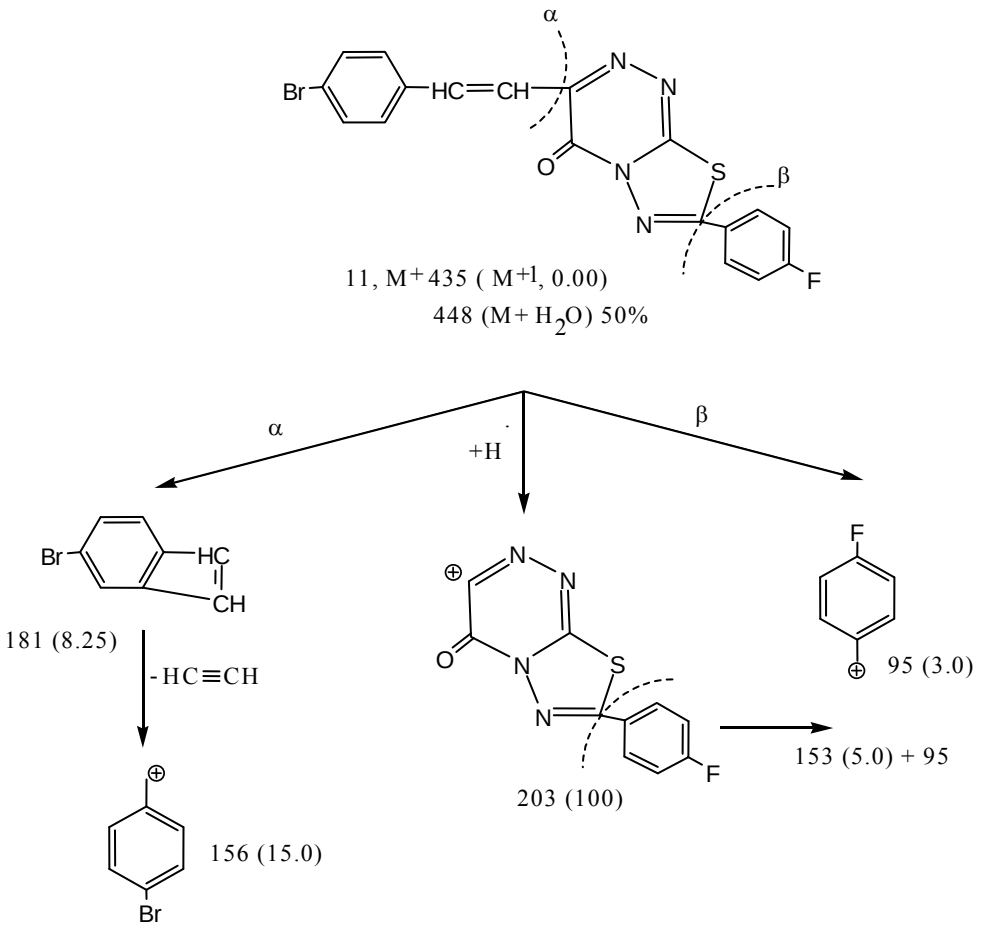


Fig. 5 Mass fragmentation pattern of compound 11.

Table 1 The mortality of Snails at various concentrations for the new compounds.

Compound No.	25 ppm	50 ppm	100 ppm
6	45	48	65
7	45	48	68
8	50	56	75
9	55	62	78
11	50	52	70
12	40	52	62
13	42	50	60
14	50	60	80
15	55	72	82
16	60	72	85
Baylucide	100	100	100

1,2,4-triazino[3,4-b][1,3,4]thiadia-zolones via ring closure reactions of chemoselectivebifunctional compounds. The use these obtained systems as molluscicidal agents to kills a type snails responsible for Bilharziasis diseases is one of the active compounds present in many standard taknic to enhance the net biological activity of a new fluorinated systems. The screening reported that the newly compounds 9, 14, 15 and 16 exhibited a higher to moderate activity against the type of snails used. These results were obtained probably due to presence of fluorine atoms substituted 1,2,4-triazinothiadiazolones which depends on the electronic distribution over all the active cites of the tested systems.

As a result, the authors say that the fluorinated 1,2,4-triazino-thiadiazolones are more active than both 1,2,4-triazines and 1,3,4-thiadiazoles.

Acknowledgements

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