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Scientific Research

Synthesis of Novel Fluorine Substituted Isolated and Fused Heterobicyclic Nitrogen Systems Bearing 6-(2'-Phosphorylanilido)-1,2,4-Triazin-5-One Moiety as Potential Inhibitor towards HIV-1 Activity

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Abstract

Novel 6-(5'-fluoro-2'-diphenylphosphorylanilido)-3-hydrazino-1,2,4-trizin-5 (2H) one (3) is achieved from hydrozinolysis of the corresponding 3-thioxo-analoges 2. Compound 2 is also obtained from phosphorylation of 6-(5'-fluoro-2'-aminophenyl)-3-thioxo-1,2,4-triazin-5(2H) one (1). Novel fluorine substituted isolated and/or fused heterobicyclic nitrogen systems bearing and/or containing, 6-phosphoryl anilido-1,2,4-trizin-5 (2H) one moiety (4 - 22) have been synthesized from ring closure reactions of compound 3 with π-acceptors activated carbon compounds in different medium and conditions. Structures of the products are characterized by MS, IR, UV-VIS, CH, N, and $^{1}H/^{13}C$NMR spectral data. The new products have been evaluated as potential inhibitors towards HIV-1 activity.

Keywords

Synthesis, Fluorine, Phosphorus, Sulfar 1,2,4-Trizinones HIV-1

1. Introduction

Organophosphorus systems are ubiquitous in nature and exhibit many applications in the field of agriculture medicine and industry [1] [2]. Many multi-ring phosphorus heterocycles are used as pesticide [3], bactericide

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[4]-[6], antibiotics [4], and acts as HIV protease inhibitors [7]. Thus, synthesis of new phosphorus bearing a heterocycles has attracted the attention of researchers. Phosphorylation of organic compounds often improves their biological activity, especially through a vital energy, because the P-O is the store of energy for metabolism process. For example, phophorylated-N in the nucleocapsid affects the interaction between the N-atom and the genomic RNA. The charge repulsion between the negatively charged phosphoserine and the negatively charged RNA may weaken the interaction between N-atom and RNA, thus enabling the viral polymerase to gain access to genomic RNA and to initiate viral RNA transcription and replication [8]. On the other hand, chemistry of N-phosphorylheterocycles showed that these compounds from two dimensional polymeric chains via intermolecular P-O^{-}$^{+}$H-N hydrogen bonds [9]. Also, phosphodiester compound had a type of action, especially enzymetic of DNA replication [10] on DNA ligase as (**Figure 1**).

It is interesting that fluorine containing aheterocycles bearing functional groups exhibits highly effective in biological process, pharmaceuticals, agrochemicals, polymers and a wide range of consumer products [11]. It reflects its resistance to metabolic change due to the strength of the C-F bond providing biological stability and the application of its nonstick-interfacial physical characteristics [12]-[16]. Abdel-Rahman *et al.* [17]-[21] reported the synthesis and chemical reactivity of 3-thioxo-1,2,4-triazin-5 one derivatives as a bioactive molecules, especially as anti-cancer, anti-AIDS, Amyllolytic, cellobiase and antimicrobial agents. Based upon these observations, the aim of this work is to study the formation of 6-(5'-fluoro-2'-phosphoryl anilido-3-hydrazino-1,2,4-triazin-5 (2H) one then study their behaviour as electron donor towards different electron acceptors such as carbo-sulfur, oxygen, halogen and nitrogen compounds; finally, a type of isolated and/or fused heterobicyclic systems obtained and evaluation as potential inhibitors towards HIV-1 virus.

2. Experimental

Melting points were determined with an electro-thermal Bibbly Stuart Scientific Melting point SMPI (UK). A perkin Elmer (Lambda EZ-2101) 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 DPX 400 MHz using TMS as an internal standard for recording the ^{1}H/^{13}C NMR spectra in deuterated DMSO (δ in pp m). AGC- MS-QP 1000 Ex model is used for recording the mass spectra. Hexafluorobenzene was used as external standard for ^{19}FNMR at 84.25 MHz and ^{31}P (in $CDCl_3$, 101.25 MHZ).

Elemental analysis was performed on Micro analytical Center of National Reaches Center-Dokki, Cairo, Egypt. Compound **1** prepared according the reported method [17].

6-(2'-aminos-5'-fluorophenyl-3-thioxo-1,2,4-triazin-5(2H)one (1)

A mixture of 5-fluoroisatin (0.01 mol) in sodium hydroxide solution (5%, 50 ml) warm for 10 min, then thiosemicarbazide (0.01 mol, in hot water, 10 ml) add and complete the refluxing for 2 h. The reaction mixture cooled then poured onto ice and neutralize with diluted HCl. The solid thus obtained filtered off and crystallized from ethanol to give **1** as yellow crystals, yield 80%; m.p. 265˚C. Analytical data; found: C, 44.91; H, 2.90; F, 7.58: N, 23.40; S, 13.29%.Calculated for $C_9H_7FN_4OS$ (238); C, 45.37; H, 2.94; F, 7.98; N, 23.52; S, 13.44%.UV: λ_{max} (EtOH) = 280 nm. IR νcm^{-1}: 3424(NH_2), 3258, 3169 (NH, NH), 1685 (C=O), 1618 (deform. NH_2), 1545 (C=N), 1263 (C-F), 858,818 (aryl CH), 685 (C-F). ^{1}H NMR (DMSO) δ = 14.66, 12.66, 10.90 (each s, 1H, 3NH), 8.68 - 8.06, 7.69 - 7.64, 7.39 - 7.30, (s, 3H, aryl protons). ^{13}C NMR (DMSO): δ 179.47(C=S), 162 (C=O), 159 - 157 (C-F), 138.54 (C=N), 131.82, 121.8, 121.51 (aromatic carbons, 78.14, 77.71 (C_5 - C_6, 1,2,4-trinzine). M/Z (Int. %); 256 (M + H_2O, 5%), 68 (100), 148(21), 138(18), 110 (30), 96 (50), 82(58.0), 70(78).

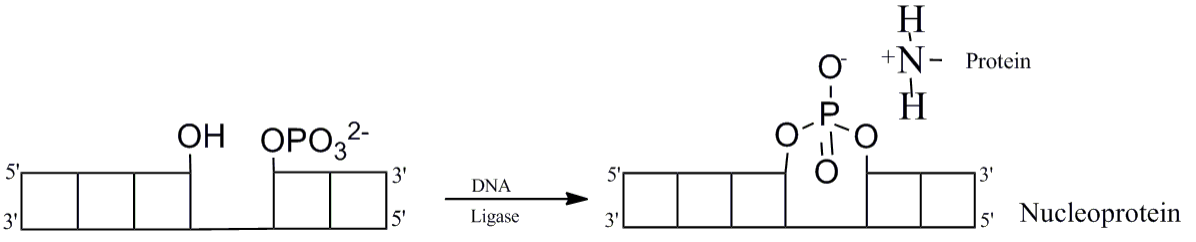


Figure 1. The reaction of DNA ligase phospho diester link.

6-(5'-Fluoro-2'-diphenylphosphorylanilido)-3-thioxo-1,2,4-triazin-5(2H)one (2)

Equimolar mixture of compound **1** and diphenylphosphoryl chloride in DMF (20 ml) warm for 1h, cooled then poured onto ice. The produce solid filter off and crystallized from methanol to give **2** as deep yellow crystals. Yield 70%; m.p. 218-220˚C. Analytical data; found: C, 53.39; H, 3.51; F, 3.88: N, 11.69%.Calculated for $C_{21}H_{16}FN_4PSO_4$(470); C, 53.61; H, 3.70; F, 4.04; N, 11.91%. IR νcm^{-1}: 3133.8 (NH), 1688.4 (C=O), 1574 (C=N), 1370 (Cyclic NCSN), 1262 (C-F), 1200 (P=O), 1150 (C-S), 10.96 (Ph-O-P), 858, 801 (substituted phenyls) M/Z: (Int.%); 473 (M + 3, 5.11), 110 (100).

3-Hydrazino-6-(5'-fluoro-2'-diphenylphosphorylanilido)-1,2,4-triazin-5(2H)one (3)

A mixture of compound **2** (1 gm) and hydrazine hydrate (2ml) in ethanol (50ml) reflux for 2h. cooled. The solid thus produce filter off and crystallized from ethanol to give **3** as orange crystals, yield 85%; m.p. 178˚C - 180˚C. Analytical data; found: C, 53.45; H, 3.59; F, 3.80%.Calculated for $C_{21}H_{18}FN_6PO_4$(468), C, 53.84; H, 3.84; F, 4.02; N, 17.14%. IR ν cm^{-1} = 3381, 3340, 3220 - 3190 (NH, NH, NH_2), 1682 (C=O), 1558 (C=N), 1266.9 (C-F), 1210-1156 (P=O). 1050 (Ph-O-P), 860,805 (substituted phenyls).^{1}H NMR(DMSO) δ = 10.7, 10.2, 8.7 (each s, 3H, 3NH, 1,2,4-triazino NH-P=O), 7.511, 7.27-2.24, 7.23-7.22 (each s, 3H, aryl protons); 7.143 - 7.002; 6.860 - 6.796 (each m, 10H, phenyl protons), 2.88 (s, 2H, NH_2 of hydrazine), ^{13}C NMR (DMSO) δ = 163.78, 159.44, 157.86, 134.97, 129.07, 127.65, 123.66, 122.87, 120.12, 120.09, 113.47, 113.31, 110.77, 110.71, 107.93, 105.27, 105.10, 77.76, 77.33.

3-(3'-Amino-4'-carboxy-5-(4-chlorophenyl)-4',5'-dihydro-pyrazolin-1'-yl)-6-(5'-fluoro-2'-diphenylphosphorylanilido)-1,2,4-triazin-5(2H)one (4)

Equimolar amounts of **3** and α-(4-chlorophenylidene) cyano acetic acid in ethanol (100 ml) and a few drops piperidine (0.5 ml) reflux for 8h, cooled, then added off and crystallized from dioxan to give **4** as yellowish crystals, yield 65% m.p., 158˚C - 160˚C. Analytical data; found: C, 54.81; H, 3.11; F, 2.55; Cl, 5.09; N, 14.29%. Calculated for $C_{31}H_{24}FClN_7PO_6$(675). C, 55.11; H, 3.55; F, 2.81; Cl, 5.18; N, 14.51%; M/S: 675 (1.11), 95(100). IR νcm^{-1}: 3420 (OH), 3381, 3155 (NH, NH_2), 1680 (C=O) 1558(C=N), 1478 (deform aliphatic CH), 1269 (C-F), 1200 (P=O), 1043 (Ph-O-P), 993.861, 804 (Aryl CH).^{1}H NMR (DMSO) δ = 10.67, 10.14, 8.72 (each δ, 3H, 3NH, 1,2,4-triazinare NH-P=O), 9.77 (δ, 1H, OH), 8.15 - 7.52, 7.36 - 7.29, 7.13 - 7.00, 6.991 - 6.811 (each m, 19H, 7H aryl, 10H phenyls pyrazole protons); 3.46 (δ, 2H, NH_2).^{13}C NMR (DMSO) δ: 179.64; 163.76; 163.05; 159.42; 157.84; 138.58; 134.94; 128.65; 127.59; 123.72; 123.66; 121.13; 121.07; 117.67; 117.51; 113.45; 113.28; 112.06; 112.01; 110.75; 110.70; 109.66; 108.09; 107.92; 105.25; 105.08; 77.78; 77.35; 23.64.

3-(3'-Methyl-5'-arylamino-pyrazolin-1'-yl)-6(5'-fluoro-2'-diphenylphosphorylanilido)-1,2,4-trinzin-5(2 H) one (5)

A mixture of **3** (0.01 mol) and acetyl acetanilide derivative (0.01 mol) in DMF (50 ml) reflux for 2h, cooled then poured onto ice. The solid thus yield filtere off and crystallized from dioxan to give **5** as deep-yellowish crystals, yield 70%; m.p. 100˚C - 101˚C. Analytical data; found C, 56.03; H, 3.41; F, 2.23; N, 16.17; S, 3.91%. Calculated for $C_{36}H_{29}FN_9PSO_6$(765). C, 56.47; H, 3.79; F, 2.48; N, 16.47; S, 4.18%. IR νcm^{-1}: 3424, 3220 - 31.70 (NH, NH), 2932 (CH_3), 1694 (C=O), 1620 (C=N), 1358 (SO_2-NH), 1268 (C-F), 1220 (P=O), 1054 (Ph-O-P), 952, 909, 810, 758 (aryl CH).^{1}H NMR (DMSO) δ = 12.28, 12.27, 10.36, 10.21 (each s, 4H, 4NH) 9.7 (s, 1H, C_4- of pyrazole), 7.979, 7.971, 7.556, 7.545 (m, 4-H of pyridine); 7.34, 7.336, 7.322, 7.091(m, 4H of aryl-P-SO_2NH) 6.95 - 6.83; 6.66 - 6.52; 6.41 - 6.16 (each m, 13H of FC_6H_3, $2C_6H_5$). 0.46 - 0.45 (s, 3H, CH_3). ^{13}C NMR(DMSO) δ = 179.64, 163.75, 163.03, 162.41, 158.08, 157.99, 157.47; 151.97; 138.58, 134.94, 130.23, 129.10, 123.72, 123.66, 117.66, 117.50, 115.11, 113.41, 113.25, 112.97, 112.07, 112.02, 110.76, 110.71, 108.09, 107.92, 105.21, 105.04, 77.83-77.40, 36.40, 31.29.

3-(3'-Amino-4',5'-dihydro-5'-oxo-pyrazolin-1'-yl)-6(5'-fluoro-2'-diphenylphosphorylanilido)-1,2,4-triazin-5(2H)one (6)

Equiomolar of **3** and ethyl cyanoacetate in THF (100ml) reflux for 4H, cooled. The solid thus produce filtered off and crystallized from THF to give **6** as faint yellow crystals, yield 68%; m.p. 200-202˚C. Analytical data; found: C, 53.53; H, 3.31; F, 3.29; N, 18.01%. Calculated for $C_{24}H_{19}FN_7PO_5$(535); C, 53.83; H, 3.55; F, 3.55; N, 18.31%. IR νcm^{-1}: 3425 (NH_2), 3220-3190 (NH $\rightleftarrows$ OH), 1694 (C=O), 1471 (deformation. CH_2), 1310 (N-N), 1250 (C-F), 1210 (P=O), 1058 (Ph-O-P), 952, 915, 808 (aryl CH).^{1}H NMR (DMSO) δ: 12.7, 10.67, 8.8 (each s, 3H, 3NH), 10.24 (s, 1H, OH of pyrazole), 7.66 - 7.400, 7.39-7.00, 6.99-6.79 (each m, 14H, aryl & phenyl protons). ^{13}C NMR(DMSO) δ:179.54, 163.70, 159.31, 157.74, 134.91, 128.98, 127.31, 123.68, 117.57, 113.29, 113.13, 111.95, 110.69, 110.64, 108.23, 105.08, 104.91, 78.0-77.54.

3-(3',5'-Diaminopyrazolin-1'-yl)-6-(5'-fluoro-2'-diphenylphosphorylanilido)-1,2,4-triazin-5(2H)one (7)

A mixture of **3** (0.01mol) and malononitrile (0.01 mol) in ethanol (50ml) and piperidine (0.5 ml) reflux for 8h, cooled. The solid obtained filtered off and crystallized from ethanol to give **7** as deep orange crystals. Yield 70%; m.p. 205˚C - 207˚C. Analytical data; found: C, 53.55, H, 3.12; F, 3.31; N, 20.71%. Calculated for $C_{24}H_{21}FN_8PO_4$ (535); C, 53.83; H, 3.55; F, 3.55; N, 20.93%. IR: νcm^{-1} 3430 - 3380 (NH_2), 1700 (C=O), 1620 (deform. NH_2), 1580 (C=N) 1265 (C-F), 1200 (Ph-P=O), 1050 (Ph-O-P), 930, 910, 850, 800(aryl CH).^{1}H NMR (DMSO) δ: 12.7, 10.7, 10.2 (each s, 3H, 3NH), 8.8 (s, 1H, NH-P=O), 7.55 - 7.311, 7.131 - 6.991, 6.87 - 6.76 (each m, 14 H, aryl & phenyl protons), 3.89 (s, 4H, $2NH_2$). ^{13}C NMR (DMSO)δ: 163.73, 159.38, 157.80, 134.93, 127.49, 123.67, 113.38, 113.22, 110.66, 105.18; 105.01, 77.84-77.41, M/S (Int.%): 534 (536, M + 2, 1.55%), 248 (1.11), 97 (3.18) 96 (5.55), 95 (100), 93 (18.11), 68 (42.00), 67 (3.11), 62 (37.15).

3-(5'-Phenyl-3'-oxo-2,3,4,5-tetrahydro-pyrazolin-1'-yl)-6-(5'-fluoro-2'-diphenyl phosphorylanilido)-1,2, 4-triazin-5-(2H)one(8)

Equimolar amounts of **3** and cinnamoyl chloride in DMF (20ml) reflux for 4 h, cooled then poured onto ice. The produce solid filtered off and crystallized from dioxan to give **8** as deep yellowish crystals, yield 60%, m.p. 160˚C. - 162˚C. Analytical data; found: C, 59.89; H, 3.55; F, 3.01; N, 13.75%. Calculated for $C_{30}H_{23}FN_6PO_5$ (597); C, 60.30; H, 3.85; F, 3.18; N, 14.07%. IR νcm^{-1}: 3428 (OH), 3180 (NH), 2937 (CH_2), 1694 (C=0), 1610 (C=N), 1482 (deform. CH_2), 1314 (N-N), 1230 (C-F), 1169 (P=O), 1059 (Ph-O-P), 954, 909, 809 (aryl CH).^{1}H NMR (DMSO) δ: 14.7, 13.5, 12.6 (each s, 3H, 3NH), 10.80 (s, 1H, OH of pyrazole), 8.8 (s, 1H, NH-P=O), 7.99 - 7.41, 7.04 - 7.32, 7.10 - 6.93, 6.88 - 6.40 (each m, 20H, aryl and phenyl protons), 3.23 (s, 2H, NH_2). ^{13}C NMR (DMSO) δ: 163.70, 163.58, 162.90, 162.24, 159.34, 157.83, 157.76, 144.07, 134.29, 130.01, 128.77, 127.84, 121.16, 118.94, 118.84, 117.43, 114.23, 113.13, 112.97, 111.94, 111.89, 111.48, 111.43, 110.64, 110.59, 108.30, 108.12, 78.13 - 77.91, 36.26, 31.14.

3-(3'-(4''-Nitrophenyl)-5'-(4''-fluorophenyl)-4'-5'-dihydro-pyrazolin-1'-yl)-6-(5'-fluoro-2'-diphenyl-p-hos-phorylanilido)-1,2,4-triazin-5(2H)one (9)

A mixture of **3** (0.01 mol) and a chalcone (0.01 mol) in ethanol (50 ml), and piperidine (0.5 ml) reflux for 8 h, cooled then poured on ice-HCl. The solid produce filtered off and crystallized from THF to give **9** as yellow crystals, yield 82%, m.p. 148˚C - 150˚C. Analytical data; found: C, 59.49; H, 3.51; F, 5.21; N, 13.29%. Calculated for $C_{36}H_{26}F_2N_7PO_6$ (721); C, 59.91; H, 3.60; F, 5.27; N, 13.59%. IR νcm^{-1}: 3180 (NH), 2827 (CH_2), 1675 (C=O), 1595 (C=N), 1547 (C=N), 1500, 1423 (deform. CH_2), 1291 (C-F), 1225 (Ph-P=O), 1097 (Ph-O-P), 921, 847, 762 (aryl CH), 684 (C-Cl). ^{1}H NMR (DMSO) δ = 10.57, 10.115 (each s, 2H, 2NH), 8.160 - 8.157, (s, 1H, NH-P=O), 8.118 - 8.095, 7.838 - 7.49, 7.23 - 7.010, 6.92 - 6.90, 6.73 - 6.70 (each m, 23H, aryl & phenyl protons) 2.49 - 2.48 (δ, 2H, CH_2). ^{13}C NMR (DMSO) δ = 163.72, 159.35, 157.78, 134.92, 130.85, 130.80, 129.46, 127.41, 123.86, 123.73, 123.67, 121.10, 113.34, 113.18, 111.98, 110.72, 110.67, 108.09, 107.92, 105.13, 104.97, 77.92 - 77.50, 39.56.

3-(3',5'-Dioxo-2',3',4',5'-tetrahydro-pyrazolin-1'-yl)-6-(5'-fluoro-2'-diphenyl phosphorylanilido)-1,2,4-triazin-5'(2H)one (10)

Equimolar mixture of **3** and diethyl malonate in THF (100 ml) reflux for 8 h, cooled. The solid thus obtain filtered off and crystallized from dioxan to give **10** as faint yellow crystals, yield 66%, m.p. 189-190˚C. Analytical data; found: C, 53.35; H, 3.18; F, 3.35; N, 15.38%. Calculated for $C_{24}H_{18}FN_6PO_6$(536); C, 53.73; H, 3.35; F, 3.54; N, 15.67%. IR νcm^{-1}: 3300 (NH), 3169 (NH), 1694 (C=O), 1626 (C=N), 1579 (C=N), 1471 (deform. CH_2), 1304 (N-N), 1265 (C-F), 1196 (P=O), 1040 (Ph-O-P), 903, 863, 809 (aryl CH).^{1}H NMR (DMSO) δ = 12.7, 10.69, 10.35 (each s, 3H, NH, OH, OH) 9.21 (s, 1H, NH-P=O), 8.15 (s, 1H, C_4 of pyrazole), 7.79 - 7.38, 7.10 - 7.003, 6.99 - 6.79 (each m, 15H, aryl & phenyl protons), 4.18 - 4.17, (δ, CH_2 of pyrazole). ^{13}CNMR (DMSO) δ = 179.39, 163.58, 162.91, 159.18, 157.61, 134.86, 126.95, 123.74, 123.68, 117.44, 117.28, 113.13, 112.97, 111.94, 110.64, 110.58, 108.12, 107.95, 104.89, 104.72, 78.29 - 77.85, 61.09, 13.94. M/S (Int.%): 536 (538, M + 2, 2.28), 99 (5.5), 96 (13.11), 95 (100), 93 (36.11), 69 (21.85), 68(42.35), 62(5.18).

3-(5'-Aryl-3'-thioxo-2',3'-dihydro-1',2',4'-triazol-1'-yl)-6-(5'-fluoro-2'-diphenylphosphorylanilido)-1,2, 4-triazin-5(2H) one (11)

A mixture of **3** (0.01 mol) and P-methoxybenzoylisothiocyanate (0.01 mol) in dioxan (20ml) reflux for 4 h, cooled. The solid produce filtered and crystallized from dioxan to give **11** as orange yellowish crystals. Yield 65%, m.p. 141˚C - 192˚C. Analytical data, found: C, 55.62; H, 3.41; F, 2.74; N, 15.02; S, 4.72%. Calculated for $C_{30}H_{23}FNPSO_5$ (643); C, 55.98; H, 3.57; F, 2.95; N, 15.24; S, 4.97%. IR νcm^{-1} = 3220-3180 (b, NH), 1693 (C=O), 1624, 1537 (C=N), 1477 (deform. MeO), 1305(N-N), 1266(C-F), 1155 (C-S), 1099 (P=O), 1039(P-O), 980, 840, 809 (aryl CH). ^{1}H NMR(DMSO) δ = 12.74, 10.80 - 1066, 8.73 (each s, 3H, 3NH), 8.40 - 7.52, 7.38 -

7.30, 7.29 - 7.00, 6.99 - 6.800 (each m, 17H) aryl & phenyl protons), 3.68 - 3.67 (s, 3H, OMe). ^{13}C NMR(DMSO) δ: 179.64, 163.77, 163.04, 159.40, 158.02, 157.85, 138.58, 134.94, 132.10, 127.60, 123.72, 123.66, 121.13, 121.07, 117.69, 117.53, 113.46, 113.28, 112.02, 110.76, 110.71, 108.10, 107.93, 105.25, 105.07, 77.81 - 77.35, 66.91.

3-(3'-(4'-Methoxyphenyl)-5'-thioxo-4',5'-dihydro-1'2',4'-triazol-1'-yl)-6-(5'-fluoro-2'-diphenylphos phorylanilido)-1,2,4-triazin-5(2H)one (12)

A mixture of **3** (0.01 mol) and 4-methoxybenzoyl isothiocynate (0.01 mol) is DMF (20 ml) reflux for 4 h, cooled then poured onto ice. The produce solid filtered off and crystallized from ethanol (to give **12** as orange crystals, yield 70%, m.p. 186˚C - 188˚C. Analytical data: found: C, 55.69; H, 3.55; F, 2.70; N, 14.89; S, 4.79%. Calculated for $C_{30}H_{23}FN_7PSO_5$ (643); C, 55.98; H, 3.57; F, 2.95; N, 15.24; S, 4.97%. IR νcm^{-1}: 3382 (NH), 3318 (NH), 3204 (NH), 1684 (C=O), 1562 (C=N), 1484 (deform. MeO), 1311 (N-N), 1270 (C-F), 1169 (C=S), 1041 (Ph-O-P), 995, 881, 807 (aryl CH).

3-Methyl-1H-7-(5'-fluoro-2'-diphenyl phosphorylanilido)-1,2,4-triazino[4,3-b][1,2,4] triazin-4,8-dione (13)

A mixture of **3** (0.01 mol) and sodium pyruvate (0.01 mol) in sodium hydroxide solution (5%, 100 ml) warm under reflux for 2 h, cooled them poured onto ice HCl. The solid thus obtained filtered off and crystallized 70%, m.p. 220˚C - 222˚C. Analytical data; found: C, 55.19; H, 3.31; F, 3.38; N, 15.88%. Calculated for $C_{24}H_{18}FN_6PO_5$ (520); C, 55.38; H, 3.46; F, 3.65; N, 15%. IR νcm^{-1}: 3380, 3162 (NH, NH) 1683 (C=O), 1589, 1553 (C=N), 1458 (deform. CH_3), 1308 (N-N), 1250 (C-F), 1204 (P=O), 1040 (Ph-O-P), 909, 861, 804 (aryl CH). ^{1}H NMR (DMSO) δ: 14.55, 12.8 (each s, 2H, 2NH), 10.06 (s, 1H, NH), 7.66 - 7.40, 7.35 - 7.26, 6.93 - 6.76 (each m, 13H, aryl & phenyl protons), 5.58 (s, 1H, OH), 1.256 (s, 3H, CH_3). ^{13}C NMR(DMSO)δ:177.40, 176.13, 158.14, 139.40, 128.24, 119.11, 118.95, 118.82, 117.83, 114.59, 114.43, 114.35, 114.29, 112.36, 112.19, 112.09, 112.04, 111.84, 111.77, 111.60, 110.87, 109.95, 109.90, 108.90, 108.37, 77.67 - 77.24, 55.38, 17.21.

Indolo[3,4-e][1,2,4] triazino [4,3-b]-1,2,4-triazin-11-one (14)

Equimolar amounts of **3** and isatin in DMF (20 ml) reflux for 2h, cooled then poured onto ice. The yielded solid filtered off and crystallized from dioxan to give **14** as deep-brown crystals, yield 80%, m.p. 198-200˚C. Analytical data found: C, 59.89; H, 3.01; F, 2.98; N, 16.59%. Calculated for $C_{29}H_{19}FN_7PO_4$ (579); C, 60.10; H, 3.28; F, 3.28, N, 16.92%. IR νcm^{-1}: 3139 (NH), 1694 (C=O), 1626, 1540 (C=N), 1305 (N-N), 1250 (C-F), 1157 (P=O), 1080 (Ph-O-P), 970, 900, 850, 811 (aryl CH).^{1}H NMR(DMSO) δ=10.76-10.61 (s, 1H, NH), 8.011 (s, 1H, NH-P=O), 7.67 - 7.28, 7.27 - 7.12, 7.05 - 6.94, 6.87 - 6.816 (each m, 17H, aryl and phenyl protons). ^{13}CNMR (DMSO) δ: 163.77, 163.68, 162.45, 159.48, 157.32, 141.29, 136.82, 134.95, 95.133.65, 130.07, 122.27, 120.80, 120.30, 117.73, 117.57, 113.54, 113.50, 113.38, 112.10, 112.04, 110.79, 110.73, 108.09, 107.92, 105.34, 105.17, 77.67 - 77.24. M/Z (Int. %) 579 (581, M + 2; 13.15%) 331 (31.88), 275 (75.19), 248 (1.15); 141 (18.20), 95 (100), 93 (20.51), 63 (5.13).

3-Phenyl-1,2,3,4-tetrahydro-7-(5'-fluoro-2'-diphenyl phosphorylanilido)-1,2,4-triazino [4,3-b] [1,2,4] triazin-8-one (15)

A mixture of **3** (0.01 mol) and phenacyl bromide (0.01 mol) in ethanolic KOH (5%, 20 ml) reflux for 2 h, then poured onto ice-HCl. The solid produced filtered off and crystallized from THF to give **15** as brownish crystals. Yield 65% m.p., 98˚C - 100˚C. Analytical data; Found: C, 59.98; H, 3.55; F, 3.20; N, 14.51%. Calculated for $C_{29}H_{22}FN_6PO_4$ (568); C, 61.26; H, 3.87; F, 3.34; N, 14.78%. IR νcm^{-1}: 3158 (NH), 1655 (C=O), 1580 (C=N), 1474 (deform. CH_2), 1308 (N-N), 1230 (C-F), 1180 (P=O), 1092 (Ph-O-P), 980, 950, 900, 850, 801 (aryl CH).^{1}H NMR(DMSO) δ = 12.75 (s, 1H, NH), 10.78 (s, 1H, NH-P=O), 7.84 - 7.55, 7.49 - 7.30, 7.29 - 7.00, 6.99 - 6.79 (each m, 18H, aryl & phenyl protons). 3.4 (s, 2H, CH_2). ^{13}C NMR (DMSO) δ:179.66, 163.04, 159.62, 158.02, 138.60, 129.51, 129.14, 128.67, 128.45, 128.18, 127.18, 126.89, 126.67, 125.86, 125.44, 123.31, 121.05, 120.20, 117.72, 117.56, 113.90, 113.74, 112.21, 112.13, 112.07, 110.47, 110.04, 108.10, 107.92, 77.72-77.29, 36.62.

7-(5'-Fluoro-2'-diphenylphophorylanilido)-1,2,3,4-tetrahydro-1,2,4-triazino[4,3-b][1,2,4]triazin-4,8-dione (16)

A mixture of **3** (0.01 mol) and monochloroacetic acid (0.01 mol) in DMF (20 ml) reflux for 2 h, cooled then poured onto ice. The solid thus obtained filtered off and crystallized from THF to give **16** as yellowish crystals. Yield 70%, m.p. 165˚C - 167˚C. Analytical data; found: C, 54.01; H, 3.25; F, 3.58; N, 16.31%. Calculated for $C_{23}H_{18}FN_6PO_5$ (508); C, 54.33; H, 3.54; F, 3.74; N, 16.53%. IR νcm^{-1}: 3382 (NH), 3224 (NH), 1685 (C=O), 1590 (C=N), 1477 (deform. CH_2), 1250 (C-F), 1180 (P=O), 1041 (Ph-O-P), 807, 760 (aryl CH). ^{1}H NMR (DMSO) δ: 12.97, 10.70, 10.42 (each s, 3H, 2NH, OH), 9.19 (s, 1H, NH-P=O), 7.99 - 7.00, 6.99 - 6.86, 6.85 - 6.79 (each m, 13H, aryl & phenyl protons), 4.33 (s, 2H, CH_2). ^{13}C NMR (DMSO) δ = 173.41, 163.77, 163.67,

159.42, 157.84, 157.70, 136.69, 136.04, 121.23, 121.06, 113.87, 113.81, 113.24, 113.08, 111.48, 111.43, 110.966, 110.699, 111.644, 109.28, 107.00, 106.83, 105.02, 104.02, 78.08 - 77.65, 31.22.

7-(5'-Fluoro-2'-diphenylphosphorylanilido)-1,2-dihydro-1,2,4-triazino [4,3-b][1,2,4] triazin-3,8-dione (17)

Equimolar mixture of **3** and 1,1-dichloroacetic acid in DMF (20ml) reflux for 2h, cooled then poured onto ice. The yield obtained filtered and crystallized from dioxan to **17** as yellowish crystals. Yield 78%, m.p. 180˚C - 182˚C. Analytical data: found C, 54.03; H, 2.89; F, 3.55; N, 16.31%. Calculated for $C_{23}H_{16}FN_6PO_5$ (506); C, 54.54; H, 3.16; F, 3.75; N, 16.60%. IR νcm^{-1}: 3100 (NH), 1791 (C=O), 1655 (C=O), 1590 (C=N), 1547 (C=N), 1295 (N-N), 1235 (C-F), 1158 (P=O), 1094 (Ph-O-P), 984, 865, 830 (aryl CH).^{1}H NMR (DMSO) δ: 12.7 (s, 1H, NH), 10.53 (s, 1H, NH-P=O), 9.07 (s, 1H, CH=N), 7.91 - 7.16, 6.92 - 6.81, 6.77 - 6.71 (each m, 13H, aryl & aryl protons). ^{13}C NMR(DMSO) δ:179.58, 163.82, 163.01, 162.39, 159.50, 157.92, 142.32, 138.56, 136.67, 136.03, 121.28, 121.12, 117.45, 115.59, 115.43, 113.90, 112.13, 111.47, 110.67, 109.50, 109.34, 108.08, 107.91, 107.12, 106.95, 77.88 - 77.45, 66.36.

7-(5'-Fluoro-2'-diphenylphosphorylanilido)-1,2,3,4-tetrahydro-1,2,4-triazino[4,3-b][4,34]triazin-3,4,8-trione (18)

A mixture of **3** (0.01 mol) in dry C_6H_6 treat with oxalyl chloride (0.01 mol) added dropwise then, TEA added drop wise (few drops) then heated under reflux for 2h, cooled. The solid produce filtered off and crystallized from C_6H_6 to give **18** as deep-yellowish crystals, yields 60%, m.p. 168˚C - 170˚C. Analytical data: found: C, 52.49; H, 2.85; F, 3.51; N, 15.88%. Calculated for $C_{23}H_{16}FN_6PO_6$ (522); C, 52.87; H, 3.06; F, 3.63; N, 16.09%. IR νcm^{-1}: 3382, 3319, 3156 (3NH), 1680 (C=O), 1557 (C=N), 1270 (C-F), 1143 (P=O), 1041 (Ph-O-P), 994, 860, 804 (aryl CH).^{1}H NMR (DMSO) δ: 14 (s, 1H, NH), 12.9 (s, 1H, NH), 10.8 (s, 1H, NH-P=O) 9.3, 8.50, 8.0 (each s, aryl protons), 7.45, 7.35, 7.039, 7.035, 7.031, 7.02, 6.886, 6.878, 6.870, 6.86 (m, 10H phenyl protons). ^{13}C NMR (DMSO) δ: 167.31, 163.07, 159.53, 158.95, 129.48, 128.26, 120.21, 118.50, 118.26, 112.38, 112.33, 112.19, 112.14, 77.62 - 77.202. M/Z (Int.%) 522 (525, M + 3, 18.55), 248 (3.15), 96 (23.11), 95 (100), 93 (8.9), 68 (15.0).

The acid hydrazido derivative 20

A mixture of **3** (0.01 mol) and oxazolone**19** (0.01 mol) in ethanol (50 ml) with H_2O (20 ml) reflux for 2 h, cooled then poured onto ice. The produced solid filtered off and crystallized from dioxan to give **20** as yellow crystals. Yield 58%, m.p. 155-157˚C. Analytical data; found: C, 59.89, H, 3.55, F, 5.00; N, 13.05%. Calculated for $C_{37}H_{28}F_2N_7PO_6$ (735); C, 60.40; H, 3.80; F, 5.17; N, 13.13%. IR νcm^{-1}: 3600 - 3200 (b, OH, NH, NH), 1592 (CONH), 1480 (deform. CH=C), 1240 (C-F), 1170 (P=O), 1050 (Ph-O-P), 850, 752 (aryl CH).

3-[5'-(4''-Fluorophenylidene)-3'-phenyl-1'H-6'-oxo-1',2',4'-triazin-2'-yl]-6-(5'-fluoro-2'-diphenylphospho-rylanilido)-1,2,4-triazin-5-(2H)one (21)

Compound **20** (1 mg) and glacial acetic acid (10ml) reflux for 2h, cooled then poured onto ice. The solid thus obtained filtered off and crystallized from ethanol to give **21** as deep yellowish crystals. Yield 80%, m.p. 233˚C - 235˚C, Analytical data; found: C, 61.81; H, 3.49; F, 5.09; N, 13.55%. Calculated for $C_{37}H_{26}F_2N_7PO_5$ (717); C, 61.92; H, 3.62; F, 5.29; N, 13.66%. IR νcm^{-1}: 3192 (NH), 2880, 2810 (aliphatic CH), 1699 (C=O), 1632 (CONH), 1479 (deform. CH=), 1303 (N-N), 1240 (C-F), 1210 (P=O), 1056 (Ph-O-P), 900, 870, 810, 801 (aryl CH).

6-[5'-fluoro-2'-(diphenylphosphato)aminophenyl]-3,3,3-triphenyl-3-λ^5-1,2,4,3-triazaphopholino[4,5-b] [1,2,4]triazine-7(8H) one (22)

A mixture of compound **2** (0.01 mol) and triphenyl phosphine (0.01 mol) in acetonitryl (20ml) warm for 30 min, cooled. The solid obtained filtered off and crystallized from dioxan to give **22** as deep yellow crystals, yield 70%, m.p. 283˚C - 285˚C. Analytical data; found: C, 64.01; H, 4.15; F, 2.39, N, 11.35%. Calculated for $C_{39}H_{31}FN_6P_2O_4$ (728); C, 64.28; H, 4.25; F, 2.60; N, 11.53%. IR νcm^{-1}: 3300 - 3100 (b, NH, NH), 1694 (C=O), 1620 (C=N), 1307(N-N), 1264 (C-F), 1179 (P=O), 1027 (Ph-O-P), 910, 880, 793, 745 (aryl CH).

3. Results and Discussion

α-Aminophosphonic acids continue to elicit study due to interest in their biological properties as herbicides [22], plant growth regulators [23] and most notably those species heaving a direct P-N bond are investigated as transition state analogues of the tetrahedral transition-state involved in peptide hydropysis [24]. Ali *et al*. [25] [26] studied the reactivity of α-amino phosphonates as dipolar ion structure and have type of tautomeric formula due to the higher e-withdrawing of two phenoxy and P=O groups (**Figure 2**). Thus, α-aminophosphonate group had

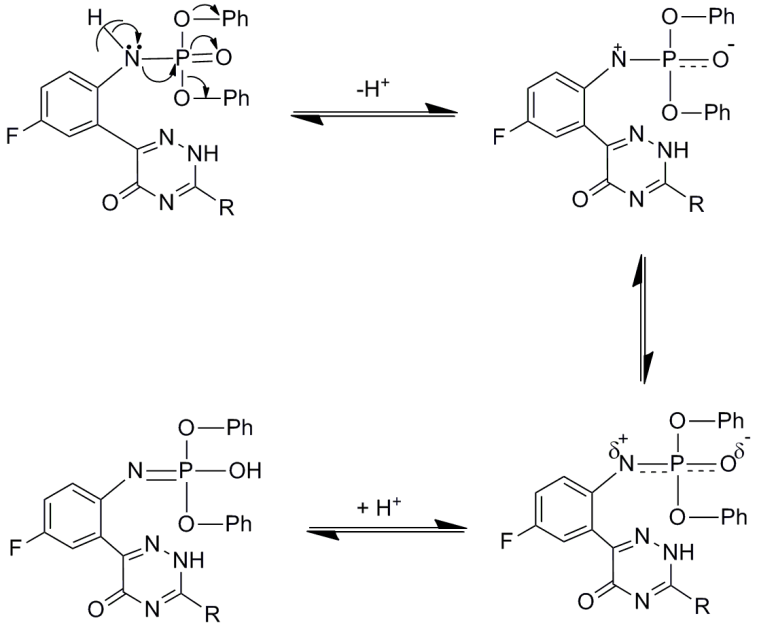


Figure 2. A possible present formula of the new synthesized isolated systems.

a higher degree of stability towards any attack of reagents, which attribute to presence of differ factors of stability [27]. Phosphorus elements in these systems, was determine by using the spectrophotomeric. The method is based on the development of floated complex of molybdophosphonic acid (MPA) and methylene blue (MB) with N, N'-diphenylbenzamide (DPBA) in toluene and its subsequent dissolution in acetone [28].

A series of some new fluorine substituted phosphoryl-amino-1,2,4-trinzines bearing a functionally pyrazole ring have been obtained via cycloaddition and/or cyclocodensation of 3-hydrazino-1,2,4-trinzinone**3** with π-acceptor activated carbon atom reagents. In addition, a type of 1,2,4-trinzino [4,3-b] [1,2,4] triazindiones have been also obtained from cyclocondensation of compound **3** with *α*, *β*-bifunctional oxygen and halogen compounds in different conditions. The former structures of the new products confirmed from correct elemental analysis and their spectral measurements. Keeping in view the diverse medicinal activities associated with organo-heterocyclilc systems substituted fluorine, phosphorus and 3-thioxo-1,2,4-trinzinone, which intend to construct novel fluorinated substituted phosphoryl amino bearing 1,2,4-triazinone moiety hoping to active additive effects towards their HIV-1 activity.

3.1. Chemistry

The starting material 3-hydrazino-6-(5'-fluoro-2'-diphenylphosphorylanilido)-1,2,4-trizino-5(2H) one (**3**) obtained from treatment of 6-(5'-fluoro-2'-aminophenyl)-3-thioxo-1,2,4-triazin-5(2H)one (**1**) with diphenylphosphoryl chloride in DMF to give 6-(5'-fluoro-2'-diphenylphosphorylanilido)-3-thioxo-1,2,4-triazin-5-one (**2**) followed by hydrozinolysis in boiling ethanol (**Scheme 1**).

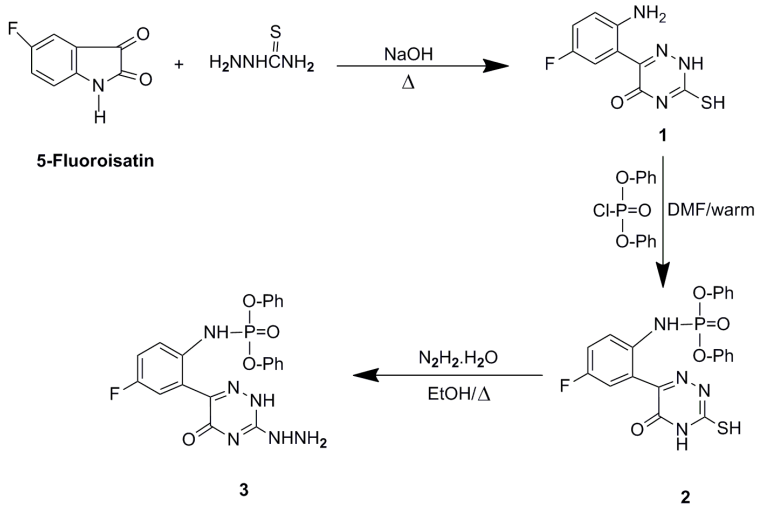
Recently, the most reactions of activated nitrites take place in basic medium leading to novel heterocyclic systems [29] [30]. Similarly, amino-pyrazolyl-1,2,4-triazinano derivatives **4-7** were obtained from the interaction between compound **3** and arylidenecyanoacetic acid (EtOH-piperidine), acetyl acetanilide (DMF), ethyl cyanoacetate (TFH) and/or malono nitrile (EtOH-piperidine) (**Scheme 2**).

These reactions are carried out via cycloaddition and/or cyclocondensation reactions [31] (**Figure 3**).

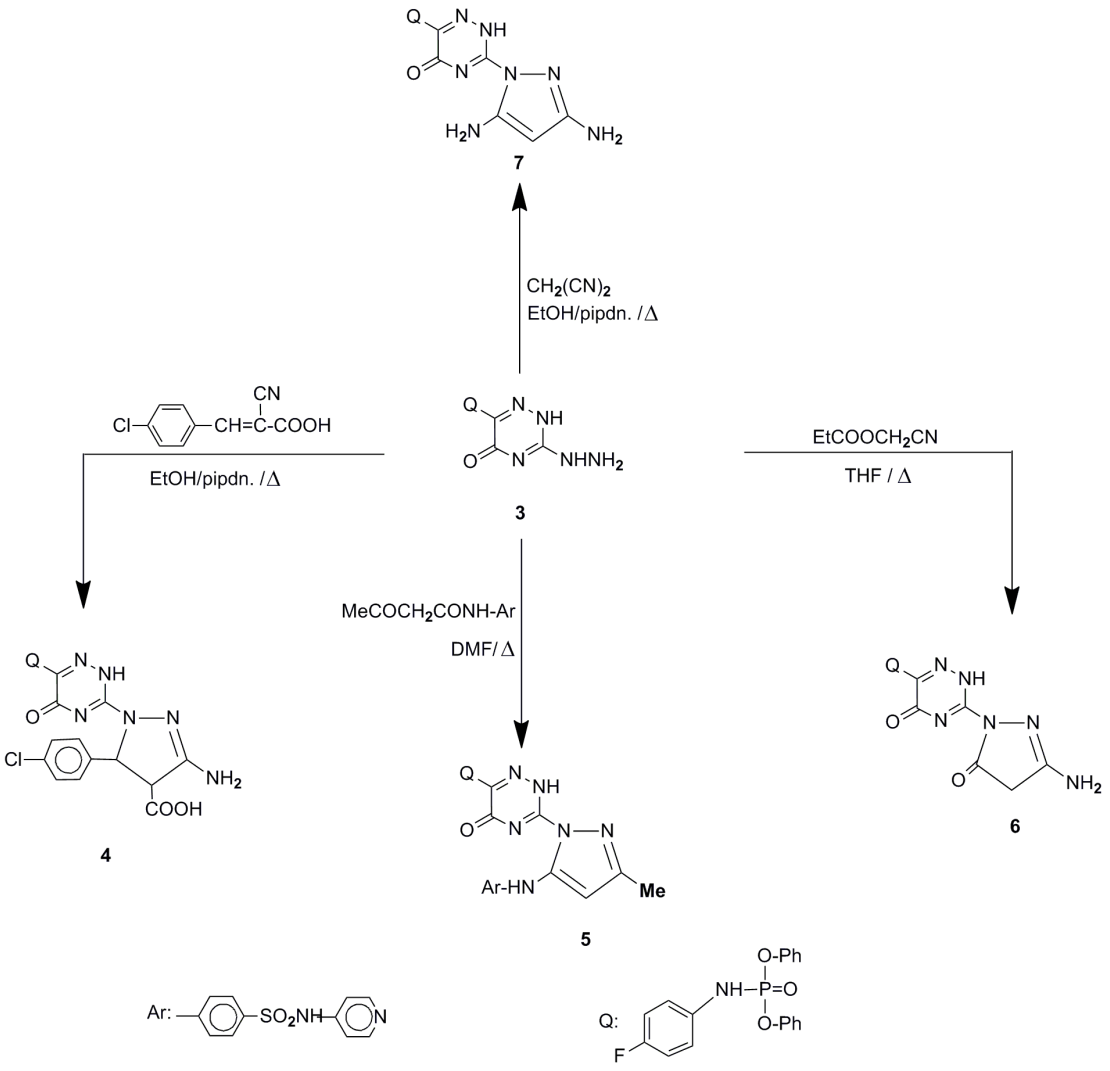
It is interested that 3-perhydropyrazo-1-yl-1,2,4-trizinones **8-10** also obtained from the ring closure reaction of compound **3** with cinnmoyl chloride (DMF), chalcone (EtOH-piperidine) and or diethylmalonate (THF) (**Scheme 3**).

Formation of **8** may be take place via aroylation then cycloadditon reaction [32] (**Figure 4**).

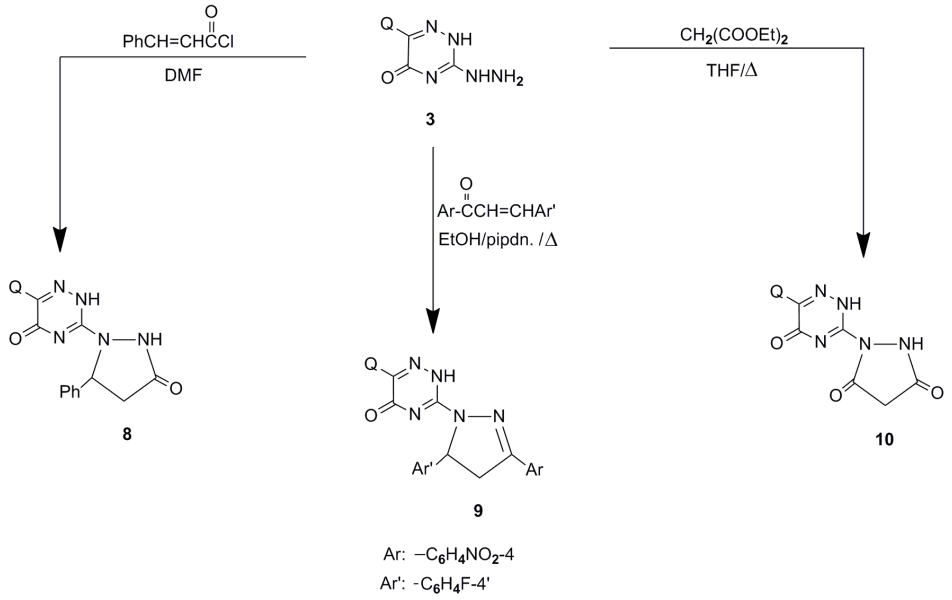
The greater reactivity of the polyfunctional compound as aroylisothiocynate towards the hydrazino group as bi-nucleophile is presumably due to its favourable location between both carbonyl and thiocarbonyl functional



Scheme 1. Formation compounds 1-3.



Scheme 2. Formation compounds 4-6.



Scheme 3. Formation compounds 8-10.

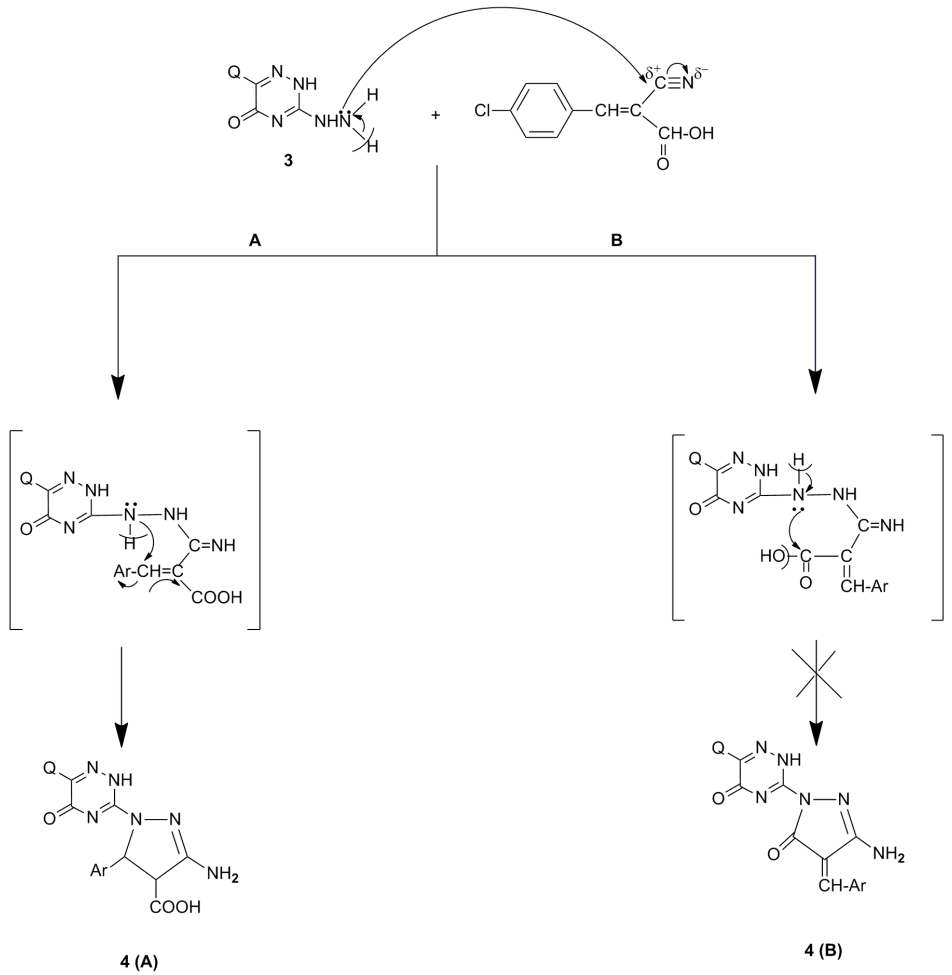


Figure 3. Formation of compound 4 from compound 3.

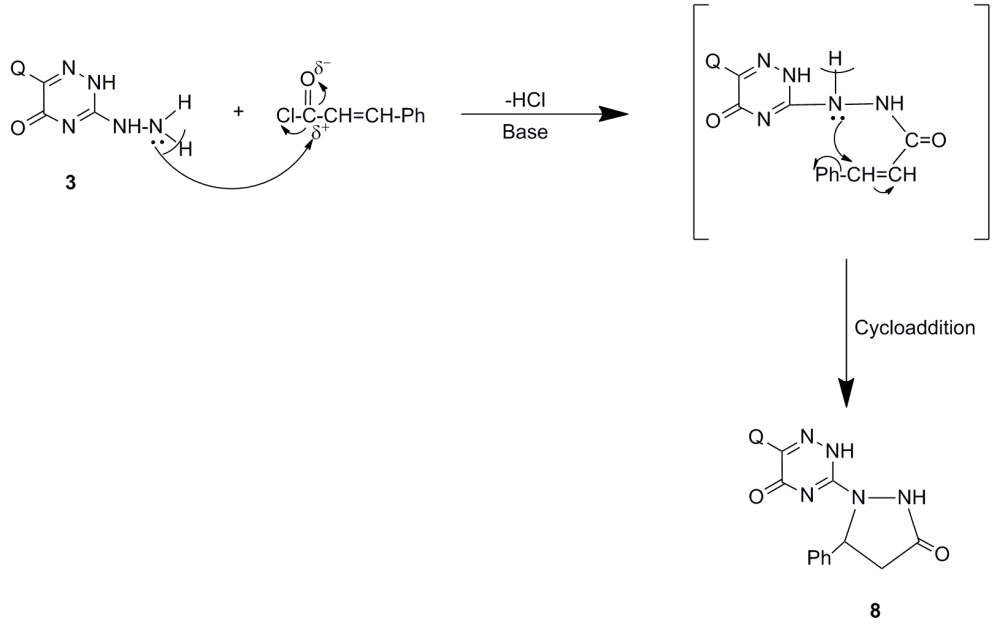


Figure 4. Formation of compound 8 from compound 3.

groups [33]. Thus, treatment of 3-hydrazino-1,2,4-trizinone **3** with aroylisothiocyanate in boiling non-polar solvent as dioxan yield 3-(5'-aryl-3'-mercapto-1',2',4'-triazol-1'-yl)-6-(5'-fluoro-2'-diphenly phosphorylanilido)-1, 2,4-triazin-5(2H)one (**11**), while that reaction when carried out in DMF, 3-(3'-aryl-5'-mercapto-1', 2',4'-triazol-1'-yl)-6-(5'-fluoro-2'-di-phenylphosphorylanilido)-1,2,4-trizin-5-(2H) one (**12**) isolated (**Scheme 4**). Formation of compounds **11** and **12** starting from compound **3** were outlined in (**Scheme 4**).

Reactivity of α,β-bifunctional carbonyl compounds towards an hydrazino groups arrived us to synthesize new fused heterobicyclic nitrogen systems. Thus, the interaction between compound **3** and sodium pyruvate in warming sodium hydroxide solution afforded 1H-3-methyl-7-aryl-1,2,4-triazino[4,3-b][1,2,4] traizin-4,8-dione (**13**), while cyclo-condensation of compound **3** with isatinas 1,2-bicarbonyl compound in boiling DMF yield indolo [2,3-e] [1,2,4] trinzino [4,3-b][1,2,4] triazin one (**14**). Refluxing of **3** with phenacyl bromide in ethanolic KOH furnish the tetrahydro-1,2,4-triazino [4,3-b][1,2,4] triazin-8-one (**15**) (**Scheme 5**).

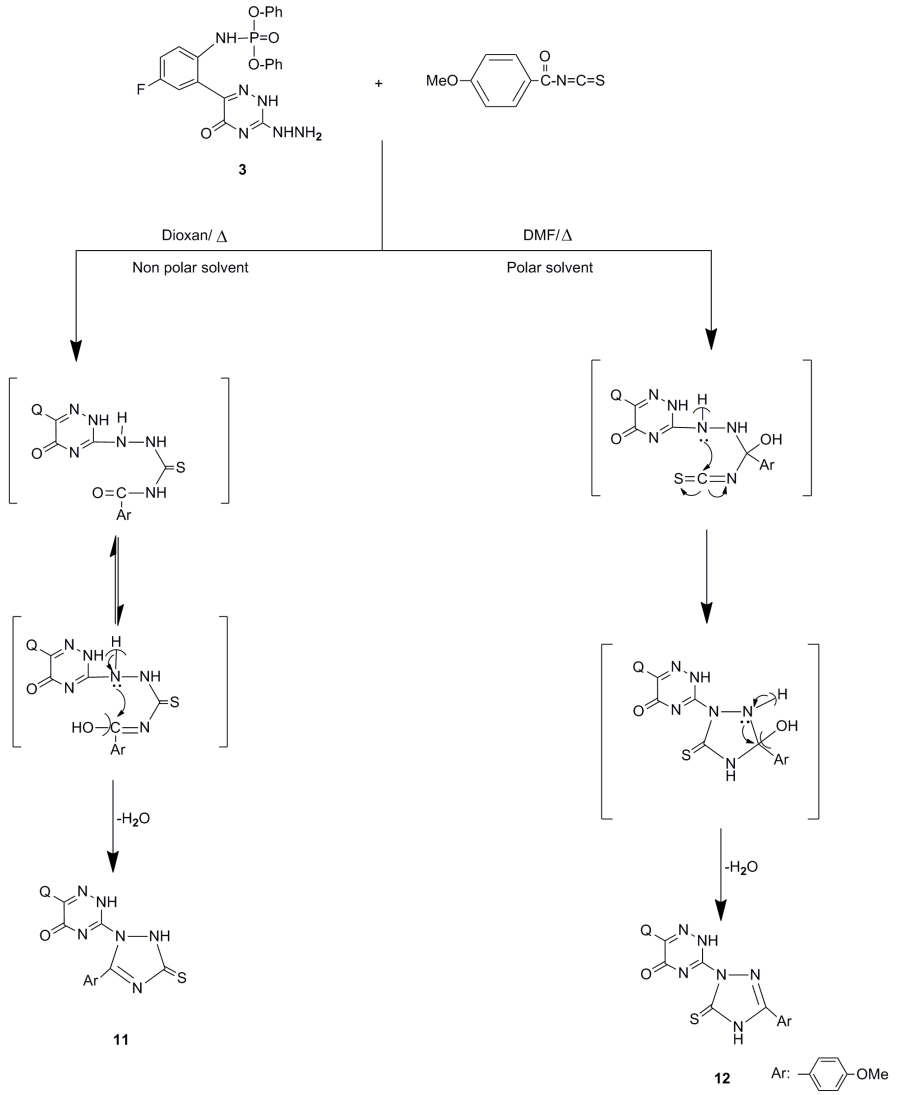
A large degree of the biological activity is attributed of the nature of substituent's and a degree of electronic distribution over the active center of the 1,2,4-triazines [34] [35]. Thus, direct nucleophilic displacement of chlorine atoms by nitrogen or other nucleophilic can easily occur if present α-carbonyl groups. Based on these facts, treatment of compound **3** with activated halogen as chloroacetic acid (DMF), dichloroacetic acid (DMF) and or oxalyl chloride (C_6H_6/TEA), produce perhydro 1,2,3,4-tetrahydro-1,2,4-triazino [4,3-b] [1,2,4] triazin-4,8-dione (**16**); 1,2-dihydro-1,2,4-triazino [4,3-b] [1,2,4] triazin-4,8-dione (**17**) and 1,2,3,4-tetrahydro-1,2, 4-triazino [4,3-b] [1,2,4] triazin-3,4,8-trione (**18**) derivatives (**Scheme 6**).

In view of interesting results obtained from the reaction of 1,3-oxazolium salts and of 1,3-oxazol-2-one derivatives with hydrazine derivatives[36], [37], it was worthwhile to investigate the behavior of oxazolone**19** towards hydrazine-derivative. Similarly, 3-hydrazino-6-aryl-1,2,4-triazin-5 (2H) one (**3**) when react with oxazole derivation **19** in boiling aqueous ethanol, the acid hydrazide derivative **20** isolated. Ring closure reaction of **20** by refluxing with glacial acetic acid afforded 3-(1'H-3-phenyl-5'-arylidene-6'-oxo-1,2,4-triazin-2'-yl-1-6-(5'-fluoro-2'-diphenylphosphorylanilido)-1,2,4-triazin-5(2H)one(**21**)Finally,6-[5'-fluoro-2'-(diphenylphosphato)aminoph-enyl]-3,3,3-triphenyl-3-λ^5-1,2,4,3-triazaphopholino[4,5-b][1,2,4]triazine-7(8H) one (**22**) isolated from treat compound **3** with triphenylphosphine in THF (**Scheme 7**).

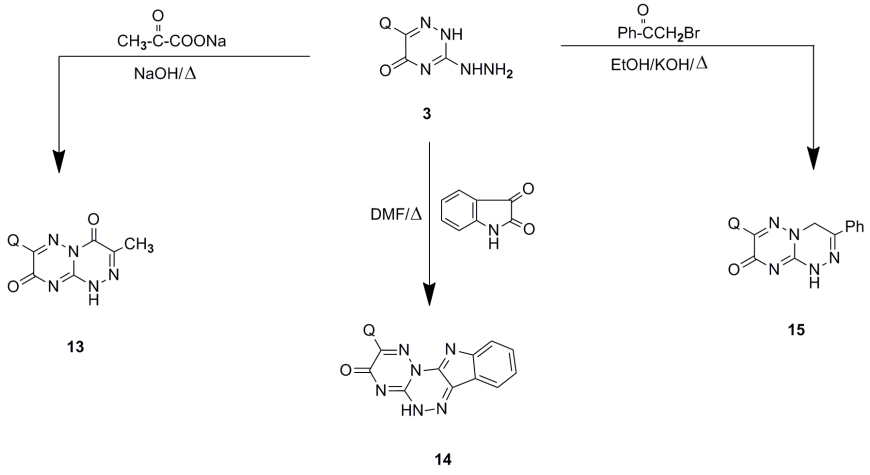
3.2. Elucidation the Former Structures

3.2.1. UV Spectra Study

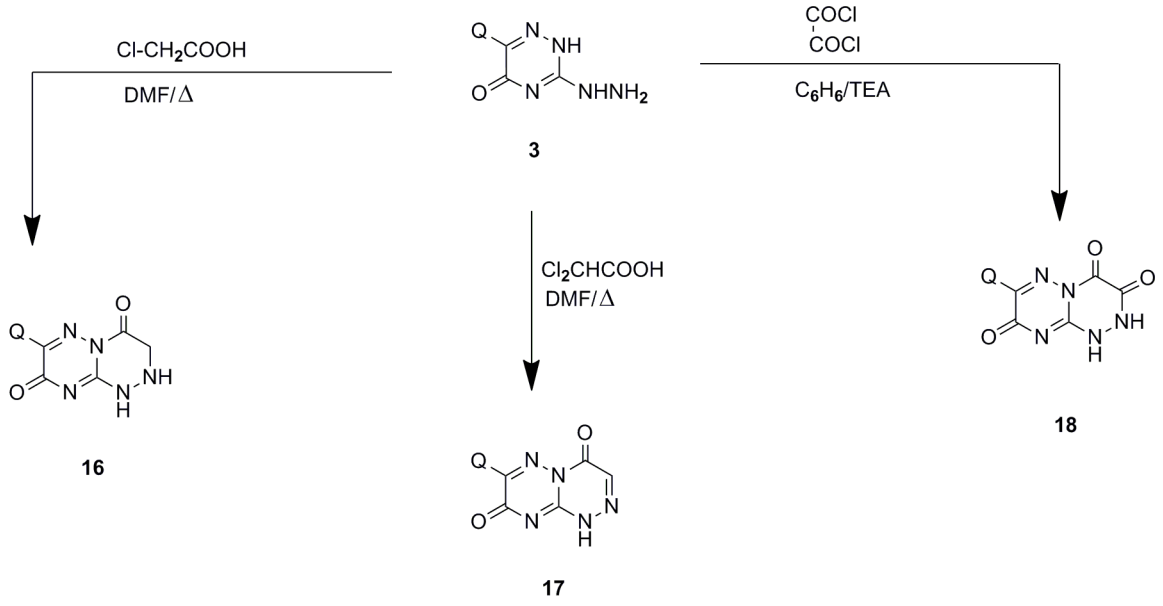
UV absorption study of the new compounds, synthesize give us a good indication about electronic distribution



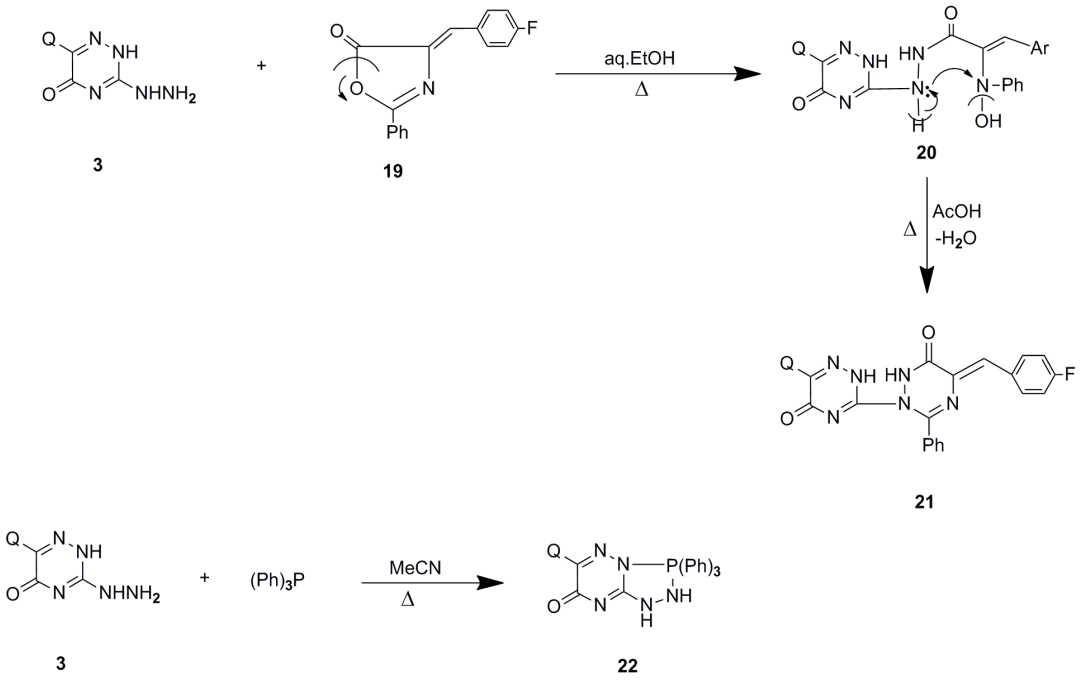
Scheme 4. Formation compounds 11 & 12.



Scheme 5. Formation compounds 13-15.



Scheme 6. Formation compounds 16-18.



Scheme 7. Formation compounds 19-22.

and molecular configuration as possible.In general, all the new compounds record the presence of n-π^*, n-σ^*, π-π^* and σ-σ^* electronic transition. UV-absorption spectrum of compound **3** as state recorded λ_{max} (EtOH) at 346.48 nm, while that of compounds **14** (361.55) and **12** (361.12). A higher value of λ_{max} for **14** and **12** than **3** is may be a lack's of -OH groups (which generate of H-bending (**Figure 5**).

On the other hand, UV absorption spectra of selected compound record a lower λ_{max} than compound **3**. λ_{max} of **10** (330.56) and **18** (317.22) nm. A lower λ_{max} of these compounds than the start is may be due to the presence of O-H group, which generate a type of H-bonding. The Keto-enol forms of **10** and **18** led to the inhibition of heteroconjugative, in addition a type of H-bonding which is closed to 1,2,4-triazine moiety (**Figure 6**).

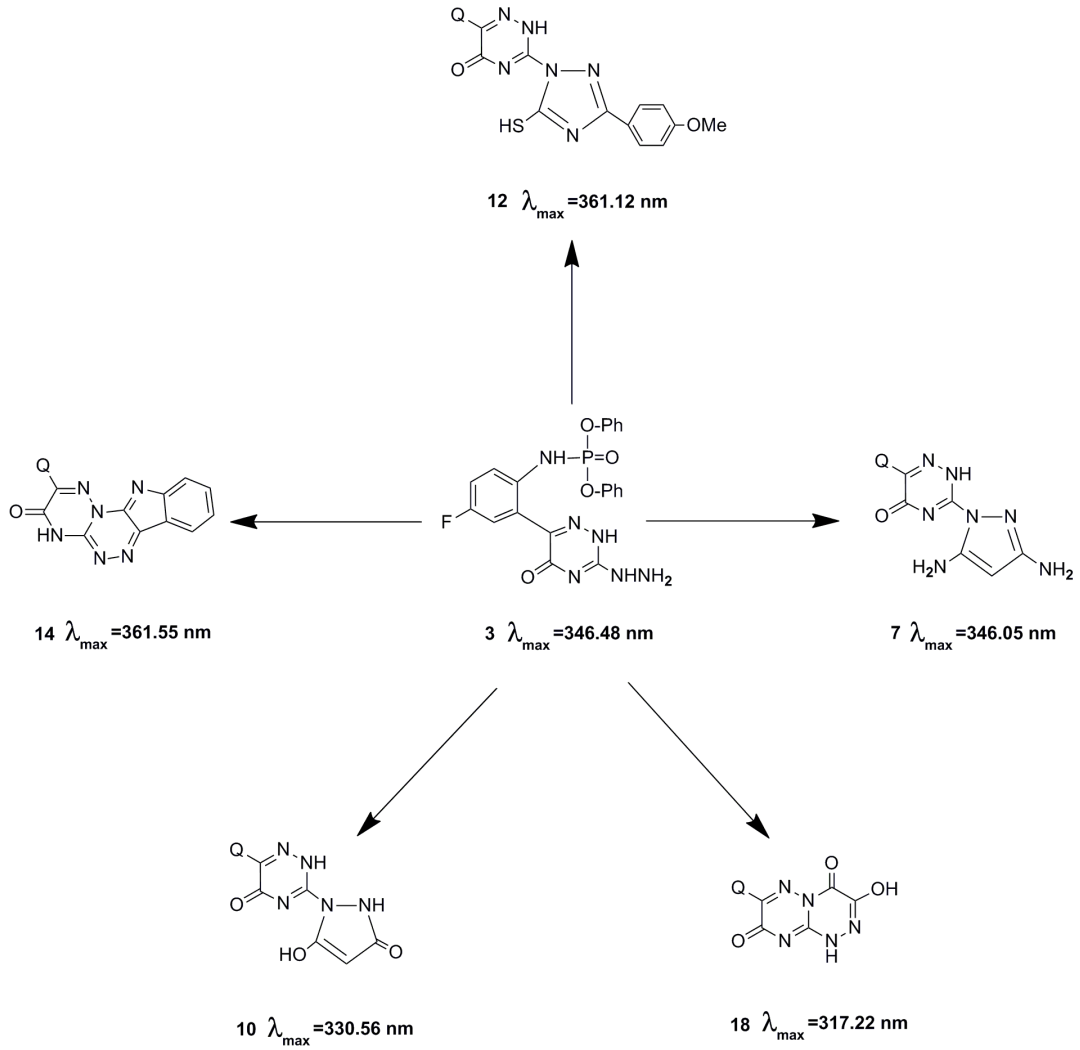


Figure 5. UV-absorbtion data of compound 3 and some prepared compounds.

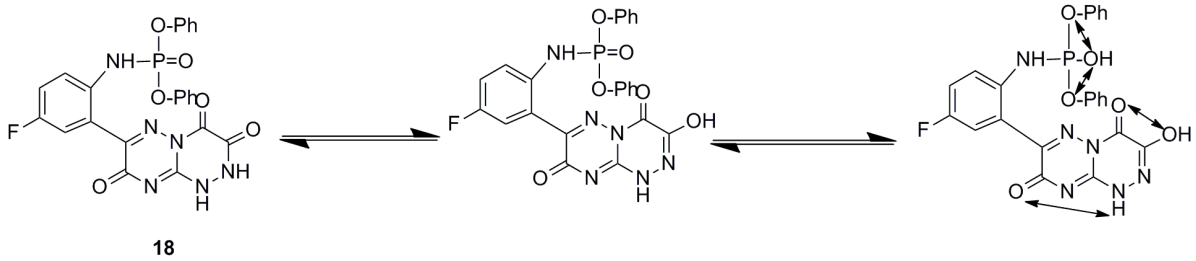


Figure 6. A possible conformer structure of 18 (fused system).

3.2.2. IR-Absorption Study

The IR absorption spectral data show that most of the new compounds lack's a band of NH-P=O, which is due to a type of H-bonding present (**Figure 6**), while that of these compounds record only NH bond of new 1,2, 4-triazinones and/or pyrazoles moiety. In addition, IR absorption spectra of all the synthesized compounds exhibit an absorption bands at 3300 - 3190 (NH), 1690 - 1650 (C=O). Moreover presence of a characteristic bands at *v* 1390 - 1370 for cyclic NCN, 1250 and 1220 - 1200 cm^{-1} for C-F and P=O functional. Also, all the new compounds record *v* at 1100 - 1050 cm^{-1} attribute to Ph-O-P group. Only, the compounds **3**, **4**, **6**, and **7** record a *v* for

NH_2 at 3390 - 3400 cm^{-1}, while that of the compounds **4**, **6**, **8**, **10**, **13**, **16-21** showed *v* for C=O in addition the original C=O of 1,2,4-trinzine. Finally, IR spectra of the compounds **4**, **5**, **6**, **8-13** and **15**, **16** record a type of bands characteristic for aliphatic groups (deformation 1480 - 1440 cm^{-1}).

3.2.3. NMR Spectral Study

1) ^{1}H NMR Spectral Study

The NH proton signals in all the new compounds appear as doublets at δ 8.8 - 8.2 ppm (JP-N-H=6 - 5.5 H_z) is due to its coupling with phosphorus. Also, H-bonding with oxygen of P=O and the deshielding effect of phenoxyphosphoryl group (Ph-O-P=O) are obviously the contributing factors for the downfield shift of the NH proton. On the other hand, phenoxy protons resonated at δ 7.50 - 7.1 ppm and their integration corresponds to five protons with no splitting of the signals. This shows that all the protons as magnetically equivalent. Normally, exo and endo NH protons of 1,2,4-triazinone reveal at δ12 - 11 ppm, while what of the 1,2,4-tiazinone addujent of CH_2 or NH protons show as enolic protons at δ11 - 10 ppm (**5,7,17,18,9**).In addition, all the new compounds **4 & 6**, exhibited a resonated signals at δ5 - 4 ppm as NH_2 protons and NH proton at δ11 - 10 ppm. Finally, the perhydro pyrazolyl-1,2,4-triazinones and the 1,2,4-trinzino-1,2,4-trinzinones which containing an aliphatic protons show a resonated signals at δ4 - 3 and 1 - 0.5 ppm for CH_2 and CH_3 protons.

2) ^{13}CNMR Spectral Study

The ^{13}C Chemical shifts of phenoxy moiety are agreeing well with the reported values [38]. But, the coupling constants for ^{2}Jare concurring with those of equationally oriented P-O-Ar groups [39] showing the 1,2,4-trinzine ring has probably half chair conformation with phosphorus atom projecting upwards and the O-Ar group orienting equationally. The carbons C, which are connected to phosphorous through NH, resonated at δ 112.97 with ^{2}J P-N-C (d, J 8.1) and the difference in their chemical shifts may be attributed to the variation of shielding effect of NH [40]. In addition, all the new compounds record the resonated attribute to C=O (170 - 160), C-F (150 - 140), C=N(140 - 130), C-N (111 - 110) of 1,2,4-triazinone, with a differ type of carbons of pyrazolyl as well as carbons of other 1,2,4-triazine formed (**Figure 7** and **Figure 8**).

3.2.4. Mass Spectrometric Measurements

The mass spectral investigations of the isolated heterobicyclic system is differ than the fused heterobicyclic systems (**14** & **18**) for example, M/Z of **7** and/or **10** recorded the molecular ion Peak's at m/z 534 and 336 respectively with a lower abounds percent's, which indicating the fragile nature of these systems. While M/Z of compound **14** showed the highest value peak at 579 with a base peak at m/z 95, which give us a high degree of stability for this Skelton. Moreover, M/Z of **18** exhibits a molecular ion peak at m/z 522 with moderate abounds percent. From these data, we can conclude that fused heterobicyclic nitrogen systems are more stabilized [41]

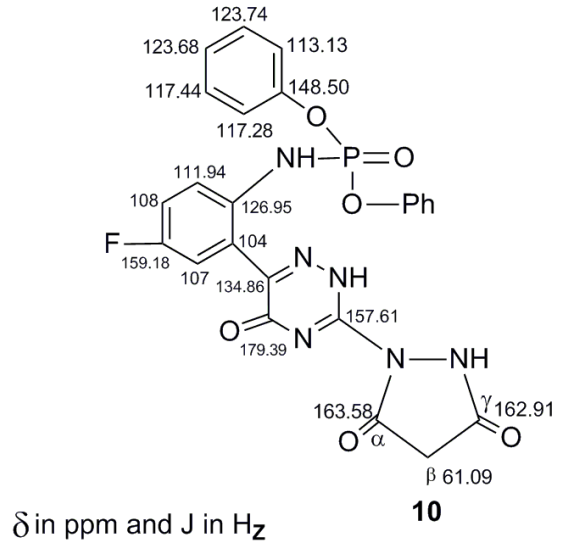


Figure 7. ^{13}C NMR data of compound 10.

than other isolated heterobicyclic systems. It's interest that in all mass fragmentation pattern, 4-fluorophenyl ion is a base peak followed by N-phosphorus oxide ions, while that heterocycle supported that a large fragmentation bath way (**Figures 9-12**).

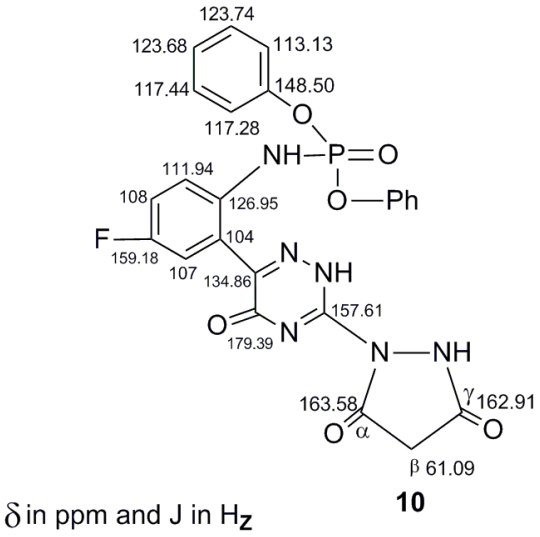


Figure 8. ^{13}C NMR data of compound 18.

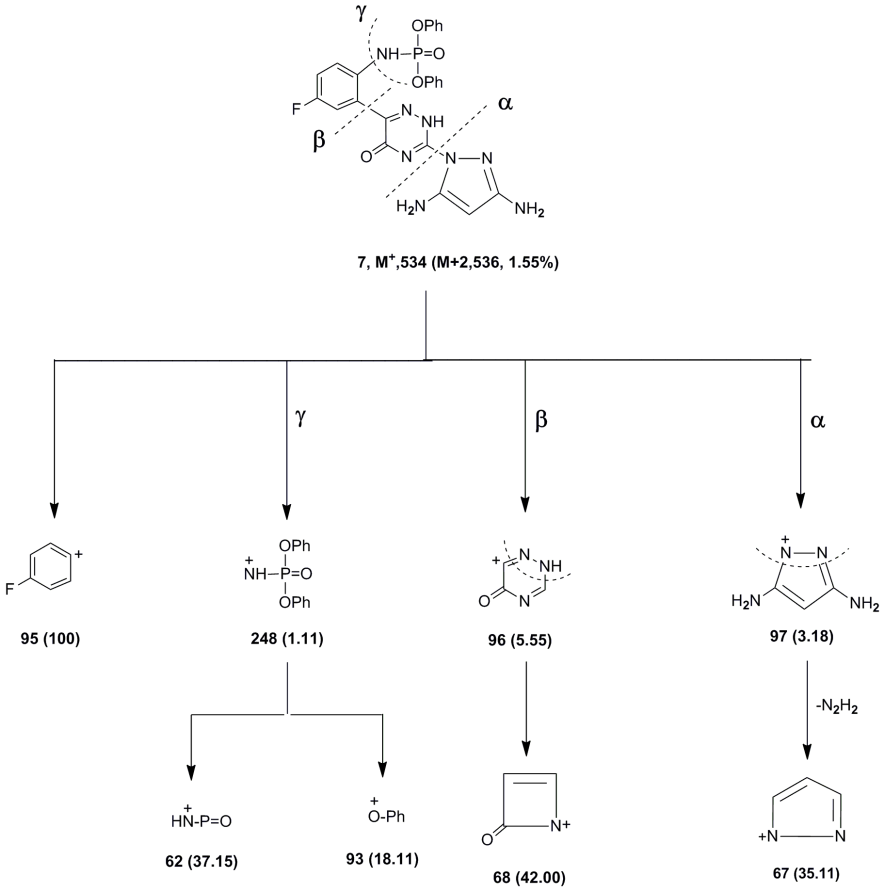


Figure 9. Mass Fragmentation pattern of compound 7.

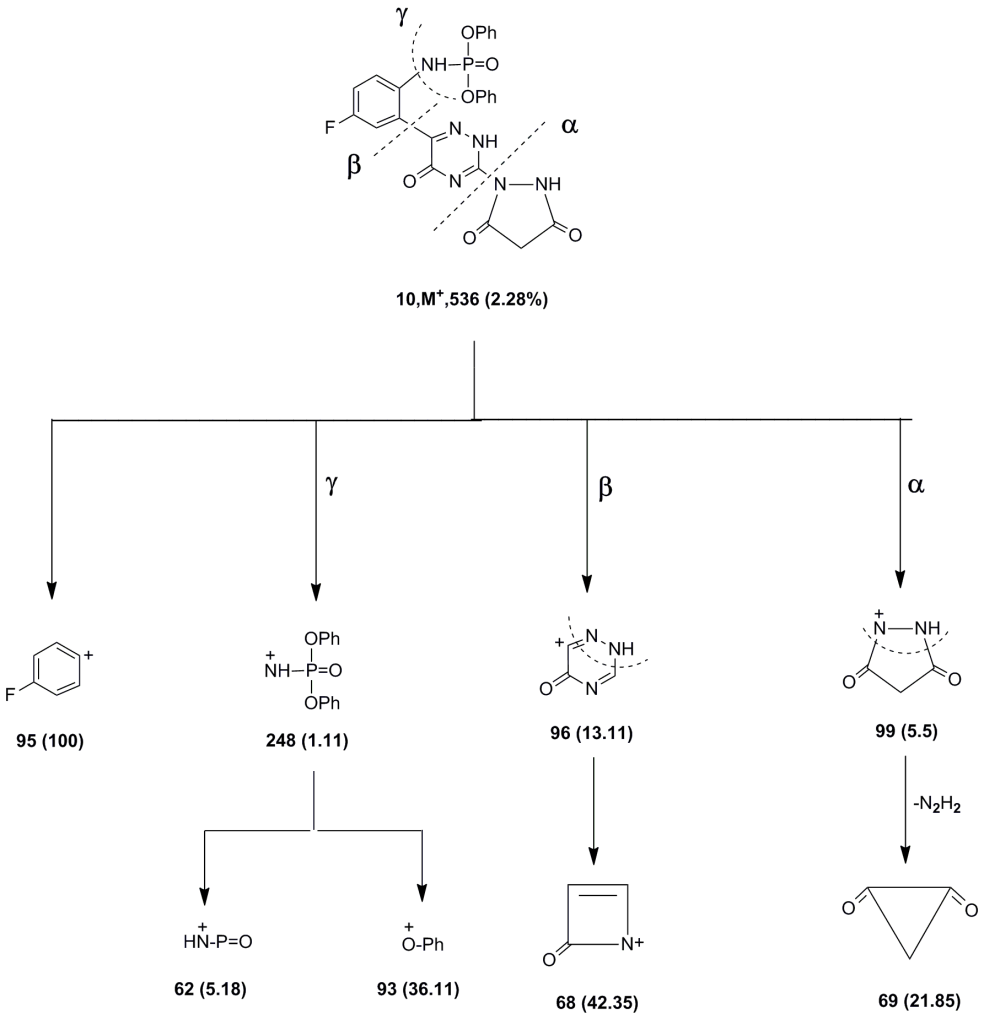


Figure 10. Mass Fragmentation pattern of compound 10.

4. HIV-1 Inhibition (Enzyme Inhibition)

Human immunodeficiency virus type-1 is the causative agent of acquired immunodeficiency syndrome (AIDS) which is one of the most serious health problems [42]. Since reverse transcriptase (RT) is an essential enzyme for the replication [43] of HIV, it is the most favoured target for the antiviral chemotherapy against HIV infection [44]. 3'-Azido-2',3'-dideoxythymidine (AZT) [45] and 2',3'-dideoxyinosine (DDI) [46], 2',3'-dideoxycytydine (DDC) [47] and 2',3'-didehydro-3-deoxythymidine (DT4) [48] are the well-known potent nucleoside reverse transcriptase inhibitors clinical use, but unfortunately they produce serious side effects such as bone marrow suppression. The search for a more effective and less toxic agent has brought into focus potent yet structurally different non-nucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs) [49]. Shakil *et al.*, [50] reported that increase or decrease of electro-negativity and hydrophobicity of the bioactive drugs, cytotoxicity will also increase or decrease accordingly. So less electronegative and less hydrophobic substituents would be preferred to design the less cytotoxic drugs. The large number of research papers published every year indicate that the development of an effective drug for the inhibition of HIV-1 via enzymes inhibitors [51] [52]. HIV PIs for example, prevent the cleavage of the gag and gag-pol precursor polyproteins to the structural proteins and functional proteins, thus arresting maturation and thereby blocking infectivity of the nascent virions. e.g. Tipranavir showed loss cross-resistance to HIV strains that were resistant to the established (peptidomimetic) inhibitors of HIV protease. Also, tipranavir retained marked activity against HIV-1 isolates derived from patients with multidrug resistance to other PIs (**Figure 13**).

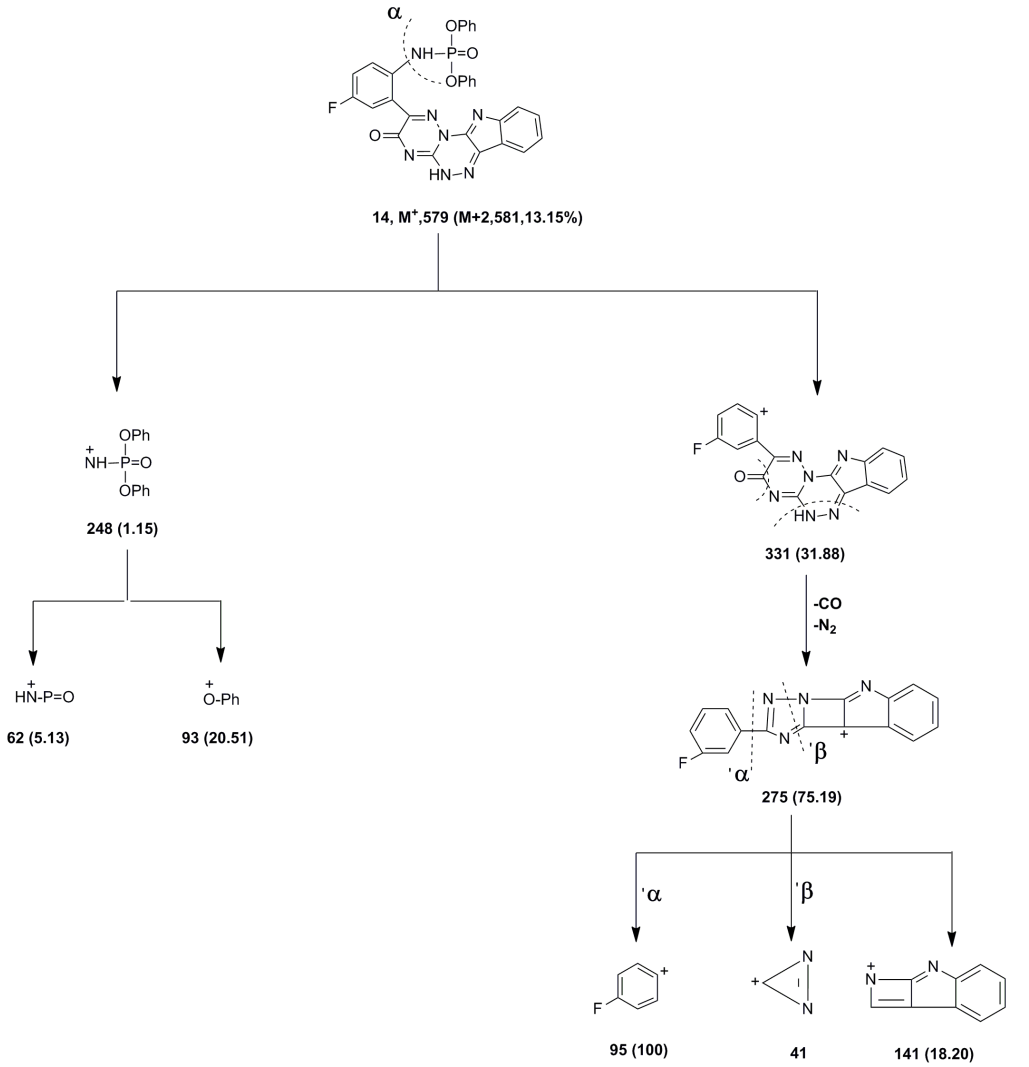


Figure 11. Mass Fragmentation pattern of compound 14.

In search for new poly substituted 1,2,4-triazine bearing a phosphoryl group. The present work is synthesize novel fluorine substituted phosphorylanilido-1,2,4-triazin-ones and evaluate as potential inhibitors for HIV-1. The procedure used in the National Cancer Institute's Test for agents active against HIV is designed to detect agents acting at any stage of the virus reproductive cycle [53]. The assay basically involves the killing of T_4 lymphocytes by HIV. Small amounts of HIV are added to cells and two cycles of virus reproduction are necessary to obtain the required cell killing. Agents that interact with virions, cells or virus gene-products to interfere with viral activities will protect cells from cytolysis. The tetrazolium salt XTT is added to all wells and cultures are incubated to allow formazan color development by viable cells used analyzed spectrophotometrically (**Figure 14**).

Anti-HIV-1 screening results of some of compounds (**Table 1**) shows that these systems found inactive, probably due to their inability to exist in butterfly like conformation as explained in a similar case [54]. Only the compounds **7**, **12**, **18** and **22** exhibited a higher protection% (concentration required in protect MT-4 cells against the cytopathogenicity of HIV by 50%). The order reactivity increases as **18** > **10** > **7** > **12** > **22**. A higher effect's of compound **18** (**Table 2**) is may be due to a higher possibility to form a type of H-bonds with proteins of virus, which led to a moderate degree of inhibition of HIV-1 activity. Also, compound **18** had a differ type of phenolic bonds, which give a variety of differ effects towards HIV-1 activity. Moreover, compound **18** had a less possibility to form a type of intra-molecular H-bond, thus their hydroxyl group become a higher degree of free action

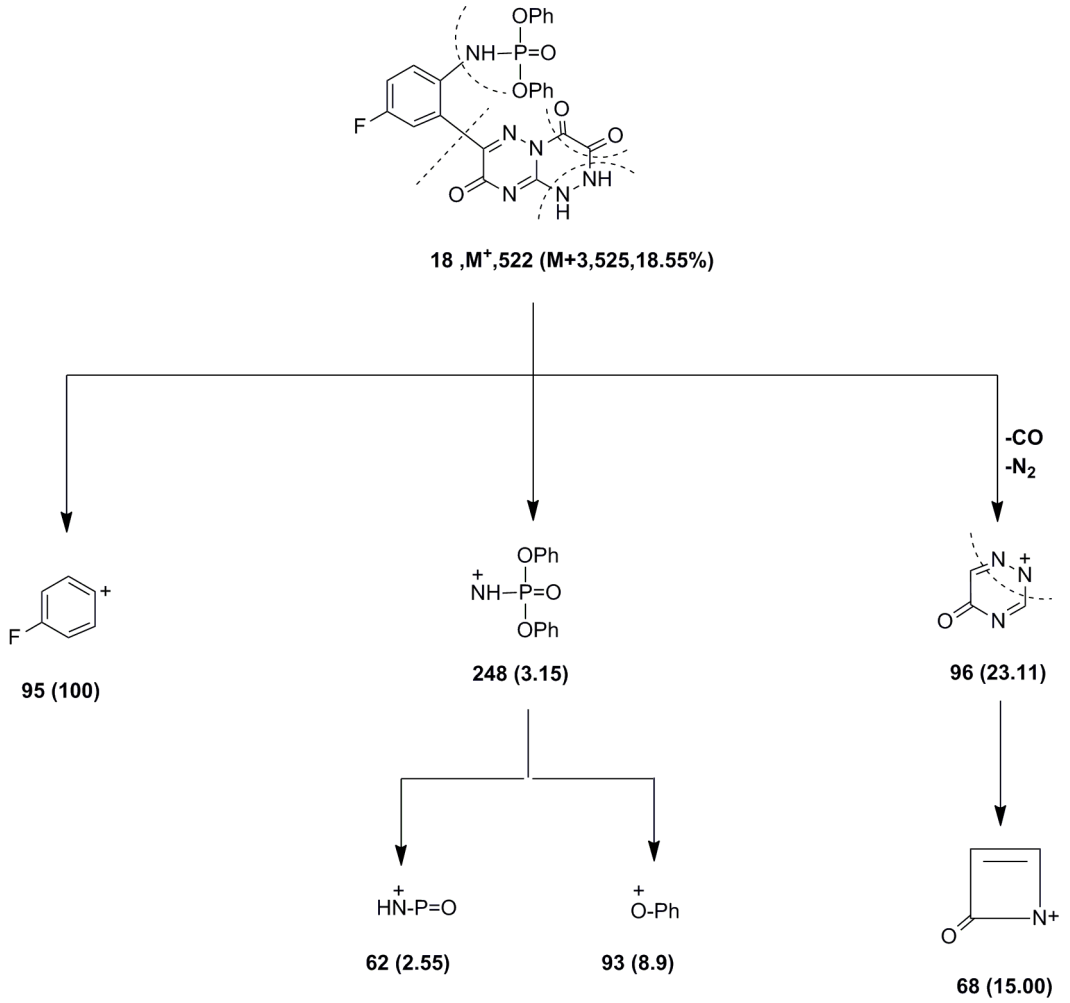


Figure 12. Mass Fragmentation pattern of compound 18.

Table 1. The *in vitro* anti-HIV-1 screening results of new compounds **3-22** in MT-4 cells.

Compd. No.	Dose (Molar)	Anti-HIV-1 Activity			
		IC_{50} (μg/mL)	Max Production %	Percent of Control	
	2.00×10^{-6}			Infected	Uninfected
3		>55.13	13.5	10.11	101.11
6		>20.20	19	17.38	106.32
7		>27.20	26.5	63.51	97.93
10		>19. 40	30.5	80.29	96.11
12		>28.57	25.0	35.40	105.77
14		>88.30	9.5	0.04	0.51
16		>3.99	16.00	14.16	101.91
18		>42.60	35.00	83.47	104.97
22		>94.40	23.5	18.19	104.12

Table 2. The *in vitro* anti-HIV-1 screening results of compound **18**.

Index	Concentration	Dose	Percent of Protection	Percent of Control	
				Infected	Uninfected
IC_{50} (Molar)	1.12×10^{-5}	6.33×10^{-9}	7.55	13.99	101.90
EC_{50} (Molar)	4.26×10^{-7}	2.0×10^{-8}	10.10	17.11	106.20
TIC_{50} (IC/E_C)	$2.63 \times 10^{+1}$	6.35×10^{-8}	12.00	18.15	104.21
		2.00×10^{-7}	30.01	32.31	105.30
		6.33×10^{-7}	60.66	62.15	98.10
		2.00×10^{-6}	82.23	83.47	104.99
		6.34×10^{-6}	75.66	80.13	99.10
		2.00×10^{-5}	-7.55	0.040	0.55

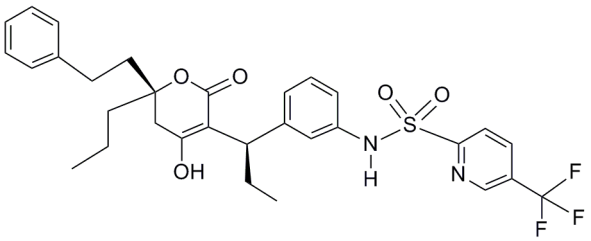


Figure 13. Tipranavir (PNU-140690).

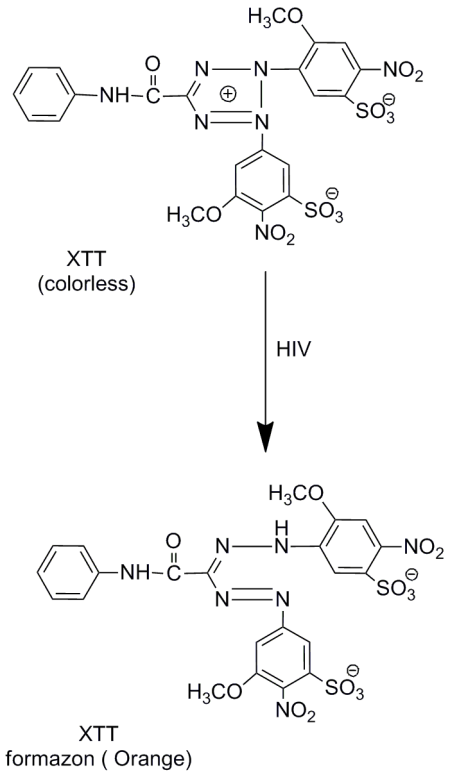


Figure 14. The standard indicator for HIV present (XXT).

with a active center of proteins of HIV-1 virus.

5. Conclusion

In search for new anti-HIV-1, novel fluorine substituted isolated and fused heterobicyclic nitrogen systems bearing 6-(2'-phosphorylanilido)-1,2,4-triazin moiety have been obtained from a ring closure reactions of the corresponding 3-hydrazino-1,2,4-triazinone with π-acceptable reagents. Some compounds exhibited a mark's inhibitors as anti-HIV-1 activity in hope to a possible control on the HIV-1 activity.

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