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Synthetic Approach for Novel Fluorine Substituted α-Aminophosphonic Acids Containing 1,2,4-Triazin-5-One Moiety as Antioxidant Agents

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Abstract

Novel fluorine substituted α-amino phosphonic acids containing 1,2,4-triazin-5-one (**6a**-**f**) have been obtained from fluoroacylation of 6-(2′-amino-5′-nitrophenyl)-3-thioxo-1,2,4-triazin-5(4H)-one (**1**) followed by ammonilysis to give the corresponding 3-amino-derivative **3**. Condensation of compound **3** with nitro/halogenated aromatic aldehydes yielded the Schiff bases **4**. The simple addition of diethyl phosphonate to compound **4** produced the α-amino phosphonates **5**. Acidic hydrolysis of compound **5** produced the fluorine substituted α-amino acids derivatives **6**. Structures of the new compounds have been established with the help of elemental analysis and spectral measurements. Also, the products evaluated as antioxidants, where the fluorinated α-amino phosphonic acids **6** are more active than the other synthesized systems.

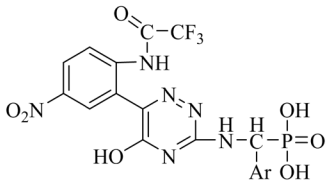
Keywords

Synthetic, Fluorine α-Amino Acids, 1,2,4-Triazin-5-One Moiety, Antioxidants Activity

1. Introduction

Recently, α-amino phosphonic acids and α-amino phosphonates have a vital importance of research chemists [1] [2] [3], which is due to these family of compounds display, enzymatic inhibitors for HIV protease antagonists [4] and collagenase inhibitors [5]. Also, they use as anticancer [6], antibacterial [7], antiviral [8] and antioxidant [9] agents. On the other hands, functionally 1,2,4-triazines have unique properties for biological, medicinal and pharmacological chemistry

[10] [11] [12]. Phosphorus compounds bearing and/or containing 1,2,4-triazine moieties exhibit a significant attention due to the specific biological properties [13] [14] [15] [16] [17]. Also, the introduction of fluorine atoms to heterocyclic nitrogen systems, mostly improve their physical, chemical and medical properties [18] [19] [20] [21]. In the present work, we focused on the reactivity of functional 1,2,4-triazines towards different reagents followed by simple addition of diethyl phosphonate to obtain a novel fluorine substituted *α*-amino phosphonic acids which considered as *α*-amino acids analog, in view of antioxidant activity.



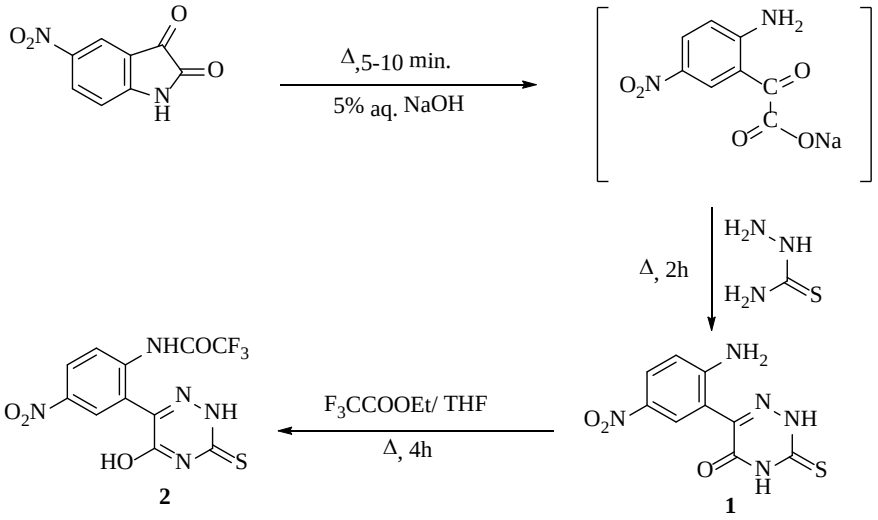
α-amino phosphonic acids

2. Chemistry

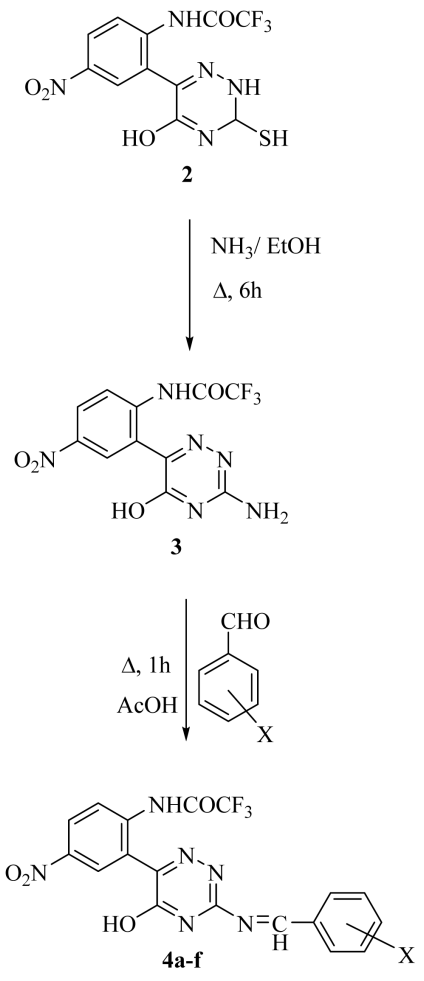
The phosphorylation of amino-organic heterocyclic systems often improves their biological activity because of the P-O bond stores energy for metabolic processes [1]. Also, the chemistry of N-phosphoryl heterocyclic indicates that these compounds form dimensional polymeric chain via intermolecular P-O^{-}·····$^{+}$NH hydrogen bond [2]. Moreover, the reactivity of the dipolar ion structures of the tautomeric form of *α*-amino phosphonates is due to the higher electron-withdrawing properties of two phenoxy and P=O groups. Thus, the *α*-amino-phosphonate group has a high degree of stability against any reagent attack [3]. To deduce the aims of this work, 6-(2′-Amino-5′-nitrophenyl)-3-thioxo-1,2,4-triazin-5(2H,4H)-one (**1**) as a starting material obtained from reflux of 5-nitroisatin with thiosemicarbazide in aq. NaOH (Scheme 1).

Fluoroacylation of compound **1** by boiling with ethyl 2,2,2-trifluoroacetate in THF yielded [22] 2,2,2-trifluoro-N-[2-(5-hydroxy-3-thioxo-2,3-dihydro-1,2,4-triazin-6-yl)-4-nitrophenyl] acetamide (**2**), which upon ammonilysis by reflux with liquid ammonia in ethanol produced [23] 3-amino-6-[2′-(trifluoroacetamido-5′′-nitrophenyl)]-1,2,4-triazin-5(4H)-one (**3**) (Scheme 2). Condensation of compound **3** with various nitro and halogenated aromatic aldehydes in boiling ethanol yielded the corresponding Schiff bases **4** (Scheme 2).

The main aims of the present work produce a novel fluorine substituted *α*-amino acids containing 1,2,4-triazinone moiety. The addition of compounds with phosphorus hydrogen bonds to azomethine (HC=N-Ar) bonds provides an economical method for the synthesis of organophosphorus derivatives. Thus, the addition of diethyl phosphonate to Schiff bases by warm at 80˚C - 100˚C along 6h with a few drops of triethylamine produced [24] *α*-amino phosphonates **5** which upon acid hydrolysis afforded [25] the novel fluorinated *α*-amino phosphonic acids **6** as a vital target (Scheme 3). Formation of both compounds **5** & **4**

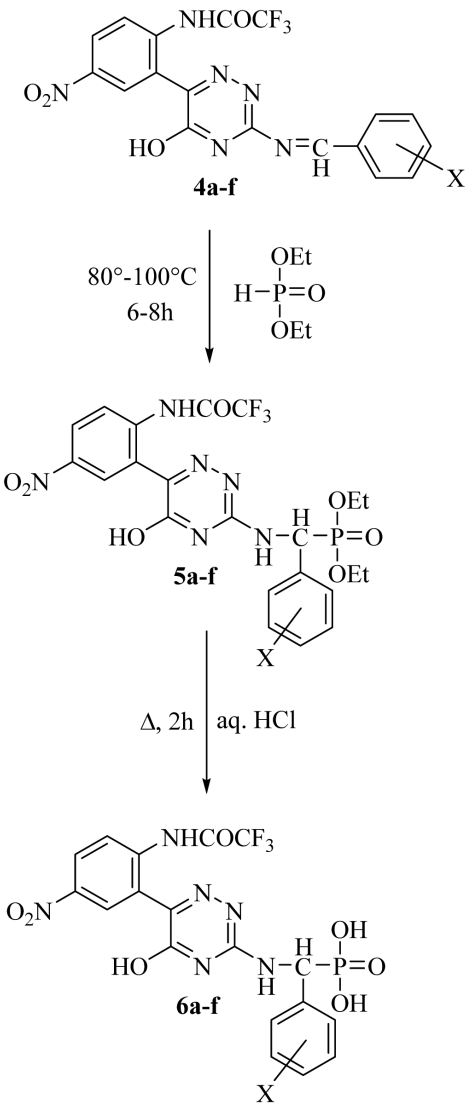


Scheme 1. Synthesis of compounds 1 and 2.



X: **a**, *o*-NO_2; **b**, *m*-NO_2; **c**, NO_2; **d**, *p*-Br; **e**, *p*-Cl; **f**, *p*-F

Scheme 2. Synthesis of compounds 3 and 4a-f.



X: **a**, *o*-NO_2; **b**, *m*-NO_2; **c**, NO_2; **d**, *p*-Br; **e**, *p*-Cl; **f**, *p*-F

Scheme 3. Synthesis of compounds 5a-f and 6a-f.

may as they shown in **Figure 1**.

3. Result and Discussion

The former structures of novel fluorinated *α*-amino phosphonic acids have been deduced from correct their elemental analysis and spectral measurements. IR spectra of both the compounds **1**-**6** recorded the absorption bands $\bar{\upsilon}$ at 1530, 1350 $cm^{-1}$for asymmetric and symmetric NO_2 groups, 3200 - 3100 and 1660 cm^{-1} for NH and C=O of 1,2,4-triazine, also $\bar{\upsilon}$ at 1630 cm^{-1} attribute to CONH group and 1250 cm^{-1} of C-F functional groups. IR of compound **3** showed $\bar{\upsilon}$ at 3300 and 1610 cm^{-1} stretching and bending of NH_2 group, which lacks in all the compounds **4**-**6**. Also, the presence of $\bar{\upsilon}$ at 1600 - 1580 cm^{-1} for the exocyclic

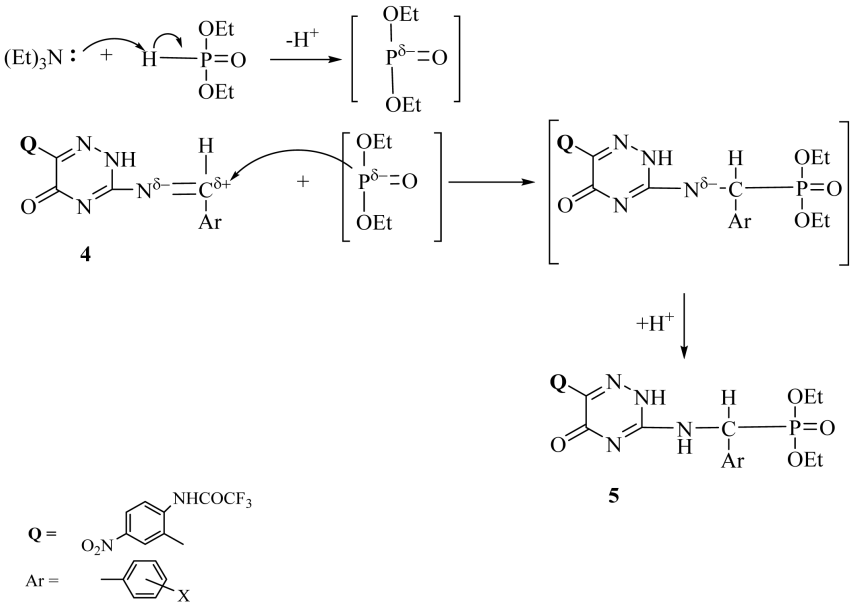
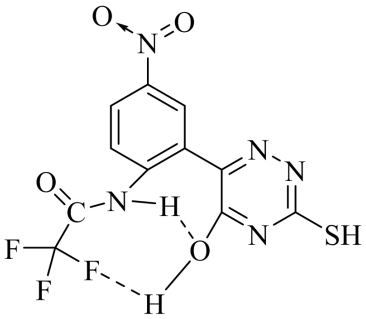


Figure1. Formation of compound **5** from **4**.

CH=N group in the compound **4**. New functional groups at $\bar{\upsilon}$ 1220 - 1215 (P=O) and 1050 (P-O-R) cm^{-1} observed in the spectrum of **5**. In addition, showed $\bar{\upsilon}$ at 2900 - 2880 and 1480 - 1440 cm^{-1} for stretching and bending of CH_3 & CH_2. On the other hand, IR spectrum of **6** showed $\bar{\upsilon}$ at 2730, 2680 cm^{-1} attribute for two hydroxy groups bonded to the phosphorus atom. All the fluorinated 1,2,4-triazinones **2** - **6** showed a stable true hydroxy group at the position-5 of 1,2,4-triazines at $\bar{\upsilon}$ 3500 - 3450 cm^{-1}. Presence of these hydroxy groups may be due to a large withdrawing from both NO_2, CF_3 groups via a type of H-bonding.



The H-bonding form's of compound **2**.

^{1}H NMR spectra of the novel fluorinated α-amino phosphonic acids give us a good indication of what those structures. Thus, ^{1}H NMR spectra of compound **1** exhibit δ at 3.5, 13.0, 11.8 ppm for NH_2, NH, NH of 1,2,4-triazinone, in addition to δ 8.8, 8.2, 7.9 ppm for aromatic protons. ^{1}H NMR spectra of **2** & **4** recorded a lack's of NH_2 protons while showed δ at 9.22 ppm for methin proton (-CH=N-) in compound **4**. Also, ^{1}H NMR spectrum of compound **5** showed a new resonated signal at δ 1.2(J = 6.8 Hz) and large signal 4.0 - 3.9 ppm for OCH_2CH_3

protons, with a broad signal at 3.0 - 2.95, 2.7, 2.5 and 1.05, 1.03 ppm for CH_2 & CH_3 protons. ^{1}H NMR spectrum of compound **6f** showed lacks both NH protons which is due to a type of F….H bond while reporting the signal at 4.95 ppm attribute to OH proton. ^{1}H NMR spectra of all new synthetic compounds **1** - **6** recorded the δ at 11.8 ppm for internal NH of 1,2,4-triazine at position-4, and 8.55 ppm for NHCO protons. ^{31}P NMR (DMSO) of the **6f** exhibit resonated signals at δ 14.0 (O=P-OH) and 20.5 (P-CH) ppm. Also, ^{1}H NMR spectra of **6** recorded the P-CHAr proton at tow doublets at 4.55 (J_{PCH} = 21 Hz) and 4.64 (J_{PCH} = 18 Hz) ppm while that showed the P-OH protons at 3.00 ppm which supported the existence of that structures. ^{13}C NMR spectrum of compound **5** supported their structure due to the presence of the characteristic carbon atoms at δ 16, 60.1, 45.2 and 177.5 ppm attributed to CH_3, CH_2, CH-P and C=O of 1,2,4-triazines. In addition, signals at δ 155 and 130 - 127 ppm for CONH and aromatic carbons. The aliphatic carbons CH_2, CH_3 of compound **5** disappeared in that of compound **6**. Finally, mass spectrometry study of novel fluorinated α-amino phosphonic acids, for example, **6b**and **6f** recorded a molecular ion fragments at low intensity, with base peaks at m/e 231 for (**6b**) and m/e 95 for (**6f**) attribute to α-amino phosphonic radicals (Figure 2 & Figure 3).

The higher stability of their base peak may be due to the tautomeric forms present and the free delocalization from HN to P=O centers (Figure 4).

4. Experimental

The melting point recorded on Stuart scientific SMP3 (Bibby, UK) melting point

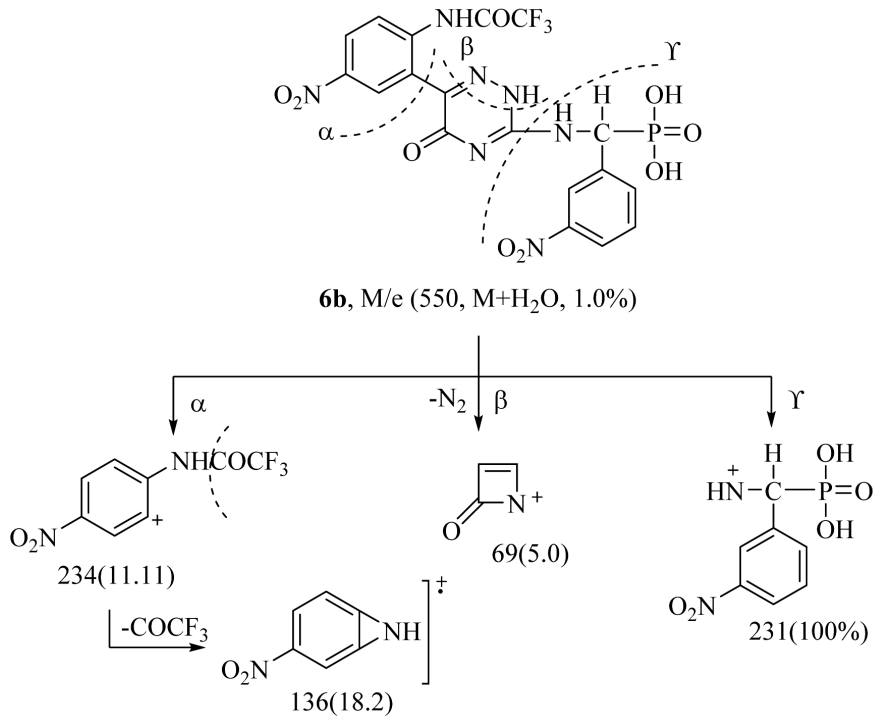


Figure 2. Mass fragmentation pattern of compound **6b**.

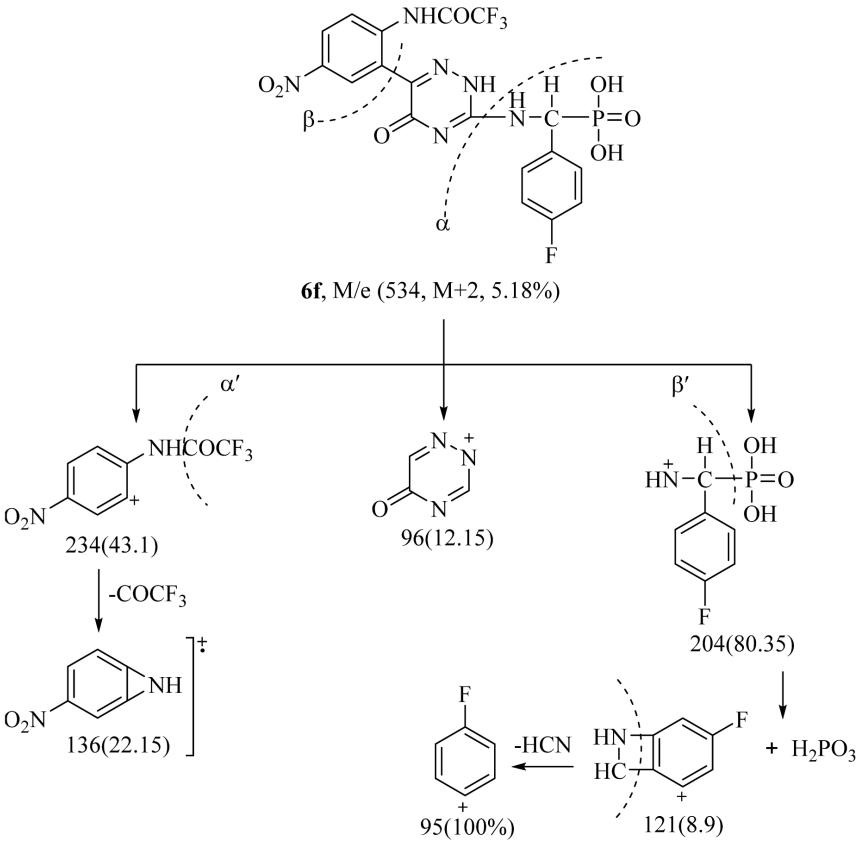


Figure 3. Mass fragmentation pattern of compound **6f**.

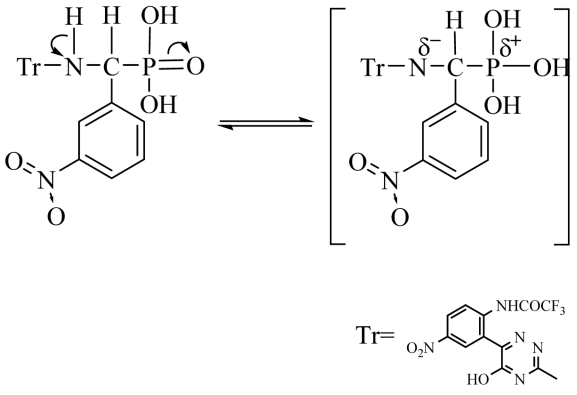


Figure 4. The stability of *α*-amino phosphonic acids **6b**.

apparatus and reported as uncorrected. 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. 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 ppm). AGC-MS-QP 1000 Ex model used for recording the mass spectra. Hexafluorobenzene used as an external standard for $^{19}FNMR$ at 84.25 MHz and ^{31}P (in

$CDCl_3$, 101.25 MHZ). Elemental analysis performed on Micro Analytical Center of National Reaches Center-Dokki, Cairo, Egypt.

6-(2′-Amino-5′-nitrophenyl)-3-thioxo-1,2,4-triazin-5(2H,4H)one (**1**) [26]

A mixture of 5-nitroisatin (0.1 mol, in 100 ml of 5% aq. NaOH) and thiosemicarbazide (0.1 mol, in 10 ml hot water) refluxed for 2 h, cooled then poured onto ice-AcOH. The solid produced filtered off, and crystallization from MeOH to give compound **1** as reddish brown solid, yield 85%, m.p. 290˚C - 291˚C. IR spectrum $\bar{\upsilon}(cm^{-1})$: 3255(NH), 3138(NH), 3082(NH), 3020(aromatic CH), 1608 (binding NH_2), 1595(C=N), 1509, 1310(asym. & sym. NO_2), 1173(C=S), 837, 817, 750 (aromatic CH). Calculated $C_9H_7N_5O_3S(M^+$ 265): C, 40.75; H, 2.66; N, 26.40; S, 12.09%. Found: C, 40.34; H, 2.60; N, 26.31; S, 11.99%.

2,2,2-Trifluoro-N-[2-(5-hydroxy-3-thioxo-2,3-dihydro-1,2,4-triazin-6-yl)-4-nitrophenyl]acetamide (**2**)

Equimolar amounts of compound **1** and ethyl 2,2,2-trifluoroacetate in THF (100 ml) refluxed for 4h, cooled. The solid obtained filtered off and crystallized from EtOH to give compound **2** as deep green solid, yield 76%, m.p: 270˚C - 272˚C. IR spectrum $\bar{\upsilon}(cm^{-1})$: 3448(OH), 3324, 3191(NH), 3080(aromatic CH), 1703($COCF_3$), 1615(C=N), 1519, 1321(asym. & sym. NO_2), 1242(C-F), 850, 810, 780(aromatic CH). ^{1}H NMR(400 MHz, DMSO-d_6) δ(ppm): 14.64(s, 1H, OH), 13.72(s, 1H, NH), 12.45(s, 1H, NH), 9.1, 8.9, 8.5, 8.3(m, 4H, aromatic protons), 3.56(s, OH).^{13}C NMR(100 MHz, DMSO-d_6) δ(ppm): 173.32(C=S), 153.61, 153.75(2C=O), 145.7, 143.10(C-F), 135.07(NCN), 128.0-121(aromatic carbons), 118.47, 114.54, 113.52(C_5, C_6 of 1,2,4-triazine). Calculated $C_{11}H_6F_3N_5O_4S(M^+$ 361): C, 36.57; H, 1.67; F, 15.78; N, 19.39; S, 8.87%. Found: C, 36.40; H, 1.61; F, 15.49; N, 19.15; S, 8.75%.

3-Amino-6-[2′-(trifluoroacetamido-5″-nitrophenyl)]-1,2,4-triazin-5(4H)one (**3**)

A mixture of **2(**0.1 mol) and a liquid NH_3(20 ml, 39%), with ethanol (100 ml), refluxed 6 h, cooled then poured onto ice-drops AcOH. The resulting solid, filtered off and crystallized from EtOH to give light green solid, yield 86%, m.p: 305˚C - 307˚C. IR spectrum $\bar{\upsilon}(cm^{-1})$: 3448(OH), 3323(NH), 3090(NH), 1702 (C=O), 1615(deformation NH_2), 1557(C=N), 1531, 1312(asym. & sym. NO_2), 1241(C-F), 988, 830, 749(aromatic CH), 607(C-F). ^{1}H NMR(400 MHz, DMSO-d_6) δ(ppm): 13.59, 12.41(each s, 2NH), 9.1(1H, OH-triazine), 8.95 - 8.60, 8.53 - 8.35 (each d, d, 2H, aromatic adjacent of NO_2), 8.27 - 8.01, 7.99 - 6.76(d, d 2H, aromatic), 3.44(s, 2H, NH_2), protons. ^{13}C NMR(100 MHz, DMSO-d_6) δ(ppm): 173.3(C=O), 153, 152(C-O), 145(C-F), 153(NCN), 128 - 121(aromatic carbons), 114, 113(triazine). Calculated $C_{11}H_7F_3N_6O_4(M^+$ 344): C, 38.38; H, 2.05; F, 16.56; N, 24.42%. Found: C, 38.18; H, 1.99; F, 16.36; N, 24.21%.

Schiff bases **4a-f**

A mixture of **3** (0.01 mol) and (*o*-, *m*-, *p*-nitrobenzaldehydes, *p*-bromo, *p*-chloro, and *p*-fluoro benzaldehydes) (0.01 ml) refluxed in AcOH (50 ml) for 1h, cooled then poured onto ice. The yielded solids filtered off and crystallized from a suit-

able solvent (EtOH, MeOH & Isopropyl alcohol) to give **4a**-**f**.

4a: Brown green solid, yield 83%, m.p: 270˚C - 272˚C. IR spectrum $\bar{\upsilon}(cm^{-1})$: 3447(OH), 3323(NH), 3080(aromatic CH), 1703(C=O), 1615(C=C), 1557(C=N), 1479(exo CH=N), 1519, 1322(asym., sym. NO_2), 1270(C-F), 927, 831, 749(aromatic CH), 607(C-F). Calculated $C_{18}H_{10}F_3N_7O_6$(M^+ 477): C, 45.29; H, 2.11; F, 11.94; N, 20.54%. Found: C, 44.78; H, 2.08; F, 11.79; N, 20.27%.

4b: Deep brown solid, yield 76%, m.p: 268˚C - 270˚C. IR spectrum $\bar{\upsilon}(cm^{-1})$: 3446(OH), 3322.55(NH), 3083(aromatic CH), 1702.56(C=O), 1615.21(C=N), 1531, 1307(asym., sym. NO_2), 1478(CH=N), 1453, 1427(deformation CH=N), 1270(C-F), 1239(C-F), 987, 928, 830, 749(aromatic CH), 607(C-F). ^{1}H NMR(400 MHz, DMSO-d_6) δ(ppm): 10.13(s, 1H, NH), 12.42 - 12.23(NHCO), 10.13(s, 1H, CH=N), 9.2 - 8.5, 8.4 - 6.75(each d, d, 8H, aromatic protons), 3.48(s, 1H, OH). ^{13}C NMR(100 MHz, DMSO-d_6) δ(ppm): 173(C=O), 153(CONH), 145(C-F), 137(CH=N), 130-123(aromatic carbons), 114, 113(carbons of 1,2,4-triazine). Calculated $C_{18}H_{10}F_3N_7O_6$(M^+ 477): C, 45.29; H, 2.11; F, 11.94; N, 20.54%. Found: C, 44.89; H, 2.00; F, 11.81; N, 20.39%.

4c: Brown green solid, yield 88%, m.p: 274˚C - 276˚C IR spectrum $\bar{\upsilon}(cm^{-1})$: 3447(OH), 3324(NH), 3084(aromatic CH), 1703(C=O), 1615(C=C), 1557(C=N), 1479(exo CH=N), 1531, 1322(asym., sym. NO_2), 1270(C-F), 900, 880, 850 (aromatic CH), 610(C-F). Calculated $C_{18}H_{10}F_3N_7O_6$(M^+ 477): C, 45.29; H, 2.11; F, 11.94; N, 20.54%. Found: C, 44.71; H, 2.01; F, 11.64; N, 20.12%.

4d: Brown solid, yield 79%, m.p: 260˚C - 262˚C. IR spectrum $\bar{\upsilon}(cm^{-1})$: 3448 (OH), 3324(NH), 3085(NH), 1704(C=O), 1616(C=C),1558(C=N), 1480(exo CH=N), 1515, 1324(asym. & sym. NO_2), 1272(C-F), 988, 929, 749(aromatic CH), 690(C-Br), 640(C-F). Calculated $C_{18}H_{10}BrF_3N_6O_4$(M^+ 509): C, 42.29; H, 1.97; Br, 15.63; F, 11.15; N, 16.44%. Found: C, 41.97; H, 1.71; Br, 15.54; F, 10.99; N, 16.24%.

4e: Brownish yellow solid, yield 77%, m.p: 267˚C - 269˚C. IR spectrum $\bar{\upsilon}(cm^{-1})$: 3447(OH), 3320(NH), 3089(NH), 1701(C=O), 1614(C=C), 1553(C=N), 1477(exo CH=N), 1516, 1322(asym. & sym. NO_2), 1269.9(C-F), 986, 929, 749.7(aromatic CH), 688(C-Cl), 646(C-F). Calculated $C_{18}H_{10}ClF_3N_6O_4$(M^+ 466): C, 46.32; H, 2.16; Cl, 7.59; F, 12.21; N, 18.01%. Found: C, 45.89; H, 2.13; Cl, 7.28; F, 11.96; N, 17.71%.

4f: Reddish brown solid, yield 84%, m.p: 271˚C - 273˚C. IR spectrum $\bar{\upsilon}(cm^{-1})$: 3446(OH), 3321(NH), 3081(NH), 1702(C=O), 1557(C=N), 1517, 1320(asym. & sym. NO_2), 1239(C-F), 928, 931, 749(aromatic CH), 647(C-F). ^{1}H NMR(400 MHz, DMSO-d_6) δ(ppm): 13.44(s, 1H, NH), 9.52(s, 1H, CH=N), 8.35 - 7.99 & 7.01 - 6.75(each d, d 7H, aromatic protons), 3.41(s, 1H, OH of C_5-1,2,4-triazine). ^{13}C NMR(100 MHz, DMSO-d_6) δ(ppm): 173(C=O), 153, 152(C-OR), 145.7(C-F), 135(NCN of 1,2,4-triazine), 128-126(aromatic carbons), 114, 113(C_5, C_6 of 1,2,4-triazine). Calculated $C_{18}H_{10}F_4N_6O_4$(M^+ 450): C, 48.01; H, 2.24; F, 16.88; N, 18.66%. Found: C, 47.83; H, 2.19; F, 16.66; N, 18.46%.

Diethyl [6-(2′-trifluoroacetamido-5′-nitrophenyl)-5-hydroxy-1,2,4-triazin-3-yl]-amino-(aryl) methyl phosphonates (**5a**-**f**)

A mixture of **4a**-**e** and/ or **4f** (0.01 mol) and diethyl phosphonate (0.01 mol) in few drops of TEA, fused at 80˚C - 100˚C for 6 - 8 h, cooled the treated with dioxan. The solid obtained crystallized from a suitable solvent to give **5a**-**f**.

5a: Deep brown solid, yield 82%, m.p: 263˚C - 265˚C. IR spectrum $\bar{\upsilon}(cm^{-1})$: 3447(OH), 3321(NH), 3085(aromatic CH), 2970(aliphatic CH), 1701(C=O), 1615(C=N), 1532, 1309(asym., sym. NO_2), 1481, 1428(deformation CH_2, CH_3), 1237(C-F), 1159(P=O), 1100(O-P-O-R), 840, 805(aromatic CH), 610(C-F). Calculated $C_{22}H_{21}F_3N_7O_9P$(M^+ 615): C, 42.94; H, 3.44; F, 9.26; N, 15.93; P, 5.03%. Found: C, 42.59; H, 3.38; F, 9.15; N, 15.70; P, 4.93%.

5b: Deep brown solid, yield 78%, m.p: 260˚C - 262˚C. IR spectrum $\bar{\upsilon}(cm^{-1})$: 3433(OH), 3316(NH), 3083(aromatic CH), 2969(aliphatic CH), 1698(C=O), 1616(C=N), 1532, 1311(asym., sym. NO_2), 1481, 1428(deformation CH_2, CH_3), 1245(C-F), 1159(P=O), 1098(O-P-O-R), 860, 810(aromatic CH), 600(C-F). ^{1}H NMR(400 MHz, DMSO-d_6) δ(ppm): 13.59(NH), 8.37(CH-NH), 8.36 - 8.0, 7.99 - 6.76(each d, d, aromatic protons), 3.82(s, 1H, OH), 3.76 - 3.44(b, NH), 2.89, 2.53 & 1.05, 1.03(each s, 2 CH_2 & CH_3). ^{13}C NMR(100 MHz, DMSO-d_6) δ(ppm): 173.3(C=O), 153, 152(C-OR), 145.80(C-F), 135(NCN), 128 - 126(aromatic carbons), 114, 113.59(C_5, C_6 of 1,2,4-triazine), 38.30(carbons of CH_2, CH_3). Calculated $C_{22}H_{21}F_3N_7O_9P$(M^+ 615): C, 42.94; H, 3.44; F, 9.26; N, 15.93; P, 5.03%. Found: C, 42.66; H, 3.25; F, 9.11; N, 15.78; P, 4.85%.

5c: Brown sold, yield 87%, m.p: 270˚C - 272˚C. IR spectrum $\bar{\upsilon}(cm^{-1})$: 3446(OH), 3320(NH), 3082(aromatic CH), 2970(aliphatic CH), 1700(C=O), 1614(C=N), 1528, 1310(asym., sym. NO_2), 1477, 1427(deformation CH_2, CH_3), 1238(C-F), 1159(P=O), 1104(O-P-O-R), 850, 810(aromatic CH), 608(C-F). Calculated $C_{22}H_{21}F_3N_7O_9P$(M^+ 615): C, 42.94; H, 3.44; F, 9.26; N, 15.93; P, 5.03%. Found: C, 42.69; H, 3.44; F, 9.26; N, 15.93; P, 5.03%.

5d: Deep brown solid, yield 92%, m.p: 302˚C - 305˚C. IR spectrum $\bar{\upsilon}(cm^{-1})$: 3434(OH), 3317(NH), 3081(aromatic CH), 2970(aliphatic CH), 1700(C=O), 1553(C=N), 1532, 1311(asym. & sym. NO_2), 1479, 1427(deformation aliphatic), 1242(C-F), 1223(P=O), 1100(P-O-Et) 987, 780, 749(aromatic CH), 700(C-Br), 605(C-F). Calculated, $C_{22}H_{21}BrF_3N_6O_7P$(M^+ 649): C, 40.70; H, 3.26; Br, 12.31; F, 8.78; N, 12.94; P, 4.77%. Found: C, 40.39; H, 3.11; Br, 12.16; F, 8.61; N, 12.80; P, 4.66%.

5e: Black brown solid, yield 86%, m.p: 296˚C - 298˚C. IR spectrum $\bar{\upsilon}(cm^{-1})$: 3434(OH), 3317(NH), 3084(aromatic CH), 2970(aliphatic CH), 1700(C=O), 1553(C=N), 1532, 1311(asym. & sym. NO_2), 1480, 1427(deformation aliphatic), 1242(C-F), 1210(P=O), 1099(P-O-Et) 987, 780, 749(aromatic CH), 730(C-Cl), 600(C-F). Calculated $C_{22}H_{21}ClF_3N_6O_7P$(M^+ 604): C, 43.69; H, 3.50; Cl, 5.86; F, 9.42; N, 13.89; P, 5.12%. Found: C, 43.48; H, 3.43; Cl, 5.57; F, 9.22; N, 13.69; P, 4.98%.

5f: Light brown solid, yield 78%, m.p: 285˚C - 287˚C. IR spectrum $\bar{\upsilon}(cm^{-1})$: 3447(OH), 3284(NH), 3198(NH), 3084(aromatic CH), 2970(aliphatic CH), 1695(C=O), 1556(C=N), 1516, 1304(asym. & sym. NO_2), 1478, 1427(deformation

aliphatic), 1240(C-F), 1222(P=O), 1070(P-O-Et) 983, 787, 749(aromatic CH), 608(C-F). ^{1}H NMR(400 MHz, DMSO-d_6) δ(ppm): 12.25(s, 1H, NH), 10.76(s, 1H, OH), 9.9(s, 1H, CH-N), 9.05 - 8.01 & 7.99 - 6.54(each d, d 7H, aromatic protons), 3.44(s, 1H, OH), 2.52, 1.24(each m, 10H, O-CH_2CH_3).^{13}C NMR(100 MHz, DMSO-d_6) δ(ppm): 173(C=O), 152(C-OH), 150(C-NH), 147(C-F), 145(C_6 of 1,2,4-triazine), 142(C-NO_2), 137(C_3 of 1,2,4-triazine)130 - 126(aromatic carbons), 116(Ar-CH-P), 113(CH_2-O), 40(CH_3-CH_2). Calculated $C_{22}H_{21}F_4N_6O_7P$(M^+ 588): C, 44.91; H, 3.60; F, 12.92; N, 14.28 P, 5.26%. Found: C, 44.66; H, 3.58; F, 12.71; N, 14.11 P, 5.01%.

***[((6-(5′-nitro-2′-(2″,2″,2″-trifluoroacetamido)phenyl)-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)amino)(phenyl)methyl]phosphonic acids*(6a-f)**

A mixture of **5** (0.01 mol) and dil. HCl (10 ml, 5%) refluxed for 2 h, cooled, then neutralized with diluted $NaHCO_3$. The solid poured, filtered off and crystallized from suitable solvents to give (**6a-f**).

6a: Brown solid, yield 85%, m.p: 282˚C - 284˚C. IR spectrum $\tilde{\upsilon}$(cm^{-1}): 3446(OH), 3321(NH), 3080(aromatic CH), 2970(aliphatic CH), 1701(C=O), 1614(C=N), 1557, 1305(asym., sym. NO_2), 1269(C-F), 1160(P=O), 1090(O-P-O), 980, 840(aromatic CH), 610(C-F). Calculated $C_{18}H_{13}F_3N_7O_9P$(M^+ 559): C, 38.65; H, 2.34; F, 10.19; N, 17.53; P, 5.54%. Found: C, 38.41; H, 2.08; F, 9.99; N, 17.30; P, 5.28%.

6b: Brown solid, yield 94%, m.p: 289˚C - 291˚C. IR spectrum $\tilde{\upsilon}$(cm^{-1}): 3447(OH), 3323(NH), 1702(C=O), 1615(C=N), 1531, 1308(asym., sym. NO_2), 1270(C-F), 1159(P=O), 1090(O-P-O), 987, 850(aromatic CH), 606(C-F). ^{1}H NMR(400 MHz, DMSO-d_6) δ(ppm): 13.5, 13.19, 12.24(each s, 3NH), 9.0(s, 1H, CH-P), 8.61 - 8.14, 7.98 - 6.75(each d, d, 7H, aromatic protons), 5.95(s, 1H, P-OH). ^{13}C NMR(100 MHz, DMSO-d_6) δ(ppm): 173.3(C=O), 153, 152(C-O), 145.80(C-F), 135.1(NCN), 128.02 - 126.68(aromatic carbons), 114.48, 113.48 (carbons of 1,2,4-triazine). Calculated $C_{18}H_{13}F_3N_7O_9P$(M^+ 559): C, 38.65; H, 2.34; F, 10.19; N, 17.53; P, 5.54%. Found: C, 38.38; H, 2.11; F, 9.98; N, 17.35; P, 5.39%. M/S(Int.%): 555(M+3, 1.00), 234(11.11), 231(100), 136(18.2), 69(5.00).

6c: Deep brown solid, yield 88%, m.p: 273˚C - 275˚C. IR spectrum $\tilde{\upsilon}$(cm^{-1}): 3446(OH), 3323(NH), 3078(aromatic CH), 2970(aliphatic CH), 1704(C=O), 1615(C=N), 1555, 1307(asym., sym. NO_2), 1271(C-F), 1158(P=O), 1093(O-P-O), 970, 825(aromatic CH), 604(C-F). Calculated $C_{18}H_{13}F_3N_7O_9P$(M^+ 559): C, 38.65; H, 2.34; F, 10.19; N, 17.53; P, 5.54%. Found: C, 38.40; H, 2.13; F, 10.01; N, 17.40; P, 5.33%.

6d: Deep brown solid, yield 78%, m.p: 251˚C - 253˚C. IR spectrum $\tilde{\upsilon}$(cm^{-1}): 3447(OH), 3323(NH), 3080(aromatic CH), 2970(aliphatic CH), 1702(C=O), 1614(C=N), 1557, 1304(asym. & sym. NO_2), 1269(C-F), 1218(C-P=O), 1060 (P-O-H) 975, 900, 880, 790(aromatic CH), 729(C-Br), 600(C-F). Calculated $C_{18}H_{13}BrF_3N_6O_7P$(M^+ 593): C, 36.45; H, 2.21; Br, 13.47; F, 9.61; N, 14.17; P, 5.22%. Found: C, 36.15; H, 2.15; Br, 13.47; F, 9.39; N, 14.05; P, 5.11%.

6e: Deep brown solid, yield 74%, m.p: 263˚C - 265˚C. IR spectrum $\tilde{\upsilon}$(cm^{-1}):

3446(OH), 3321(NH), 3080(aromatic CH), 2970(aliphatic CH), 1702(C=O), 1615(C=N), 1557, 1307(asym. & sym. NO_2), 1269(C-F), 1219(C-P=O), 1060 (P-O-H) 980, 900, 870, (aromatic CH), 748(C-Cl), 605(C-F). Calculated $C_{18}H_{13}ClF_3N_6O_7P$(M^+ 548): C, 39.40; H, 2.39; Cl, 6.46; F, 10.39; N, 15.32; P, 5.64%. Found: C, 39.15; H, 2.19; Cl, 6.31; F, 10.15; N, 15.20; P, 5.45%.

6f: Brown solid, yield 83%, m.p: 245˚C - 247˚C. IR spectrum $\tilde{\upsilon}(cm^{-1})$: 3448(OH), 3325(NH), 3088(NH), 1703(C=O), 1616(C=N), 1517, 1324(asym. & sym. NO_2), 1240(C-F), 1216(C-P=O), 1060(P-O-H) 988, 910, 880, 790(aromatic CH), 607(C-F). ^{1}H NMR(400 MHz, DMSO-d_6) δ(ppm): 8.35(s, 1H, CH-N), 8.04 - 7.48 & 7.47 - 6.75(each d, d, 7H, aromatic protons), 4.98(s, 1H, OH), 4.95(s, 1H, OH), 4.011(s, 1H, OH). ^{13}C NMR(100 MHz, DMSO-d_6) δ(ppm): 173.44 (C=O), 153, 152(C-O), 145.81(C-F), 135.12(NCN), 129.28 - 126.47(aromatic carbons), 114.68, 113.67(C_5, C_6 of 1,2,4-triazine). Calculated $C_{18}H_{13}F_4N_6O_7P$(M^+ 532): C, 40.62; H, 2.46; F, 14.28; N, 15.79; P, 5.82%. Found: C, 40.45; H, 2.30; F, 14.12; N, 15.56; P, 5.69%. M/S(Int.%): 534(M+2, 5.18), 234(43.1), 204(80.33), 136(22.15), 121(8.9), 96(12.15), 95(100).

5. The Antioxidant Evaluation

1,1-Diphenyl-2-picrylhydrazyl (DPPH) use to produce and reduce the odd electron stable-free radical which showed a strong UV-absorption maximum at λ = 517 nm. The new systems obtained dissolved in DMSO/EtOH at 150 & 300 μmol·L^{-1} added to DPPH at 100 μmol·L^{-1}. The tube kept at room temperature for 20 minutes and the absorption measured at λ 517 nm. The difference between the test and the control taken as the percent scavenging of the DPPH radical by use the formula: % inhibition = $\left(AB-AA\right)/AB\times 100$

where *AB*: absorption of blank; *AA*: absorption of the tested compound. The radical scavenging activity of ascorbic acid also measured and compared with that of the different synthesized compounds [27]. The observed data on the antioxidant-activated of the compounds and control shown in **Table 1**.

From the results obtained (**Table 1**) we can conclude that:

Presence of CF_3 and NO_2 of 6-aryl-1,2,4-triazinone and *α*-amino phosphonate bearing 3-substituted amino-1,2,4-triazinones deployed a good to perfect scavenging activities. The ordering activity is **6f** > **6e** > **6d** > **6b** > **6a** > **6c**, which mainly attribute to the presence of C-halogen and C-NO_2 of aryl-amino derivatives. The activity of *α*-amino phosphonic acids **6** is higher than the activity of *α*-amino phosphonates **5**. Also, high activity of **6f** comparing with the other systems is may be due to a rich of fluorine atoms bonded to a 1,2,4-triazinone moiety, and the phosphonate groups are the potent antioxidant agent.

6. Conclusion

In the search for new antioxidant agents, the present work reports a simple route to synthetic novel fluorine substituted nitroaryl-1,2,4-triazine bearing *α*-amino phosphonic acids. Presence of rich aliphatic/aromatic fluorine atoms and nitro

Table 1. The DPPH radical scavenging activity of the novel fluorinated *α*-amino phosphonates and the related *α*-amino phosphonic acids at 150 and 300 μmol·L^{-1}.

Compd. No.	DPPH % inhibition antioxidant ± SD	
	150 μmol·L^{-1}	300 μmol·L^{-1}
5a	52.08 ± 0.05	55.50 ± 0.15
5b	52.20 ± 0.20	55.65 ± 0.29
5c	51.76 ± 0.21	53.39 ± 0.11
5d	51.88 ± 0.15	51.78 ± 0.08
5e	56.01 ± 0.14	59.01 ± 0.05
5f	52.85 ± 0.11	60.00 ± 0.01
6a	56.65 ± 0.25	61.77 ± 0.31
6b	53.25 ± 0.11	73.44 ± 0.05
6c	53.25 ± 0.01	55.69 ± 0.05
6d	60.01 ± 0.01	64.66 ± 0.05
6e	61.33 ± 0.13	64.55 ± 0.15
6f	71.70 ± 0.11	64.55 ± 0.15
Ascorbic acid	43.00	50.70

groups bonded to 1,2,4-triazinone bearing *α*-amino phosphonic acids enhance the antioxidant activities, which may use the feature of medicinal treatments.

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