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Synthesis of New Fluorine Compounds Bearing 5-Aryl-1,3-Di(Acyl/Alkyl)-6-Azauracil Derivatives as Pharmacological Probes

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Abstract

New fluorine compounds bearing 5-aryl-1,3-di(trifluoroacetyl;4'-fluorobenzoyl;4'-fluorothiaanilido; methyl; substituted methyl)-6 azauracil derivatives (2-11) have been achieved derived from the interactions of 5-(2'-amino-5'-fluorophenyl)-6-azauracil (1) with α,β-bifunctional reagents in differ media and conditions. 5-Substituted-8-fluoro-1,2,4-triazino[5,6-b] indol-3(2H)ones (12-16) also produced from dehydration of compounds 2-11 by refluxing with dry acetone. Structures of the new products have been established from their elemental analysis and spectral measurements (UV, IR, 1H/13C/19F NMR and mass). These new fluorinated compounds evaluated as antioxidant agents by using DPPH and ascorbic acid as standard.

Keywords: *Synthesis; Fluorinated 6-azauracils; Antioxidant activity; Trifluoroacetyl*

Introduction

The synthesis, reactions and medicinal application of 1,3-disubstituted-6-azauracil derivatives have been subject of interest according to their biological importance. The high reactivity of 1,2,4-triazinones towards nucleophilic makes the metallation of these compounds more difficult than with the uracils. Fluorine substituted 1,2,4-triazin-5-ones exhibit a wide range of pharmacological and medicinal properties such as anticancer, anti-HIV, anti CDK2 activity antimicrobial, antioxidant, molluscicidal agent against some type of snails activity and as resistance in saccharomyces cerevisiae. In other hand, a few articles published in the area of fluorinated 1,3-disubstituted-6-azauracils. Thus, this investigation describes a simple methods and the important chemical reactivity's of new fluorinated 1,3-disubstituted-5-aryl-6-azauracil derivatives in view of their antioxidant activity [1].

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Materials and Methods

Presence of an amino-groups on the heterocyclic systems are highly reactive intermediates and use for the building various substituted heterocyclic systems. The electron withdrawing nature of substituent control in the nucleophilicity of the amino-group present. Thus, fluorinated acylation of 5-(2'-amino-5'-fluorophenyl)-6-azauracil using ethyl trifluoroacetate in THF under reflux produced 5-(2'-(trifluoroacetyl amino)-5'-fluorophenyl)-6-azauracil, while on using 4-fluorobenzoyl chloride in warm DMF yielded 5-[(2'-(4''-fluorobenzoylamino)-5'-fluorophenyl]-6-azauracil.

Structure of compounds 2 and 3 are confirmed by spectroscopic analysis. The IR spectra showed at medium peaks at 3300, 3180 and 3120 for NH, NHCO and OH respectively, while strong peaks for 2C=O and NHCO at 1700 cm^{-1} and 1670 cm^{-1}, the C-F peak adjacent to carbonyl group appears at 1230 in compound 3 only. 1H NMR spectrum for both 2 and 3 showed the broad singlet of 2NH of 6-azauracil at 11.66 and 11.11 respecively. While NH-CO of side chain appears at 9.88, in addition, 13C NMR showed α at 162, 155, 150 (3C=O), 140 (C=N), 135 (C-F) and 130 ppm -120 ppm for aromatic carbons (Figure 1) [2].

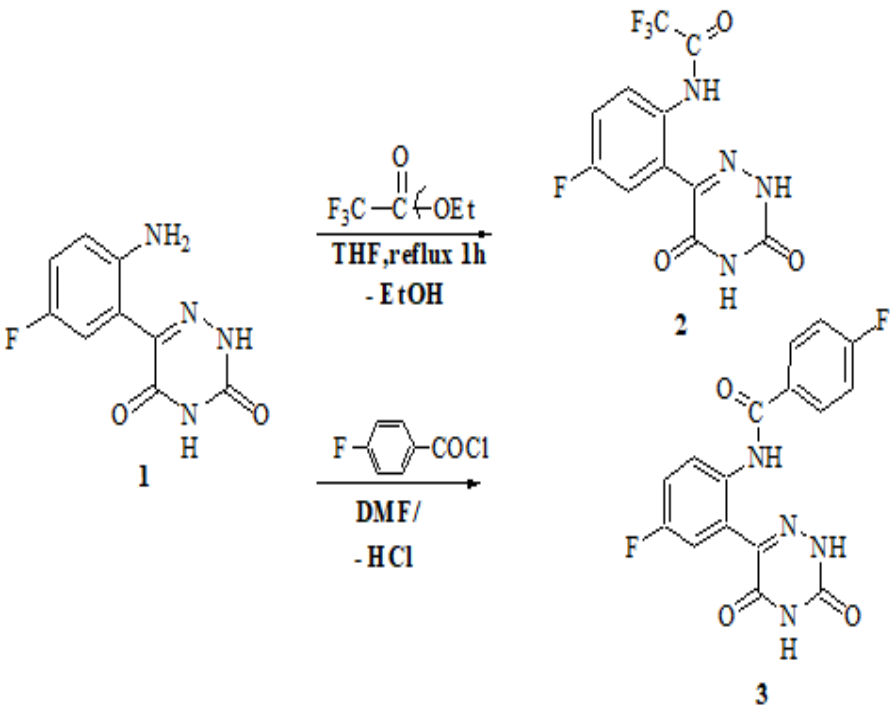

FIG. 1. **Formation of compounds 2 and 3 from 1.**

The behavior of compound 1 towards α-acceptor electrophilic carbons was evaluated. Thus, addition of cyclohexyl isocyanate and 4-fluorophenyl isothiocyanate to amino-group of compound 1 in warm DMF yielded N,N'-disubstituted urea and thioureas (5 and 6) respectively (Figure 2) [3].

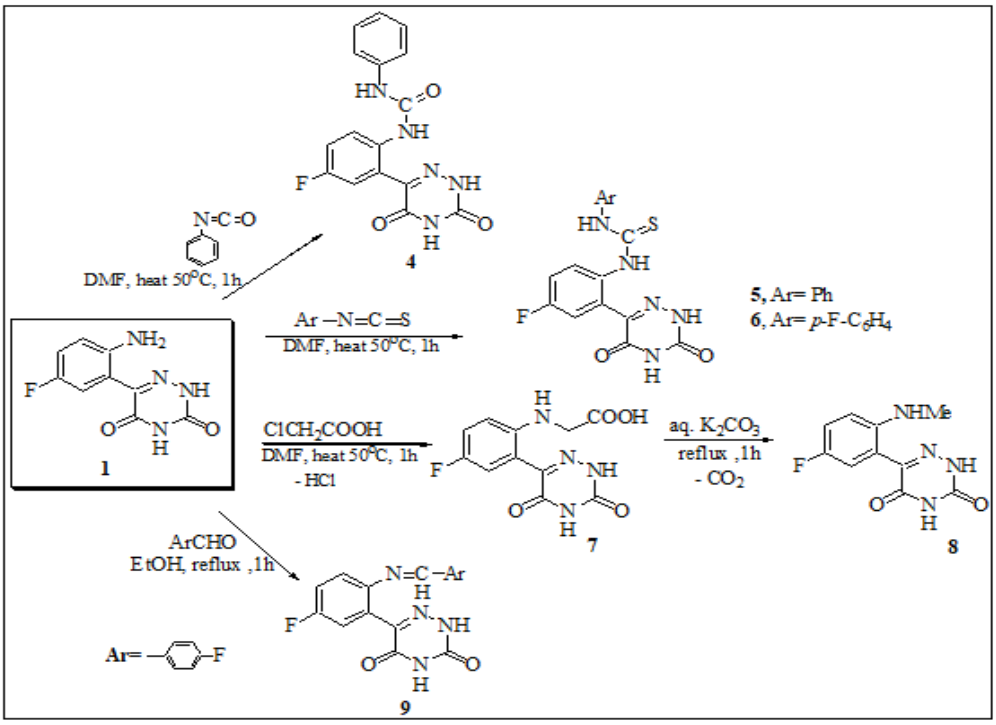

FIG. 2. **Formation of 4-9 from 1.**

The IR spectrum of compound 5 and 6 showed CONH and CSNH in addition to N2H and N4H of 6-azauracil. Compound 5 showed an absorption bands of CH_2 at α 2928, 2850 and 1483 cm^{-1} with the carbonyl peaks at 1717 cm^{-1}, 1670 cm^{-1} and 1600 cm^{-1} respectively. 1H NMR of 6 showed a resonated signals at α 12.70, 11.26, 10.85 and 9.00 ppm attributed to 4NH of N_2H, N_4H of 1,2,4-triazine and two NH of diarylthiourea with aromatic protons at 8.67 ppm, 7.67 ppm -7.62 ppm, 7.55 ppm, 4.45 ppm, 7.2 ppm, 7.18 ppm and 7.12 ppm. In addition, 13C NMR of 6 spectrum showed a signals at α 182 ppm, 159 ppm and 157 ppm for C=S, C=O, C=O carbons [4]. Alkylation of compound 1 by treated with monochloroacetic acid in reflux DMF, produced α-(aryl) amino acid 7. Decarboxylation of 7 yield 5-[2'-(methylamino-5'-fluorophenyl)]-6-azauracil [5].

Results

The IR spectrum of 7 (as α-amino acid derivative) revealed the presence of CH_2 function group at 2900 cm^{-1}, 2800 cm^{-1} and 1466 cm^{-1} with broad band 3400-3179 for OH-NH. While that of 8 (as methyl amino derivative) showed only peak at 3221 for N_2H, N_4H of azauracil) with CH_3 group at 1482 cm^{-1}. Compound 8 did not give acidity test which confirm that decarboxylation of 7. 1H NMR of 8 recorded a signal at α 2.34 ppm for CH_3, while that 13C NMR showed a signal at α 38.93 ppm in additional of C=O and aromatic carbons. The Schiff's base exhibited a wide-spectrum of biological activity and forms a type of metal complex with metal ion. Thus, Schiff base 9 were obtained from condensation of compound 1 with aromatic aldehydes for example p-fluorobenzaldehyde in reflux ethanol. IR spectrum of 9 showed peaks at 3236 cm^{-1}, 1735 cm^{-1}, 1626 cm^{-1} and 1586 cm^{-1} for NH, two C=O and N=C respectively, with 1272 cm^{-1} and 597 cm^{-1} for C-F functional groups with lacks of NH_2 group. 1H NMR spectrum of 9 recorded mainly a resonated signals at α 11.69 ppm, 11.01 ppm and 8.73 ppm attributed to two NH and azomethin protons. While 13C NMR of 9 showed the important C=N carbon at 107 ppm. This investigated aimed to prepare the N-alkyl of fluorinated 6-azauracils in view of their biocidal effects.

Thus, reaction of compound 9 with MeI (1:2 by mol) in aqueous KOH at room temperature, yielded N',N3-dimethyl-6-azauracil derivative, while hydroxyl methylation of compounds 9 attributed by reflux with HCHO-MeOH to produce N',N3-di(hydroxyl methyl)-6-azauracil [6]. The IR spectra of 10 recorded a lack's of NH bands, with appearance of peaks at 2960 cm^{-1}, 2880 cm^{-1} and 1470 cm^{-1}, 1414 cm^{-1} for CH_3 and α at 1700 cm^{-1}, 1690 cm^{-1} attribute to C=O with 1610 cm^{-1}, 1240 cm^{-1} for C=N and C-F. While compound 11 showed characteristic broad peak for CH_2-OH hydrogen bonding at 3500-3400. 1H NMR spectra of compound 11 recorded the presence a resonated signals at 1.2 ppm and 1.45 ppm of two CH_3 with 9.3 ppm and 9.4 ppm for azomethano proton, while that of 11 showed α at 5.5 ppm -5.3 ppm, 2.45 ppm, 9.55 ppm attributed to the presence of OH, CH_2, and azomethin protons respectively. The high stability (higher melting point) of compound 11 may be due to formation of two type of tautomoresm (inter and intra-Hydrogen bonding). In addition to a highly electro-negative charge over the both of C=O and OH functional groups (Figures 3 and 4) [7].

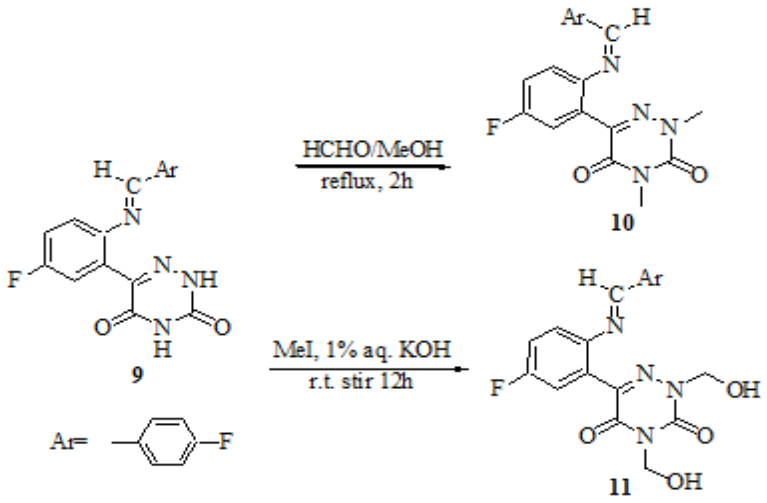

FIG. 3. **Formation of 10 and 11 from 9.**

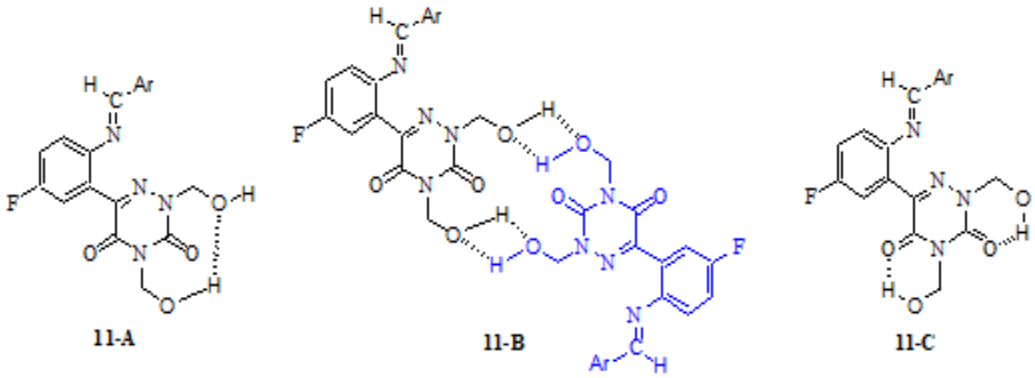

FIG. 4. **The possible stable-tautomeric formula of compound 11.**

Moreover, Abdel-Rahman, reported that Mannich base of 1,2,4-triazines exhibit anticancer properties. Thus, reflux compound 9 with methanol-formaldehyde in the presence of piperidine (1:2 by mol) afforded the Mannich bases10; while that reaction of 9 in the presence of 4-fluoroaniline yielded N',N3-di(4'-fluoroanilinomethyl)-6-azauracil derivatives (Figure 5).

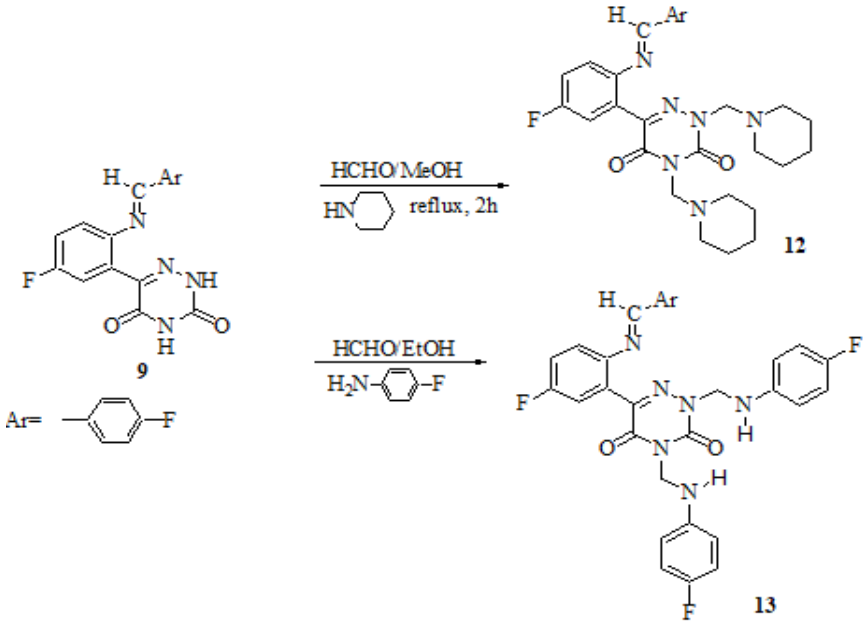

FIG. 5. **Formation of compounds 12 and 13 from 9.**

The IR spectra of 12 showed a lack's of NH functional groups, while that of 13 recorded α at 3200 cm^{-1}-3180 cm^{-1} attribute to NH-aryl. Compounds 12 and 13 recorded α at 2980 cm^{-1}, 2880 cm^{-1}, 1480 cm^{-1}, 1440 cm^{-1} for CH_2 and 1710 cm^{-1}, 1700 cm^{-1} for two C=O groups, with α 1240 cm^{-1} for C-F. 1H NMR spectra of 12 recorded a two type of CH_2 (*exo* and *endo*) while that 13 showed only α at 2.55 ppm for *exo*-CH_2, with at 11.0 ppm for N-CH_2-NH-, with α at 8.35 and 6.55 ppm attribute to CH-adjacent of F-aromatic. Furthermore, mass spectral study of compound 13 gives us a good indication about the degree of stabilization. In addition, Abdel-Rahman, reported that 6-(2'-trifluoroacetamido)-3-thioxo-1,2,4-triazin-5(2H,4H)one underwent dry dehydration by refluxing with dry acetone, 5-substituted-7-fluoro-1,2,4-triazino[5,6-b]indol-3(2H)one isolated. Similarly, refluxing compounds 2-6 under the same conditions, afforded 5-(acyl,aroyl)-8-fluoro-1,2,4-triazino[5,6-b] indol-3(2H)one respectively (Figure 6) [8].

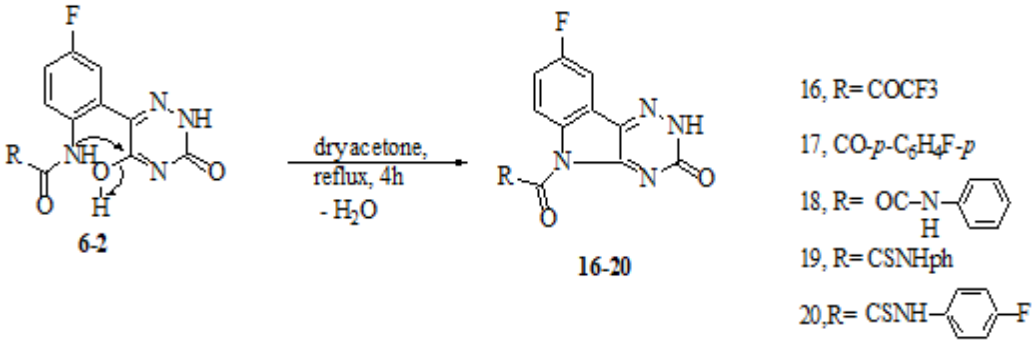

FIG. 6. **Formation of 16-20 from heterocyclization of compounds 6-2.**

Structure of 16-20 confirmed by lack of one C=O, NH from the molecular structure of their IR spectra. In addition, mass spectrum of 21 showed the molecular ion peak at 319.7 (M^{+2} and H_2O) which under fragmentation process give a base peak at m/e 173 (171.9, 100) as more stabilized fragment (Figure 7).

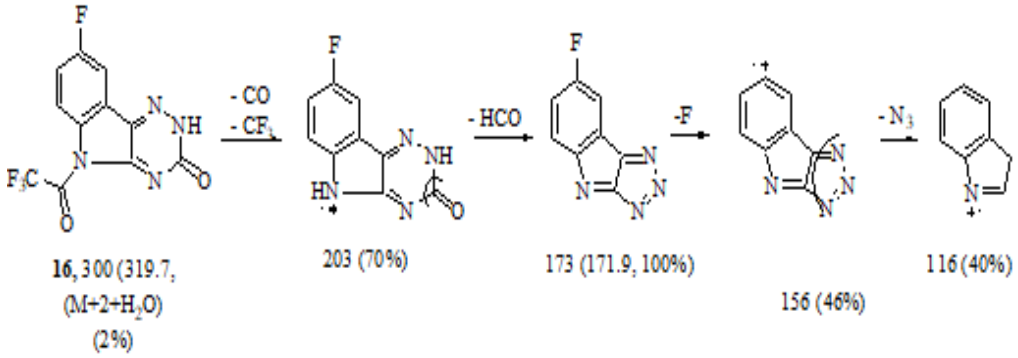

FIG. 7. **Suggested mass fragmentation pattern of compound 16.**

5-(2'-Trifluoroacetylamino-5'-fluorophenyl)-6-azauracil is equimolar mixture of 1 and trifluoroethyl acetate in THF (20 ml) was refluxed for 2 h, cooled. The produced solid filtered off and crystallized from dioxan to give 2 as faint yellow crystals, yield 65%, m.p.>35°C. UV (DMF) α max 330 nm, IR (α cm^{-1}): 3300, 3350, 3214 (3NH), 1718, 1690, 1640 (2C=O, NHCO), 1220 (C-F), 786 (substituted phenyl), 598 (C-F). 1H NMR (DMSO-d6) (α): 11.66, 11.11 (each s, 2NH), 10.64 (s, 1H, NH), 9.8 (s, 1H, OH), 8.76 (s, 1H, aromatic), 7.47-7.45, 7.18-7.14, 7.00-6.84 (m, 2H, aromatic protons). 13C NMR (DMSO-d6) (α): 162.9, 162.7, 159.4 (3C=O), 137.68 (C-F), 134.73 (C-F), 130.81-121.72 (aromatic carbons), 111.89-110.72 (C-C). Mass data (Int.%): 322 (M+4, 14%), 269 (100), 220 (5), 200 (1.5), 203 (96), 174 (7), 138 (8), 104 (25). CHNF analysis for $C_{11}H_6N_4F4O_3$ (318). Calcd: C, 41.50; H, 1.88; N, 17.61; Found: C, 41.58; H, 1.85; N, 17.69; M/S (Int.%): 318 (322, M^+4, 14%), 269 (268, M^+1, 100), 220 (5), 200 (1.5), 203 (96), 174 (7.0), 132 (8.0), 104 (25.11).

5-[2'-(4''-Fluorobenzoyl)amino-5'-fluorophenyl]-6-azauracil is a mixture of 1 (0.01 mol) and 4-fluorobenzoyl chloride (0.01 mol) in DMF (10 ml) warmed under reflux for 1 h, cooled then poured onto ice. The solid thus obtained filtered off and crystallized from dioxan to give 3 as deep yellow. Yield 60%, m.p. 220°C -222°C. IR (α cm^{-1}): 3300-3150 (b, 3NH), 1690, 1670 (2C=O), 1604. (CONH), 1234 (C-F), 854, 817 (substituted phenyl), 597 (C-F). 1H NMR (DMSO-d6) (α): 13.0, 12.58, 11.41, (each s, 3NH), 10.47 (s, 1H, OH), 9.63-9.59, 8.50, 8.0, 7.48, 7.35, 7.19, 6.97 (each s, 7 aromatic protons). 13C NMR (DMSO-d6) (α): 166, 158, 154 (3C=O), 132 (C-F), 130-125 (aromatic carbons), 115.70, 115.48 (C-C). CHNF analysis for $C_{16}H_{10}N_4F_2O_3$ (344), calcd:C, 55.81; H, 2.90; N, 16.27; F, 11.04%. Found: C, 55.85; H, 2.95; N, 16.21; F, 10.99% [9].

5-[(2'-N-Cyclohexyl-N'-(5'-fluorophenyl)ureido]-6-azauracil is a mixture of 1 (0.01 mol) and cyclohexyl isocyanate (0.01 mol) in DMF (20 ml) warmed for 1h, cooled then poured onto ice. The solid obtained, filtered off and crystallized from dioxan to give 4 as pale yellow crystals, yield 68%, m.p. 228°C -230°C. IR (α cm^{-1}): 3324 (NH), 2928, 2850 (aliphatic CH_2), 1717, 1670 (2C=O), 1625 (CONH), 1483 (deformation CH_2), 1244 (C-F), 815 (aromatic CH), 585 (C-F). CHNF analysis for $C_{16}H_{18}N_5FO_3$, calcd:C, 55.33; H, 5.18; N, 20.17; F, 5.47%. Found: C, 55.32; H, 4.98; N, 20.19; F, 5.43%. 5-[2'-(N-Phenyl)-N'-(5'-fluorophenyl)thioureido]-6-azauracil and 5-[2'-(N-(4''-fluorophenyl)-N'-(5''-fluorophenyl)thioureido]-6-azauracil (6) is the equimolar amounts of 1, phenyl isothiocyanate and/or 4-fluorophenyl isothiocyanate in DMF (20 ml) was warmed for 1 h, cooled then poured onto ice. The solids produced were filtered off and crystallized from dioxan to give 5 and 6 respectively [10].

5: Yield 55%, m.p. 228-230°C; IR (α cm^{-1}): 3198 (NH), 1700, 1692 (2C=O), 1593 (C=C aromatic), 1314 (NCSN), 1266 (C-F), 1168 (C=S), 813, 797 (substituted phenyl), 589 (C-F). CHNFS analysis for $C_{16}H_{12}N_5FO_2S$ (357), calcd:C, 53.78; H, 3.36; N, 19.60; F, 5.32; S, 8.96%. Found: C, 53.75; H, 3.39; N, 19.65; F, 4.98; S, 8.99%. 6: yield 70%, m.p. 248-250 α C IR (α cm^{-1}): 3210 (NH), 1702 (C=O), 1629, 1614 (CONH), 1546 (C=C aromatic), 1314 (NCSN), 1203 (C-F), 1139 (C=S), 814, 785 (substituted phenyl), 585 (C-F). 1H NMR (DMSO-d6) (α): 12.7, 12.16, 11.26, 11.19, (each s, 4NH), 8.67, 7.6, 7.55, 7.45, 7.29, 7.18, 6.97 (each s, 7H aromatic protons). 13C NMR (DMSO-d6) (α): 162 (C=S), 159, 157 (2C=O), 151 (C-F), 137, 134 (C-F), 133.94, 127.93, 127.85, 126.30, 126.22, 121.66, 119.99, 116.83 (C-C). CHNFS analysis for C16H11N5F2O2S (375), calcd:C, 51.24; H, 2.39; N, 18.66; F, 10.13; S, 8.53%. Found: C, 51.26; H, 2.37; N, 18.66; F, 10.09; S, 8.59%.

5-[2'-Carboxymethylamino-5'-fluorophenyl]-6-azauracil is a mixture of 1 (0.01 mol) and monochloroacetic acid (0.01 mol) in DMF (20 ml) warmed for 1 h, cooled then poured onto ice. The produced solid filtered off and crystallized from ethanol to give 7 as faint yellow crystals. Yield 50%, m.p.>35°C. IR (α cm^{-1}): 3400-3179 (OH-NH), 2900, 2800 (aliphatic CH_2), 1702, 1631 (C=O), 1466 (deformation CH2), 1255 (C-F), 813 (substituted phenyl), 597 (C-F). CHNF analysis for $C_{11}H_9N_4FO_4$ (280), calcd. : C, 47.14; H, 3.21; N, 20.0; F, 6.78%. Found: C, 47.11; H, 3.21; N, 19.97; F, 6.75%.

5-[2'-(Methylamino)-5'-fluorophenyl]-6-azauracil is a compound 7 (0.20 gm) and K_2CO_3 solution (5%, 20 ml) warmed for 30 min, then cooled and neutralized with diluted HCl. The solid thus obtained filtered off and crystallized from ethanol to give 8 as faint yellow crystals. Yield 50%, m.p. 219-220 α C. Compound 7 (0.20 gm) was fused above its melting point (>60°C) for 5 min, cooled then treated with MeOH, m.p. 218-220 α C. IR (α cm^{-1}): 3221 (b, NH, NH), 1697, 1630 (C=O), 1482 (deformation CH_3), 1230 (C-F), 815 (substituted phenyl), 592 (C-F). 1H NMR (DMSO-d6) (α): 11.67, 11.30, 11.00 (each s, 3NH), 7.47, 7.18, 6.97-6.53 (3H aromatic), 2.34 (s, 3H, CH_3). 13C NMR (DMSO-d6) (α): 158, 154 (2C=O), 136.70 (C-F), 133.32 (C=N), 38.93 (CH_3). CHNF analysis for $C_{10}H_9N_4FO_2$ (236), calcd:C, 50.84; H, 3.81; N, 23.72; F, 8.05%. Found: C, 50.83; H, 3.89; N, 23.71; F, 7.95%. Schiff bases is a equimolar mixture of 1 and 4-fluorobenzaldehyde in absolute ethanol (50 ml) was refluxed for 1 h, cooled. The yielded solids were filtered off and crystallized from ethanol to give 9, yield 75%; m.p. 249°C-250°C.

Analysis of (α cm^{-1}): 3236 (NH), 1735, 1626 (C=O), 1586 (C=N), 1272 (C-F), 811, 789 (substituted phenyl), 597 (C-F). 1H NMR (DMSO-d6) (α): 11.66, 11.01 (each s, NH, NH), 8.73 (s, 1H, azomethin protons), 8.11-7.98, 7.70, 7.47, 7.35, 7.19, 7.14, 6.93 (7H, aromatic protons). 13C NMR (DMSO-d6) (α): 162.79, 159.41, 154.83 (3C=O), 137.70 (C-F), 130.70-122.8 (aromatic carbons), 116.69-111.81 (C-C), 107 (CH=N). Analysis for ($C_{16}H_{10}N_4F_2O_2$, 238), calcd: C, 58.53; H, 3.04; N, 17.07; F, 11.85%. Found: C, 58.51; H, 2.98; N, 17.09; F, 11.83%. CHNF analysis for 11a ($C_{16}H_{10}N_4FO_2Br$, 389), calcd:C, 45.35; H, 2.57; N, 14.39; F, 4.88%. Found: C, 44.95; H, 2.38; N, 14.13; F, 4.55%. 11b, ($C_{16}H_{10}N4ClFO_2$, 345), calcd. : C, 55.65; H, 2.89; N, 16.23; F, 5.50%. Found: C, 55.33; H, 2.60; N, 15.89; F [11].

5-Aryl-1,3-dimethyl-6-azauracil of MeI (0.02 mol) and compounds 9 (0.01 mol) in KOH solution (1%, 100 ml) was stirred at room temperature along 24 h, then acidified and extracted with Me_2O. The solid thus obtained recrystallized from dioxan to give 10, yield 55%, m.p. 213-215°C. IR (α cm^{-1}): 3230 (NH), 2900, 2820 (CH_3), 1700, 1688 (C=O), 1586 (C=N), 1479 (deformation CH_3), 1228 (C-F), 827 (substituted phenyl), 562 (C-F). 1H NMR (DMSO-d6) (α): 9.03 (s, 2NH), 8.99, 7.24, 7.95, 6.85 (3H, aromatic protons), 2.55 and 2.13 (each s, $2CH_3$), 1.19 (CH_3, NH). 13C NMR (DMSO-d6) (α): 167.61, 162.55 (2C=O), 137 (C-F), 132 (C-N), 130-127 (aromatic carbons), 111.68, 111.44 (C-C), 40.18, 39.77 and 38.93 ($3CH_3$). Analysis for $C_{18}H_{14}N_4F_2O_2$ (356); calcd:C, 60.67; H, 3.93; N, 15.37; F, 10.67%. Found: C, 60.62; H, 3.90; N, 15.38; F, 10.69%.

Mannich bases is a mixture of 9 (0.01 mol) and piperidine (0.02 mol) with HCHO (0.02 mol) in MeOH (50 ml) refluxed for 2 h, cooled then poured onto ice. The solid thus obtained filtered off and crystallized from dioxan to give 12. Yield 60%, m.p. 170-172°C. 12: IR (α cm^{-1}): 3010 (aromatic CH), 2923, 2880 (aliphatic CH), 1700, 1680 (C=O), 1475, 1434 (deformation CH_2), 1268 (C-F), 1210 (C-F), 741, 722 (substituted phenyl). CHNF analysis for 12 ($C_{39}H_{42}N_6FPO_2$, 676), calcd:C, 69.23; H, 6.21; N, 12.42; F, 2.81%. Found: C, 69.20; H, 6.25; N, 12.41; F, 2.85%.

Mannich bases is a mixture of 9 (0.01 mol) and 4-fluoroaniline (0.02 mol), HCHO (0.02 mol) with MeOH (100 ml) was refluxed for 2 h, cooled then poured onto ice. The yielded solid filtered off and crystallized from dioxan to give 13. Yield 60%, m.p. 199-200°C. IR (α cm^{-1}): 3244 (NH), 1683, 1660 (C=O), 1480 (deformation CH_2), 1386 (NCN), 1274 (C-F), 814 (substituted phenyl), 637, 594 (C-F). 1H NMR (DMSO-d6) (α): 9.9, 9.5 (each s, 2NH), 2.55, 2.15 (each s, $2CH_2$), 8.75-6.73 (m, 23H, aromatic protons). 13C NMR (DMSO-d6) (α): 163.21, 162.79, 160.84 (2C=O), 142.26 (C-F), 137 (C-N), 130-127 (aromatic carbons), 40.17, 38.91 (two CH_2). Mass data (Int.%): 574 (575, M^{+1}, 1%), 326 (8), 159 (64), 148 (96), 109 (100), 107 (13). CHNF analysis for C30H22N6F4O2 (574), calcd:C, 62.71; H, 3.83; N, 14.63; F, 13.24%. Found: C, 62.68; H, 3.81; N, 14.60; F, 13.21%. M/S (Int.%): 574 (575, M^{+1}, 1.1%); 326 (8.0), 159 (54.1), 148 (149.96, $M^{+}1$), 121 (18.0), 109 (100), 107 (13.0). 8-Fluoro-5-(substituted acyl/aroyl)-1,2,4-triazino[5,6-b] indol-3(2H)one (16-20) is the compounds 2-6 (0.100 gm) in DMF (20 ml) refluxed for 2 h, cooled then poured onto ice. The solid thus obtained filtered off and crystallized from ethanol to give 16-20 respectively.

- Yield 66%, m.p.>35°C
- Yield 60.2%, m.p.>350°C
- Yield 48%, m.p. 207-208°C
- Yield 45%, m.p. 237-238°C
- Yield 50%, m.p.>350°C.

IR (α cm^{-1}): 1181 (NH), 1700, 1660 ($COCF_3$, CONH), 1610 (C=N), 1250 (C-F), 820 (aromatic CH). Mass (Int%): 00 (319.7, M^{+2}+H_2O), 203 (70), 173 (171.9, 100), 156 (46), 116 (40). CHNF analysis for 16 ($C_{11}H_4N_4F_4O_2$, 300), calcd:C, 44.03; H, 1.33; N, 18.66; F, 25.33%. Found: C, 43.98; H, 1.35; N, 18.65; F, 25.31% [12].

- ($C_{16}H_8N4F_2O_2$, 326), calcd. : C, 58.98; H, 2.45; N, 17.17; F, 11.65%. Found: C, 58.94; H, 2.43; N, 17.08; F, 11.69%.
- ($C_{21}H_{14}N_4FPO_4$, 436), calcd. : C, 56.77; H, 3.21; N, 13.84; F, 4.35%. Found: C, 56.75; H, 3.21; N, 13.89; F, 4.30%.
- ($C_{16}H_{16}N_5FO_2$, 329), calcd. : C, 58.35; H, 4.86; N, 21.27; F, 5.77%. Found: C, 58.37; H, 4.89; N, 21.19; F, 5.75%.
- ($C_{16}H_9N_5F_2SO$, 357), calcd. : C, 53.78; H, 2.50; N, 19.60; F, 10.64%. Found: C, 53.78; H, 2.50; N, 19.50; F, 10.63%.
- ($C_{16}H_{10}N_5FSO$, 387), calcd. : C, 49.61; H, 2.58; N, 18.08; F, 4.90%. Found: C, 49.61; H, 2.58; N, 18.03; F, 4.95%.

Antioxidant activity

Antioxidants is a molecule capable of inhibiting the oxidation of other vital molecules. Thus, oxidation is a chemical reaction that transfer hydrogen from a substance to oxidizing agent. Likewise, oxidation reactions can produce free radicals. In turn, these radicals can start chain reactions leading to cancers. Substances that are able to neutralize reactive molecules and reduce oxidative are called antioxidants. Thus, antioxidants prevents the transfer of electron from O_2 to vital organic molecule within the body, stabilizes free radicals and terminates free radical reaction as, hydroxyl radical (OH), superoxide anion radical (O^{2-}), nitric oxide, lipid peroxyl free radical. Moreover, antioxidant protect an nutrient derived antioxidants like ascorbic acid (vitamin C), tocopherols, tocotrienols (vitamin and carotenoids as well as low molecular weight compounds as glutathione and lipoic acid.

Similarly, it is protect the numerous other antioxidant phytonutrients present in a wide variety of plant foods [13]. The antioxidant evaluation of fluorine substituted heterocyclic nitrogen systems especially 1,2,4-triazinone moieties have been incorporated into drug discovery research to improve and enhance the physiochemical properties of drugs. Also, fluorine atoms bonded the heterocyclic nitrogen systems effect on the modulation of electronic, lipophilic and steric parameters all of which can critically influence both the pharmacodynamic and pharmacokinetic properties. Thus, fluorine increases binding affinity, reduces plasma protein binding leading to a higher free fraction of drug and increases cell penetration. Recently reported that fluorinated heterocyclic systems bearing an S and P elements exhibit an antioxidant activities. Similarly, the present work, synthesized a novel of fluorinated 6-azauracils bearing an S and P atoms, which promoted us to evaluate them as antioxidant agents [14].

All the synthesized compounds were evaluated for antioxidant activity by used 1,1-Di Phenyl-2-Picryl Hydrazyl (DPPH) methods. The results of scavenging the stable DPPH radical. Where it is documented that 100, 200, and 300 α mol L^{-1} of the synthesized compounds using scavenged between 50% and 80% of the DPPH radicals which evaluate the antioxidant activity. The results obtained showed that, compounds have a good to moderate antioxidative activities in the range of 60%-80%. A higher activity percentage of some compounds is attribute to presence of CF_3 and PO^{3-} groups, in addition of 6-azauracil moiety. Also, increase in the DPPH%, is caused by the type of reaction between the compounds with DPPH radicals. The DPPH solution was used a negative control and ascorbic acid was an reference standard. The difference between the test and the control experiments was determined and expressed as the present scavenging of the DPPH radical using the following equation [15].

DPPH scavenging activity%=(Absorbance of control-Absorbance of sample)/(Absorbance of control) × 100.

Discussion

The stable free radical DPPH=as often used to characterize antioxidants. Reduced and the odd electron in the DPPH free radical gives a strong absorption at α max 517 nm, which is purple in color. A radical scavenging antioxidant reacts with DPPH stable free radical and coverts into 1,1-diphenyl-2-picrylhydrazine. The resulting decolorization is stoichiometric with respect to the number of electrons captured. The change in the absorbance produced in this reaction has been used to measure antioxidant properties. The solutions of the tested compounds (100, 200 and 300) α mol L^{-1}) were added to DPPH (100 α M) in DMSO/ethanol. The tubes were kept at ambient temperature for 30 min and the absorbance was measured at α 517 nm. The radical scavenging activity of ascorbic acid was also measured and compared with that of the various synthesized compounds (Table 1) [16].

TABLE 1**. The DPPH radical scavenging activities (%) of the new fluorinated systems 2-20.**

Compd. No.	DPPH% inhibition ± SD at 100 mmol L^{-1}	Compd. No.	DPPH% inhibition ± SD at 100 mmol L^{-1}
1	70.20 ± 0.1	10	55.11 ± 0.01
2	50.01 ± 0.1	11	40.88 ± 0.01
3	62.01 ± 0.1	12	54.1 ± 0.01
4	51.11 ± 0.01	13	50.48 ± 0.1
5	70.01 ± 0.1	14	41 ± 55 ± 0.1
6	40.11 ± 0.1	15	40.11 ± 0.1
7	40.5 ± 0.1	16	60.10 ± 0.2
8	57.33 ± 0.01	17	69.9 ± 0.1
9	50.11 ± 0.1		
Ascorbic acid	40		40

All the fluorinated systems showed a degree of antioxidant active, while the compounds 2>6>20>4>19 and 9>11>13>16 in the order of increase activity. It is interest that presence of CF_3 in addition of aromatic compounds enhances the antioxidant activity [17-20].

Conclusion

A simple and safe routs for the synthesize fluorinated 1,3-disubstituted-6-azauracil derivatives have been deduced derived from the interaction between 5(2'-amino-5'-fluorophenyl)-6-azauracil with bifunctional oxygen/sulfur reagents in differ media and conditions. Most of the obtained systems have been evaluated as antioxidant agents. Only the compounds have higher antioxidant affects in compare of DPPH and ascorbic acid as standard.

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