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Synthesis of some new fluorine substituted thiobarbituric acid derivatives as anti HIV1 and cyclin-dependent kinase 2 (CDK2) for cell tumor division: Part I

Abdulrahman Salim Al-Harbi [1,*], Reda Mohammady Abdel-Rahman [1] and Abdullah Mohamed Asiri [1,2]

[1] Department of Chemistry, Faculty of Science, King Abdul Aziz University, Jeddah, 21589, Kingdom of Saudi Arabia
[2] Centre of Excellence for Advanced Materials Research, King Abdulaziz University, Jeddah 21589, Kingdom of Saudi Arabia

* Corresponding author at: Department of Chemistry, Faculty of Science, King Abdul Aziz University, Jeddah, 21589, Kingdom of Saudi Arabia.
Tel.: +966.12.6859154. Fax: +966.12.6952292. E-mail address: magiceyes2002@hotmail.com (A.S. Al-Harbi).

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ABSTRACT

New potential enzyme inhibitors, fluorine-substituted thiobarbituric acid derivatives (**2**, **3**, **9**, **8** and **12**) and their fused/isolated heterocyclic nitrogen systems (**5**, **6**, **10** and **14**) have been obtained from heterocyclization of fluorinated *N, N'*-disubstituted thiourea (**1**, **7** and **11**) with malonic acid followed by ring closure reactions with primary nitrogen reagents. Structures of the synthesized products have been deduced from their elemental analysis and spectral data. Anti-HIV-1 and inhibition of cyclin-dependent kinase2 (CDK2) for cell tumor division for the synthesized compounds were also evaluated.

1. Introduction

Increased use of anti-HIV1 and anti-AIDS agents in recent years have been resulted in the development of resistance to commercially available drugs [1-3]. Thiobarbituric acids have been reported to possess interesting biological and pharmacological activities [4-7] including the inhibitors of hepatitis C virus NS5B polymerase [8], against nonalcoholic fatty liver disease [9], potent anticonvulsant [10], measured auto-oxidation of brain homogenates from various animals [11], determining formaldehyde and acetaldehyde in food [12], HIV-1 integrate inhibitors [13] and decreases liquid peroxide in human plasma [14,15]. The introduction of fluorine atoms to bioactive molecules enhance and improve their pharma-cological properties [16-18]. Also, presence of hetero-atoms increased membrane, permeability, which enhances the electrostatic force and hydrophobic binding stability against metabolic transformations [18-22]. As part of the interested research program in the fluorine substituted heterocyclic nitrogen systems as biocidal agents [23-27], the present work tends to synthesize, some new fluorinated-thiobarbituric acids full fused in view of their anti-HIV and cyclin-dependent kinase 2.

2. Experimental

2.1. Instrumentation

Melting points determined with an electrothermal Bibly Stuart Scientific melting point Sample (UK). A Perkin Elmer Model RXI-FT IR system 55529 was used for recording IR spectra of the prepared compounds. A Bruker advance DPX 400 MHz model uses TMS as internal standard was used for recording the ^1H and ^{13}C NMR spectra of the compounds on deuterated $CDCl_3$. A GC-MS-GP 1000 Ex model used for recording the mass spectra of the compounds. Electronic spectra recorded in ethanol on Shimadzu UV and visible 310 IPC Spectrophotometer. Elemental analyses were performed in microanalytical Center of Cairo University, Egypt.

2.2. Synthesis

2.2.1. Synthesis of compounds 1a-c

Equimolar amounts of 4-fluoroaniline (0.001 mol) and aryl isothiocyanates (0.001 mol) were warmed in THF for 1 h then cooled. The solid product was filtered off and crystallized from ethanol to give compound **1a-c** as yellow crystals (Scheme 1).
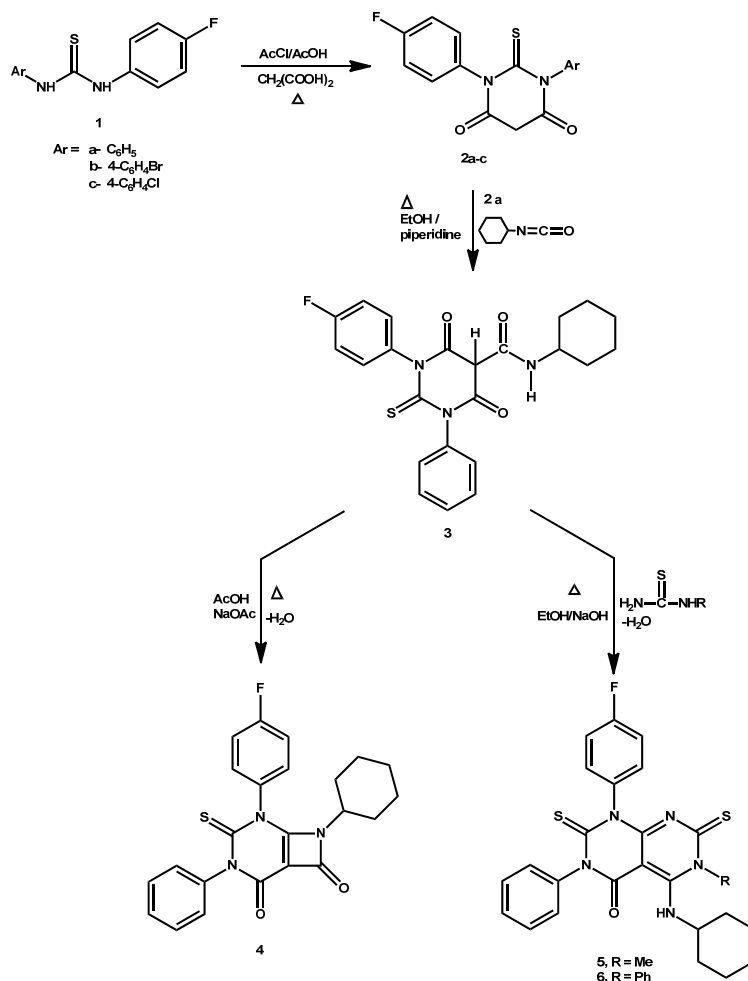
Scheme 1

1-(4-Fluorophenyl)-3-phenylthiourea (**1a**): Color: Yellow. Yield: 78%. M.p.: 140-141 °C. FT-IR (KBr, ν, cm⁻¹): 3180 (NH), 1385 (cyclic NCSN), 1255 (C-F), 1210 (C=S), 864 (Aryl-CH), 657 (C-F). MS (EI, *m/z* (%)): 247 (M+1, 100). UV/Vis (EtOH, λ_{max}, nm, (ε)): 238 (0.877). Anal. calcd. for $C_{13}H_{11}FN_2S$: C, 63.39; H, 4.50; N, 11.37; S, 13.02. Found: C, 63.11; H, 4.44; N, 11.20; S, 13.01%.

1-(4-Bromophenyl)-3-(4-fluorophenyl)thiourea (**1b**): Color: Yellow. Yield: 82%. M.p.: 160-161 °C. FT-IR (KBr, ν, cm⁻¹): 3200 (NH), 1380 (Cyclic NCSN), 1250 (C-F), 1190 (C=S), 900 (Aryl-CH), 650 (C-F). MS (EI, *m/z* (%)): 325.90 (100). UV/Vis (EtOH, λ_{max}, nm, (ε)): 275 (0.95). Anal. calcd. for $C_{13}H_{10}BrFN_2S$: C, 48.01; H, 3.10; N, 8.61; S, 9.86. Found: C, 47.89; H, 2.88; N, 8.41; S, 9.66%.

1-(4-Chlorophenyl)-3-(4-fluorophenyl)thiourea (**1c**): Color: Yellow. Yield: 87%. M.p.: 162-164 °C. FT-IR (KBr, ν, cm⁻¹): 3210 (NH), 1370 (Cyclic NCSN), 1260 (C-F), 1185 (C=S), 850 (Aryl-CH), 700 (C-Cl), 660 (C-F). MS (EI, *m/z* (%)): 280.32 (M⁺, 100). UV/Vis (EtOH, λ_{max}, nm, (ε)): 310 (1.20). Anal. calcd. for $C_{13}H_{10}ClFN_2S$: C, 55.62; H, 3.59; N, 9.98; S, 11.42. Found: C, 54.43; H, 3.22; N, 9.40; S, 10.91%.

2.2.2. Synthesis of compounds 2a-c

A mixture of compound **1a-c** (0.001 mol) and malonic acid (0.001 mol) in a few drops of acetyl chloride and glacial acetic acid (20 mL) was refluxed for 2h then poured onto ice. The

solid product was filtered off and crystallized from dioxan to give compounds **2a-c** as yellow crystals (Scheme 1).

1-(4-Fluorophenyl)-3-phenyl-2-thioxodihydropyrimidine-4,6 (1H,5H)-dione (**2a**): Color: Yellow. Yield: 75%. M.p.: 86-88 °C. FT-IR (KBr, ν, cm⁻¹): 3476 (OH), 2856 (Str. CH₂), 1680 (C=O), 1497 (Deform. CH₂), 1387 (Cyclic NCSN), 1255 (C-F), 1180 (C=S), 864 (Aryl CH), 659 (C-F). ¹H NMR (400 MHz, CDCl₃, δ, ppm): 2.59-2.58 (s, 2H, CH₂), 7.96-7.01 (m, 9H, Ar-H), 9.81 (s, 1H, O*H*). ¹³C NMR (100 MHz, CDCl₃, δ, ppm): 166.32, 159.75, 158.17, 135.15, 135.10, 135.08, 128.29, 127.69, 122.37, 115.20, 115.05, 77.81, 40.43. MS (EI, *m/z* (%)): 314 (M⁺, 100). UV/Vis (EtOH, λ_{max}, nm, (ε)): 258 (0.984). Anal. calcd. for $C_{16}H_{11}FN_2O_2S$: C, 61.14; H, 3.53; N, 8.91; S, 10.20. Found: C, 61.10; H, 3.35; N, 8.69; S, 10.00%.

1-(4-Bromophenyl)-3-(4-fluorophenyl)-2-thioxodihydropyri midine-4,6(1H,5H)-dione (**2b**): Color: Yellow. Yield: 78%. M.p.: 120-122 °C. FT-IR (KBr, ν, cm⁻¹): 3500 (OH), 2852 (Str. CH₂), 1700 (C=O), 1488 (Deform. CH₂), 1380 (Cyclic NCSN), 1188 (C=S), 800 (Aryl CH), 710 (C-Br), 680 (C-F). MS (EI, *m/z* (%)): 394.1 (M+1, 95). UV/Vis (EtOH, λ_{max}, nm, (ε)): 345 (1.88). Anal. calcd. for $C_{16}H_{10}BrFN_2O_2S$: C, 48.87; H, 2.56; N, 7.12; S, 8.14. Found: C, 48.58; H, 2.41; N, 7.01; S, 8.00%.

1-(4-Chlorophenyl)-3-(4-fluorophenyl)-2-thioxodihydropyri midine-4,6(1H,5H)-dione (**2c**): Color: Yellow. Yield: 81%. M.p.: 116-118 °C. FT-IR (KBr, ν, cm⁻¹): 3410 (OH), 2848 (Str. CH₂), 1675 (C=O), 1445 (Deform. CH₂), 1370 (Cyclic NCSN), 1188 (C=S), 870 (Aryl CH), 700 (C-Br), 676 (C-F). UV/Vis (EtOH, λ_{max},

nm, (ε)): 375 (0.98). MS (EI, *m/z* (%)): 348 (100). Anal. calcd. for $C_{16}H_{10}ClFN_2O_2S$: C, 55.10; H, 2.89; N, 8.03; S, 9.19. Found: C, 54.83; H, 2.66; N, 7.89; S, 8.77%.

2.2.3. Synthesis of compound 3

A mixture of compound **2a** (0.001 mol) and cyclohexyl isocyanate (0.001 mol) in ethanol (20 mL) with a piperidine (0.5 mL) was refluxed for 8 h, cooled, and concentrated. The solid product was crystallized from dioxan to give compound **3** as white crystals (Scheme 1).

1-(4`-Fluorophenyl)-3-(phenyl)-5-(cyclohexylcarbamido)-2, 3-dihydro-2-thioxo-4,6-(1H,5H) pyrimidine-dione (**3**): Color: White. Yield: 75%. M.p.: 98-99 °C. FT-IR (KBr, ν, cm⁻¹): 3492 (OH), 3180 (NH), 1668 (C=O), 1502 (Deform. CH₂), 1386 (Cyclic NCSN), 1255 (C-F), 1180 (C=S), 864 (Aryl CH), 659 (C-F). ¹H NMR (400 MHz, CDCl₃, δ, ppm): 2.14-2.02 (s, 11H, CH₂+CH), 7.95-7.00 (m, 5H, C₆H₅), 8.02-8.11 (m, 4H, Ar-H), 8.95 (s, 1H, NH), 10.5 (s, 1H, OH). MS (EI, *m/z* (%)): 439(M⁺, 49). UV/Vis (EtOH, λmax, nm, (ε)): 275. Anal. calcd. for $C_{23}H_{22}FN_3O_3S$: C, 62.85; H, 5.05; N, 9.56; S, 7.30. Found: C, 62.51; H, 4.88; N, 9.39; S, 7.01%.

2.2.4. Synthesis of compound 4

Compound **3** (0.050 mol) in glacial acetic acid (10 mL) and anhydrous sodium acetate (0.50 g) was refluxed for 2 h cooled and poured onto ice. The solid product was filtered off, then crystallized from ethanol to give compound **4** as yellowish brown crystals (Scheme 1).

8-Cyclohexyl-2-(4-fluorophenyl)-4-phenyl-3-thioxo-2,4,8-tri azabicyclo[4.2.0]oct-1(6)-ene-5,7-dione (**4**): Color: Yellowish brown. Yield: 80%. M.p.: 110-112 °C. FT-IR (KBr, ν, cm⁻¹): 1710, 1680 (C=O), 1500 (Deform. CH₂), 1382 (Cyclic NCSN), 1255 (C-F), 1181 (C=S), 864 (Aryl CH), 657 (C-F). ¹H NMR (400 MHz, CD₃Cl, δ, ppm): 2.22-2.01 (s, 11H, CH₂+CH), 7.70-7.10 (m, 5H, Ar-H), 8.12-8.02 (m, 4H, Ar-H). MS (EI, *m/z* (%)): 422 (M⁺, 25.13). UV/Vis (EtOH, λmax, nm, (ε)): 278 (0.88). Anal. calcd. for $C_{23}H_{20}FN_3O_2S$: C, 65.54; H, 4.78; N, 9.97; S, 7.61. Found: C, 65.28; H, 4.55; N, 9.77; S, 7.42%.

2.2.5. Synthesis of compounds 5 and 6

A mixture of compound **3** (0.001 mol) and *N*-methyl/phenyl thioureas (0.001 mol) in ethanolic sodium hydoxide (25 mL, 5%) was refluxed for 2 h, cooled then poured into ice-HCl. The solid product was filtered off, washed with cold water and crystallized from ethanol to give compound **5** and **6**, respectively (Scheme 1).

5-(Cyclohexylamino)-1-(4-fluorophenyl)-6-methyl-3-phenyl-2,7-dithioxo-2,3,6,7-tetrahydropyrimido[4,5-d]pyrimidin-4(1H)-one (**5**): Color: Yellow. Yield: 66%. M.p.: 218-220 °C. FT-IR (KBr, ν, cm⁻¹): 3119 (NH), 1659 (C=O), 1500, 1441 (Deform. CH₂), 1384 (Cyclic NCSN), 1253 (C-F), 1184 (C=S), 863 (Aryl CH), 657 (C-F). MS (EI, *m/z* (%)): 492.90 (M⁺, 46). UV/Vis (EtOH, λmax, nm, (ε)): 315 (1.28). Anal. calcd. for $C_{25}H_{24}FN_5OS_2$: C, 60.83; H, 4.90; N, 14.19; S, 12.99. Found: C, 60.59; H, 4.60; N, 14.01; S, 12.39%.

5-(Cyclohexylamino)-1-(4-fluorophenyl)-3, 6-diphenyl-2, 7-dithioxo-2,3,6,7-tetrahydropyrimido[4,5-d] pyrimidin-4(1H)-one (**6**): Color: Yellow. Yield: 75%. M.p.: 130-132 °C. FT-IR (KBr, ν, cm⁻¹): 3123 (NH), 1661 (C=O), 1499, 1438 (Deform. CH₂), 1386 (Cyclic NCSN), 1255 (C-F), 1185 (C=S), 864 (Aryl CH), 658 (C-F). ¹H NMR (400 MHz, CDCl₃, δ, ppm): 2.59-2.60 (m, 10H, 5CH₂ of cyclohexane), 2.95-2.96 (s, 1H, CH), 7.96-7.49 (m, 14H, Ar-H), 11.55 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃, δ, ppm): 207.02 (C=S), 157.10 (C=O), 130.01-126.01 (Ar-C). MS (EI, *m/z* (%)): 554.85 (79). UV/Vis (EtOH, λmax, nm, (ε)): 287 (1.12). Anal. calcd. for $C_{30}H_{26}FN_5OS_2$: C, 64.84; H, 4.72; N, 12.60; S, 11.54. Found: C, 64.26; H, 4.51; N, 12.33; S, 11.31%.

2.2.6. Synthesis of compounds 7a-c

A mixture of benzoyl isothiocyanate (0.001 mol) and sulfa-drugs, namely sulfathiazole, sulfamerazine or sulfadiazine (0.001 mol) in THF (20 mL) was refluxed for 1 h, cooled. The solid product was filtered off and crystallized from THF to give compounds **7a-c** as yellow crystals (Scheme 2).

N-((4-(N-(Thiazol-2-yl) sulfamoyl) phenyl) carbamothioyl) benzamide (**7a**): Color: Yellow. Yield: 89%. M.p.: 218-219 °C. FT-IR (KBr, ν, cm⁻¹): 3300-3100 (NH-NH), 3005 (Aryl CH), 1580 (NHCO), 1499, 1386 (NCSN), 1218 (C=S), 865 (Aryl CH). ¹H NMR (400 MHz, CDCl₃, δ, ppm): 4.23 (s, 1H, NH), 7.99-7.88, 7.65-6.00 (each m, 11H, Ar-H), 10.70 (s, 1H, NH), 13.07 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃, δ, ppm): 179.16, 169.24, 168.37, 140.92, 139.82, 131.70, 128.73, 128.11, 126.91, 123.68, 123.59, 107.51, 77.80, 67.76, 40.44-39.49, 25.44. MS (EI, *m/z* (%)): 418.31 (100). UV/Vis (EtOH, λmax, nm, (ε)): 238. Anal. calcd. for $C_{17}H_{14}N_4O_3S_3$: C, 48.79; H, 3.37; N, 13.39; S, 22.98. Found: C, 48.59; H, 3.21; N, 13.25; S, 22.59%.

N-((4-(N-(4-Methylpyrimidin-2-yl) sulfamoyl) phenyl) carba mothioyl)benzamide (**7b**): Color: Yellow. Yield: 86%. M.p.: 196-197 °C. FT-IR (KBr, ν, cm⁻¹): 3300-3100 (NH-NH), 2910 (Str. CH₃), 1610 (C=N), 1590 (NHCO), 1480 (Deform. CH₃), 1380 (Acyclic. NCSN), 1350 (SO₂NH), 1188 (C=S), 850, 810 (Aryl CH). MS (EI, *m/z* (%)): 427 (100). UV/Vis (EtOH, λmax, nm, (ε)): 266 (1.11). Anal. calcd. for $C_{19}H_{17}N_5O_3S_2$: C, 53.38; H, 4.01; N, 16.38; S, 15.00. Found: C, 53.20; H, 3.69; N, 16.11; S, 14.68%.

N-((4-(N-(Pyrimidin-2-yl)sulfamoyl) phenyl) carbamothioyl) benzamide (**7c**): Color: Yellow. Yield: 82%. M.p.: 150-151 °C. FT-IR (KBr, ν, cm⁻¹): 3280-3090 (NH-NH), 1625 (C=N), 1600 (NHCO), 1388 (Acyclic. NCSN), 1340 (SO₂NH), 1190 (C=S), 880, 815 (Aryl CH). MS (EI, *m/z* (%)): 412.56 (100). UV/Vis (EtOH, λmax, nm, (ε)): 269 (0.66). Anal. calcd. for $C_{18}H_{15}N_5O_3S_2$: C, 52.29; H, 3.66; N, 16.94; S, 15.51. Found: C, 52.09; H, 3.55; N, 16.48; S, 15.32%.
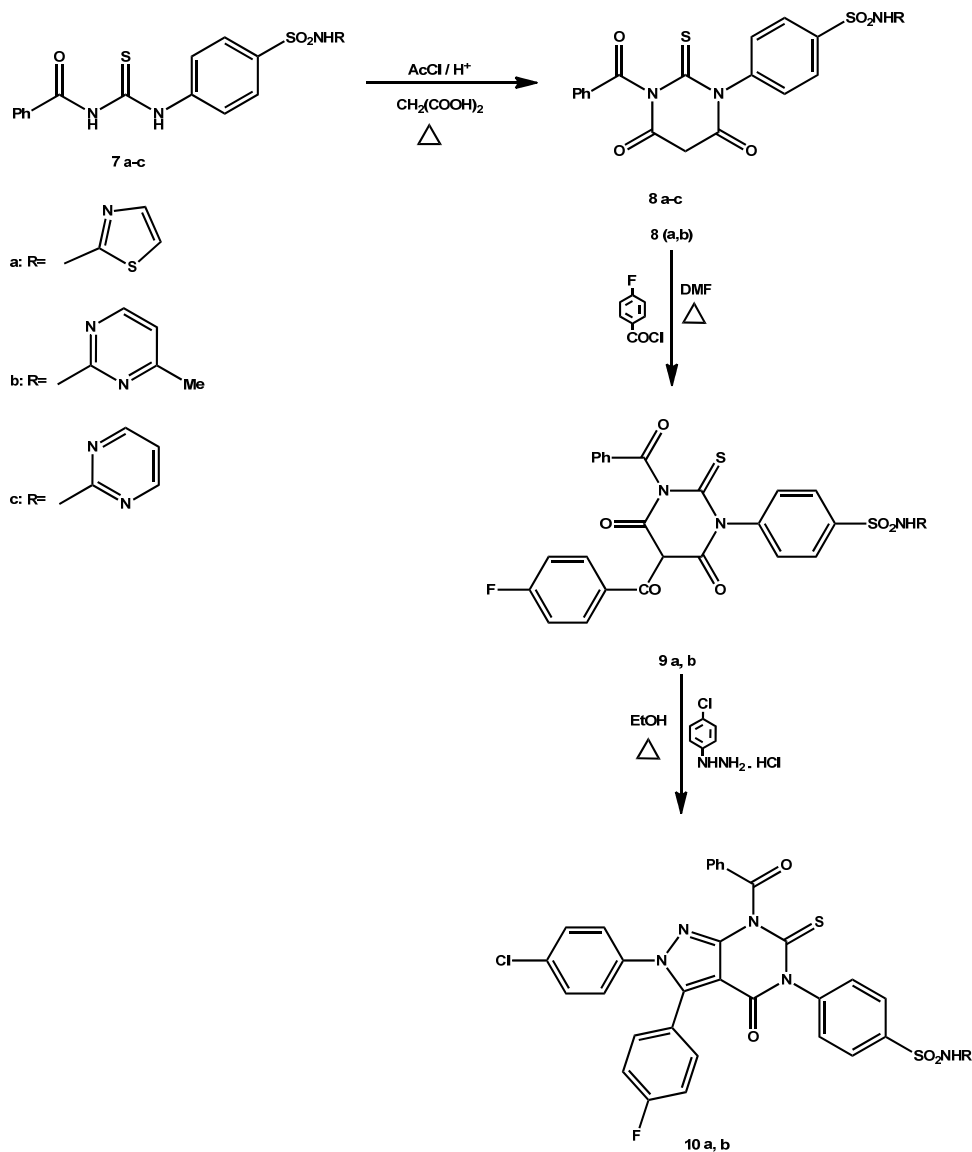
2.2.7. Synthesis of compounds 8a-c

A mixture of compounds **7a-c** (0.001 mol), malonic acid (0.001 mol) in acetyl chloride (drops) and glacial acetic acid (20 mL) was refluxed for 2 h, cooled and concentrated. The solid product was crystallized from 1,4-dioxan to give compounds **8a-c** as yellow crystals (Scheme 2).

4-(3-Benzoyl-4,6-dioxo-2-thioxotetrahydropyrimidin-1(2H)-yl)-N-(thiazol-2-yl)benzenesulfonamide (**8a**): Color: Yellow. Yield: 71%. M.p.: 190-191 °C. FT-IR (KBr, ν, cm⁻¹): 3540 (OH), 3100 (NH), 1661 (C=O), 1502 (Deform. CH₂), 1438 (Deform. CH₂), 1385 (NCSN), 1147 (C=S), 929 (aryl CH). ¹H NMR (400 MHz, CDCl₃, δ, ppm): 2.60-2.21 (m, 2H, CH₂), 6.93-7.52, (m, 11H, aromatic), 11.28 (s, 1H, OH), 12.84 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃, δ, ppm): 179.26, 173.06, 169.22, 140.96, 139.52, 126.84, 123.67, 123.44, 107.50, 123.68, 77.75-77.36, 40.42-39.47, 24.08. MS (EI, *m/z* (%)): 485.94 (23). UV/Vis (EtOH, λmax, nm, (ε)): 280 (0.246). Anal. calcd. for $C_{20}H_{14}N_4O_5S_3$: C, 49.37; H, 2.90; N, 11.52; S, 19.77. Found: C, 49.21; H, 2.77; N, 11.28; S, 19.58%.

4-(3-Benzoyl-4,6-dioxo-2-thioxotetrahydropyrimidin-1(2H)-yl)-N-(4-methylpyrimidin-2-yl)benzenesulfon amide (**8b**): Color: Yellow. Yield: 76%. M.p.: 250-251 °C. FT-IR (KBr, ν, cm⁻¹): 3545 (OH), 3100 (NH), 2912 (Str. CH₃),1667 (C=O), 1500 (Deform. CH₂), 1384 (NCSN), 1357 (SO₂NH) 1144 (C=S), 923 (aryl CH). MS (EI, *m/z* (%)): 494.51 (47). UV/Vis (EtOH, λmax, nm, (ε)): 305 (0.95). Anal. calcd. for $C_{22}H_{17}N_5O_5S_2$: C, 53.32; H, 3.46; N, 14.13; S, 12.94. Found: C, 53.21; H, 3.21; N, 14.00; S, 12.80%.

4-(3-Benzoyl-4,6-dioxo-2-thioxotetrahydropyrimidin-1(2H)-yl)-N-(pyrimidin-2-yl)benzenesulfonamide (**8c**): Color: Yellow. Yield: 72%. M.p.: 224-226 °C. FT-IR (KBr, ν, cm⁻¹): 3547 (OH), 3104 (NH), 1667 (C=O), 1507 (Deform. CH₂), 1386 (NCSN), 1355 (SO₂NH), 1147 (C=S), 920 (Aryl CH).

Scheme 2

MS (EI, *m/z* (%)): 480.25 (46). UV/Vis (EtOH, λmax, nm, (ε)): 315 (1.15). Anal. calcd. for $C_{21}H_{15}N_5O_5S_2$: C, 52.38; H, 3.14; N, 14.54; S, 13.32. Found: C, 52.15; H, 3.01; N, 14.31; S, 13.09%.

2.2.8. Synthesis of compounds 9a and b

To compound **8a** and **8b** (0.001 mol) in DMF (20 mL) 4-fluorobenzoyl chloride (0.001 mol) was added and warmed for 1h, cooled and poured onto ice. The solid product was crystallized from 1,4-dioxan to give compounds **9a** and **9b** as yellow crystals (Scheme 2).

4-(3-Benzoyl-5-(4-fluorobenzoyl)- 4,6-dioxo-2-thioxotetra hydropyrimidin-1(2H)-yl)-N-(thiazol-2-yl)benzene sulfonamide (**9a**): Color: Yellow. Yield: 66%. M.p.: 172-173 °C. FT-IR (KBr, ν, cm-1): 3528 (OH), 1680, 1660 (C=O), 1385 (NCSN), 1255 (C-F), 1180 (C=S), 864 (Aryl CH), 658 (C-F). 1H NMR (400 MHz, CD3Cl, δ, ppm): 7.39-8.05 (m, 15H, Ar-H), 8.51 (s, 1H, OH), 9.80 (s, 1H, NH). 13C NMR (100 MHz, CDCl3, δ, ppm): 167.52, 166.37, 164.69, 132.29, 132.23, 127.21, 127.19, 77.50-77.08, 40.44-39.54. MS (EI, *m/z* (%)): 607.89 (100). UV/Vis (EtOH, λmax, nm,

(ε)): 244 (0.1035). Anal. calcd. for $C_{27}H_{17}FN_4O_6S_3$: C, 53.28; H, 2.82; F, 3.12; N, 9.21; S, 15.80. Found: C, 53.01; H, 2.66; N, 9.11; S, 15.58%.

4-(3-Benzoyl-5-(4-fluorobenzoyl)- 4, 6-dioxo-2-thioxotetra hydropyrimidin-1 (2H)-yl)-N-(4-methylpyrimidin-2-yl) benzene sulfon amide (**9b**): Color: Yellow. Yield: 68%. M.p.: 159-160 °C. FT-IR (KBr, ν, cm-1): 3480 (OH), 1700, 1670 (C=O), 1590 (C=N), 1360 (NCSN), 1330 (SO2NH), 1250 (C-F), 1188 (C=S), 850,820 (Aryl CH), 660 (C-F). MS (EI, *m/z* (%)): 616.85 (0.43). UV/Vis (EtOH, λmax, nm, (ε)): 265 (0.110). Anal. calcd. for $C_{29}H_{20}FN_5O_6S_2$: C, 56.39; H, 3.26; N, 11.34; S, 10.38. Found: C, 56.27; H, 3.08; N, 11.32; S, 10.21%.

2.2.9. Synthesis of compounds 10a and b

A mixture of compounds **9a** and **9b** (0.001 mol) and 4-chlorophenyl hydrazine.HCl (0.001 mol in 5 mL H2O) in absolute ethanol (20 mL) and sodium acetate (0.001 mol) was refluxed for 4 h, cooled and poured onto ice.
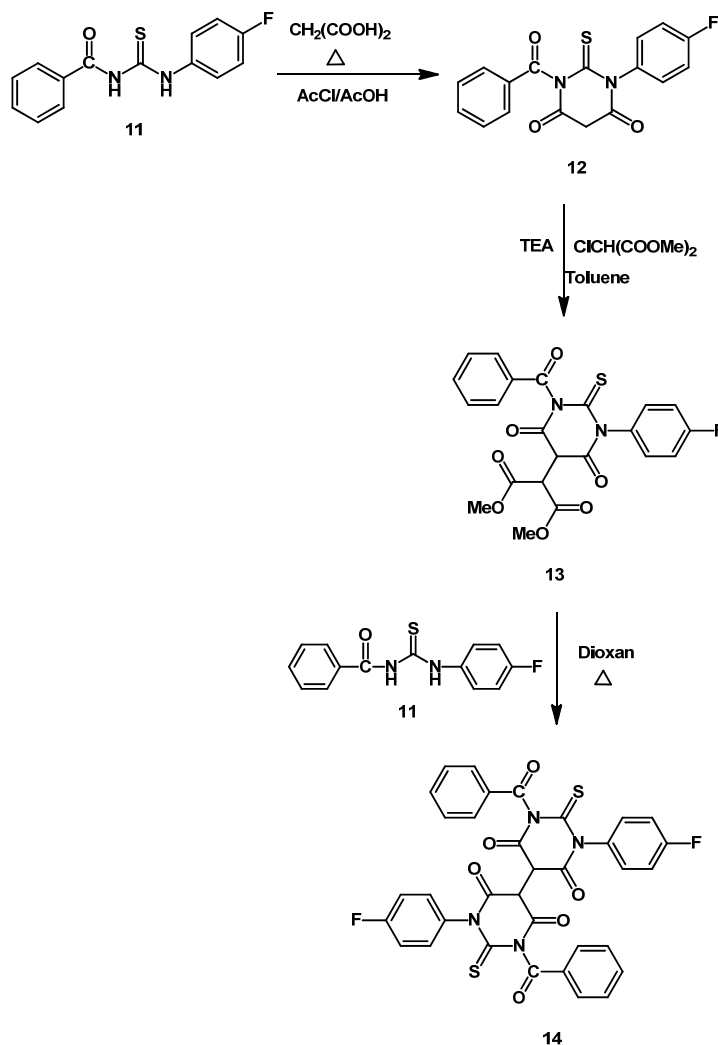
Scheme 3

The solid product was filtered off and crystallized from ethanol to give compounds **10a** and or **10b** as yellow crystals (Scheme 2).

4-(7-Benzoyl-2-(4-chlorophenyl)-3-(4-fluorophenyl)-4-oxo-6-thioxo-6,7-dihydro-2H-pyrazolo[3,4-d]pyrimidin-5(4H)-yl)-N-(thiazol-2-yl)benzenesulfonamide (**10a**): Color: Yellow. Yield: 55%. M.p.: 131-132 °C. FT-IR (KBr, ν, cm⁻¹): 3120 (NH), 1662 (C=O), 1580 (C=N), 1385 (NCSN), 1340 (SO₂NH), 1255 (C-F), 1180 (C=S), 865 (Aryl CH), 710 (C-Cl), 657 (C-F). ¹H NMR (400 MHz, CDCl₃, δ, ppm): 4.30 (s, 1H, NH), 7.11-6.72 (d, 2H, Thiazol), 7.16-7.15 (m, 5H, phenyl), 7.29-7.27 (d, 4H, 4-chloro phenyl), 7.53-7.47 (d, 4H, Ar-H), 8.20-7.51 (d, 4H, 4-fluoro phenyl). ¹³C NMR (100 MHz, CDCl₃, δ, ppm): 176.72, 170.30, 147.50, 146.90, 128.94, 128.68, 124.29, 114.39, 113.49, 77.82, 40.41. MS (EI, *m/z* (%)): 714.01 (92). UV/Vis (EtOH, λmax, nm, (ε)): 315 (0.1118). Anal. calcd. for C₃₃H₂₀ClFN₆O₄S₃: C, 55.42; H, 2.82; N, 11.75; S, 13.45. Found: C, 55.23; H, 2.55; N, 11.56; S, 13.20%.

4-(7-Benzoyl-2-(4-chlorophenyl)-3-(4-fluorophenyl)-4-oxo-6-thioxo-6,7-dihydro-2H-pyrazolo[3,4-d]pyrimidin-5(4H)-yl)-N-(4-methylpyrimidin-2-yl)benzenesulfonamide (**10b**): Color: Yellow. Yield: 65%. M.p.: 138-140 °C. FT-IR (KBr, ν, cm⁻¹): 3160 (NH), 2880 (Str. CH₃), 1690, 1660 (C=O), 1520 (C=N), 1480 (Defom. CH₃), 1365 (NCSN), 1320 (SO₂NH), 1255 (C-F),

1190 (C=S), 880 (Aryl CH), 710 (C-Cl), 680 (C-F). MS (EI, *m/z* (%)): 722.76 (59). UV/Vis (EtOH, λmax, nm, (ε)): 308 (1.11). Anal. calcd. for C₃₅H₂₃ClFN₇O₄S₂: C, 58.05; H, 3.20; N, 13.54; S, 8.86. Found: C, 57.85; H, 2.99; N, 13.31; S, 8.55%.

2.2.10. Synthesis of compounds 11

A mixture of 4-fluoroaniline (0.001 mol) and benzoyl isothiocyanate (0.001 mol) in THF (20 mL) was refluxed for 1 h, cooled. The solid product was filtered off and crystallized from dioxan to give compound **11** as greenish yellow crystals (Scheme 3).

N-((4-Fluorophenyl)carbamothioyl)benzamide (**11**): Color: Greenish yellow. Yield: 88%. M.p.: 94-96 °C. FT-IR (KBr, ν, cm⁻¹): 3230, 3150 (NH, NH), 1680, 1660 (C=O), 1504 (C=N), 1385 (NCSN), 1152 (C=S), 864, 808, 719 (Aryl CH), 657 (C-F). ¹H NMR (400 MHz, CDCl₃, δ, ppm): 4.23 (s, 1H, NH), 7.00-8.01 (m, 9H, Ar-H), 8.70 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃, δ, ppm): 176.79, 168.19, 161.44, 159.86, 133.86, 131.81, 128.77, 128.73, 128.69, 128.21, 126.57, 126.52, 126.48, 126.43, 115.61, 115.46, 77.83-77.41, 40.41-39.46. MS (EI, *m/z* (%)): 274.03 (100). UV/Vis (EtOH, λmax, nm, (ε)): 265 (1.700). Anal. calcd. for C₁₄H₁₁FN₂OS: C, 61.30; H, 4.04; N, 10.21; S, 11.69. Found: C, 61.01; H, 4.00; N, 9.82; S, 11.44%.

2.2.11. Synthesis of compounds 12

A mixture of compound **11** (0.001 mol) and malonic acid (0.001 mol) in a few drops of acetyl chloride and glacial acetic (20 ml) was refluxed for 2 h, cooled and poured onto ice. The solid product was filtered off and crystallized from 1,4-dioxan to give compound **12** as yellowish crystals (Scheme 3).

1-Benzoyl-3-(4-fluorophenyl)-2-thioxodihydropyrimidine-4, 6(1H,5H)-dione (**12**): Color: Yellowish. Yield: 80%. M.p.: 170-171 °C. FT-IR (KBr, ν, cm^{-1}): 3539 (OH), 1680, 1660 (C=O), 1506 (Deform. CH$_2$), 1438 (Deform. CH$_2$), 1385 (NCSN), 1255 (C-F), 1211 (C=S), 864, 840, 772, 710 (Aryl CH), 658 (C-F). MS (EI, *m/z* (%)): 341.59 (48). UV/Vis (EtOH, λ_{max}, nm, (ε)): 288 (1.029). Anal. calcd. for C$_{17}$H$_{11}$FN$_2$O$_3$S: C, 59.64; H, 3.24; N, 8.18; S, 9.35. Found: C, 59.41; H, 3.10; N, 8.00; S, 9.13%.

2.2.12. Synthesis of compounds 13

A mixture of compound **12** (0.001 mol) and methyl 2-chloromalonate (0.001 mol) in dry toluene (20 mL) with a few drops of triethylamine (TEA) was refluxed for 1h, cooled and addition the pet-ether 80-100 °C. The solid product was filtered off and crystallized from 1,4-dioxan to give compound **13** as yellowish crystals (Scheme 3).

Dimethyl 2-(1-benzoyl-3-(4-fluorophenyl)-4, 6-dioxo-2-thioxohexahydropyrimidin-5-yl)malonate (**13**): Color: Yellow. Yield: 65%. M.p.: 144-146 °C. FT-IR (KBr, ν, cm^{-1}): 3550 (OH), 3080 (aryl CH), 2950, 2880 (aliphatic CH), 1700, 1680, 1660 (C=O), 1506, 1438 (deform. CH$_2$), 1385 (NCSN), 1255 (C-F), 1211 (C=S), 1090 (C-O-R), 864, 840, 772, (aryl CH), 658 (C-F). ^{1}H NMR (400 MHz, CD$_3$Cl, δ, ppm): 1.39-1.37 (m, 6H, 2CH$_3$), 2.59-2.58 (m, 2H, CH of malonate and thiobarbituric acid), 7.01-7.97 (m, 9H, Ar-H), 9.80 (s, 1H, OH). ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 166.32, 159.79, 158.18, 135.15, 135.07, 131.45, 128.30, 127.69, 122.40, 122.35 115.20, 115.05. 77.74-77.36, 45.87, 40.44-39.49. MS (EI, *m/z* (%)): 472 (100). UV/Vis (EtOH, λ_{max}, nm, (ε)): 268 (1.311). Anal. calcd. for C$_{22}$H$_{17}$FN$_2$O$_7$S: C, 55.93; H, 3.63; N, 5.93; S, 6.79 %. Found: C, 55.79; H, 3.50; N, 5.77; S, 6.45%.

2.2.13. Synthesis of compounds 14

Equimolar amounts (0.01 mol) of compounds **11** and **13** was refluxed in dry 1,4-dioxan (50 mL) for 4h and cooled. The solid product was filtered off and crystallized from 1,4-dioxan to give a white crystal (Scheme 3).

1,1'-Dibenzoyl-3, 3'-bis(4-fluorophenyl)-2, 2'-dithioxotetra hydro-[5, 5'-bipyrimidine]-4, 4', 6, 6'(1H, 1'H, 5H, 5'H)-tetraone (**14**): Color: White. Yield: 70%. M.p.: 124-126 °C. FT-IR (KBr, ν, cm^{-1}): 3528 (OH), 1700, 1680, 1661 (C=O), 1385 (NCSN), 1255 (C-F), 1180 (C=S), 864 (Aryl CH), 658 (C-F). ^{1}H NMR (400 MHz, CDCl$_3$, δ, ppm): 2.589-2.583 (m, 2H, 2CH), 7.01-7.97 (m, 18H, Ar-H), 9.84 (s, 1H, OH), 11.32 (s, 1H, OH). ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 166.31, 159.76, 158.16, 135.12, 135.10, 131.44, 128.29, 128.23, 127.69, 126.60 122.39, 122.35 115.97, 115.82. 115.17, 115.03, 77.84, 45.85, 40.32. MS (EI, *m/z* (%)): 684 (M^{+2}, 3.53). UV/Vis (EtOH, λ_{max}, nm, (ε)): 282 (0.2011). Anal. calcd. for C$_{34}$H$_{20}$F$_2$N$_4$O$_6$S$_2$: C, 59.82; H, 2.95; N, 8.21; S, 9.39. Found: C, 59.77; H, 2.90; N, 7.99; S, 9.28%.

3. Results and discussion

3.1. Chemistry

Thiobarbituric acids have activated tautomers, and the CH$_2$ at position-5 is an active site for addition, alkylation, acylation and also condensation reactions [9,28,29]. Thus, careful addition of 4-fluoroaniline to aryl isothiocyanates in warmed THF produced compound **1a-c**. Heterocyclization of compounds **1a-c** by reflux with malonic acid in the presence of acetyl chloride-acetic acid mixture, yielded compounds **2a-c**.

Addition of compounds **2a** to cyclohexyl isocyanate in warmed ethanol-piperidine furnished compound **3** (Scheme 1). Formation of compound **3** took place by a nucleophilic attack of CH$_2$ at position-5 of compound **2a** with a more electrophilic carbon of isocyanate.

Structures of compounds **1-3** were characterized from correlated elemental analysis and spectral data. The IR spectrum of compound **1a** recorded absorption band at 3180 cm^{-1} attributed to presence of NH functional groups, which lacks in compound **2a**. Compounds **2a-b** and **3** showed an absorption bands at 1680, 1668 and at 2856, 1488 cm^{-1} due to the presence of both two carbons and active methylene. Only, the spectrum of compound **3** showed the third C=O and one NH functional group at 1668 and 3180 cm^{-1}. The ^{1}H NMR spectrum of compound **2a** display doublets at δ 2.59-2.58 (s, 2H, CH$_2$) ppm due to active ethylene at 5-positions. ^{13}C NMR of both compound **2a** showed a resonated signal at 166.32 and 158.17 ppm for C=O and C=S carbons with resonated =CH at δ 40.43 ppm. Compound **2a** exhibited *m/z* at 314 as base peak. UV spectra of compound **3** are more than compound **2** at λ_{max} (275 and 258 nm) attributed to heteroconjugation systems formed. It is interest that, compounds **2** and **3** showed a violet color with FeCl$_3$ solution which confirm that these systems exist as enolic form rather than ketonic formula. Reflux compound **3** with glacial acetic acid in a fused sodium acetate yielded compound **4**.

Polyfunctional pyrimidopyrimidines use as multi-targeted small molecule inhibitors and resistance modifying agents [30,31]. Similar, cycloaddition of substituted thiourea **1** with compound **3** in methanolic NaOH produced compounds **5** and **6** (Scheme 1). Structures of compounds **4-6** deduced from their correct elemental analysis and spectral measurements. IR spectra of compound **5** and **6** showed ν at 3150-3123 cm^{-1} attributed to exo -NH- while that lacks in compound **4**. ^{1}H NMR spectra of compound **6** recorded signal at δ 11.55 ppm for NH protons. ^{13}C NMR spectra of compounds **6** showed δ at 207.02 and 157.10 ppm for C=S, and C=O appeared for compound **4**. UV absorption spectrum of compound **6** exhibited λ_{max} at 287 nm which higher than compound **3**, which is due to more conjugation system. Compound **4** showed a molecular ion and a base peak at *m/z* 422. Addition sulfa drugs as primary aromatic amines to benzoyl isothiocyanates in warm THF, produced compound **7a-c**. Heterocyclization of compound **7** with malonic acid in warm acetyl chloride-acetic acid produce compounds **8a-c**. Which contain active CH$_2$ at position-5. Treatment of compounds **8a, b** with 4-fluorobenzoyl chloride in warm DMF yielded compound **9**. Ring closure reaction of compound **9** with 4-chlorophenyl hydrazine in reflux absolute ethanol afforded compound **10a, b** (Scheme 2).

The former structure of compounds **7-10** have been established from their corrected elemental analysis and spectral data. IR spectra showed an absorption band at 3500-3150 and 1580 cm^{-1} for (HO-C=N ⇌ CO-NH) for compound **7a-c**. Also, compound **9** recorded a multi-absorption bands at 1680-1660 cm^{-1} attributed to four C=O functional groups. Only the compound **10b** recorded an absorption band for C=N at 1520 cm^{-1}. All the IR spectra of compounds **7-10** showed an absorption band at ν for the acidic -NHSO$_2$- group. ^{1}H NMR spectra of compound **8a** recorded a resonated signal at δ 2.60-2.21 ppm for active CH$_2$ at position-5. In addition ^{13}C NMR spectrum of compound **8a** showed a resonated signal at δ 179.26, 173.06 and 169.22 ppm attributed to C=S and C=O carbons with δ 40.42-39.47 ppm for CH$_2$. M$^+$/S of compound **8a** recorded a base peak at *m/z* 485.94. UV absorption spectrum of compound **10a** exhibited λ_{max} at 315 nm higher than compounds **9, 8** and **7** (λ at 294, 280 and 238 nm. Mass of compound **10b** showed a molecular ion of M-24 with a base peak at 722 *m/z*. Compound **7** showed a violet color when treated with FeCl$_3$ solution, which confirm that enolic structure than ketonic formula (enolization preferred towards aryl groups).

Table 1. Anti-HIV activity data of the thiobarbituric acids *.

Compound	IC_{50} (µM)	EC_{50} (µM)	CC_{50} (µM)	SI	Present of protection	Present of infected
2	9.3±1.5	48±1.7	87.0±3.8	1.81	4.90	7.15
8a	4.5±0.2	31±1.1	60.0±5.5	19.35	7.95	9.88
8b	4.6±0.8	2.3±0.5	48.8±81	21.21	7.55	10.30
8c	3.1±0.5	6.6±0.8	41.01±40	6.21	12.15	13.55
9a	3.2±0.6	24.08 ±2.8	75.0±1.0	3.12	10.70	11.51
12	7.7±0.1	6.8±0.8	36±2.6	5.29	5.88	7.90
14	2.7±0.1	13.8±1.8	28.5±1.3	2.06	16.01	15.11

* IC_{50}: The half maximal inhibitory concentration is a measure of the effectiveness of a compound in inhibiting biological or biochemical function; EC_{50}: The term half maximal effective concentration refers to the concentration of a drug, an antibody or toxicant which induces a response halfway between the baseline and maximum after a specified exposure time; CC_{50}: Cytotoxicity concentration; SI: Selectivity Index CC_{50}/EC_{50}.

Similarly, the addition of 4-fluoroaniline to benzoyl isothiocyanate in warm THF produce compound **11**. Heterocyclization of compound **11** by refluxing with malonic acid in acetyl chloride-acetic acid [32] yielded compound **12** (Scheme 3). It is interest that a simple alkylation of α-active proton of compound **12** via nucleophilic attack to labile chloride atom containing α-keto-alkylating agents [33,34].

Alkylation of compound **12** by using dimethyl 2-chloro malonate in boiling dry toluene in the presence of drops triethylamine, compound **13** isolated. Full hetero-cyclization of compound **13** by reaction with compound **11** in reflux THF, afforded the *bis*-compound **14** (Scheme 3). Former structures of compound **11**-**14** have been deduced from the corrected elemental analysis and spectral data. IR spectrum of compound **11** recorded the absorption band at 3230-3150 cm⁻¹ due to CONH ⇄ HO-C=N, in addition at 1385 cm⁻¹ for NCSN. On the other hand IR spectra of compounds **12**-**14** showed absorption bands at ν 1680, 1660 cm⁻¹ attributed to 1,3-dicarbonyl groups with characteristic bands at ν 1211 and 1180 cm⁻¹ for C=S groups and 1255 cm⁻¹ for C-F. ¹³C NMR spectrum of compound **14** showed a resonated signals at 166.31 and 159.76 ppm attributed to C=S and C=O carbons, in addition at δ 131.41-122.35 and 45.85, 40.32 ppm for aromatic and aliphatic carbons. UV absorption spectra of compounds **11**-**14** give us indication about the ring closure reactions of compound **11** to **13** and **14**. Compound **11** showed λ$_{max}$ at 265 nm, compound **12** at 288 and compound **14** at 282 nm. These data confirm that formation of heterocyclic systems from compounds **11** to **12**. Mass of compound **14** exhibited a molecular ion and the base peaks at *m/z* 684 (M+2) and 685 (M+3).

3.2. Pharmacological Evaluation

Recently, thiobarbituric acid derivatives proved to be virus inhibitors, especially hepatitis's C virus (HCV) NS5B polymerase. Besides, they suppressed the synthesis of RNA by recombinant HCV NS5B polymerase dependent manner [35-39]. The prominent role of fluorine substituent on bioactivity is due to the effect C-H acidity which depends on several factors, including the site of fluorination and the geometry of the conjugate carbon ion. Based on these observations, The present work depends on the synthesis of fluorine substituted thiobarbituric acid derivatives and their related heterocyclic systems and their evaluation as potential inhibitors, especially HIV-1 and inhibition of cyclin-dependent kinase 2 (CDK2) for tumor cell.

3.2.1. Anti-HIV-1 Testing

All the new synthesized compounds evaluated for their *in vitro* anti-HIV activities were performed on T-4 Lymphocytes uninfected or infected with HIV-1 using DMSO as solvent. The assay basically involves the killing T-4 Lymphocytes by HIV. Compounds that degenerate or are rapidly metabolized in the culture conditions may not show activity in this screening. The viability of the cells was determined spectrophotometrically using the tetrazolium assay procedure. The concentration was

tested range 1×10⁻⁴ to 1×10⁻⁸ M and determined GI$_{50}$, TGI and LC$_{50}$ values.

The arrangements of atoms across the skeleton, concepts of steric relations and molecular bulk branched ness and relationships among various non-branched parts of the molecule are considered in these methods. Thus, we report here the correlation of cytotoxicity and anti-HIV activity of fluorinated thiobarbituric acid derivatives in view to provide a better rational approach for the design of potent drugs. The electronic parameter (equalized electronegativity) hydrophobic parameter and steric parameter of the tested systems synthesized give us a good indication about the role of electronic nature, hydrophobicity, and molecular size of the fluorinated thiobarbituric acid derivatives molecules on the activity. HIV-1 envelope glycoprotein (Env) transmembrane submit glycoprotein 41 (gp41) plays a crucial role in mediating virus, fusion and entry. When the human immunodeficiency virus (HIV) fuses to the host cell, the N-terminal heptads repeat (NHR) and C-terminal heptads repeat (CHR) of gp41 interact to form a six-helix bundles (6-HB) core structure, bringing the viral and host cell membranes into sufficient proximity to allow fusion. The fluorinated thiobarbituric acid derivatives synthesized were evaluated as anti-HIV and the results were obtained reported in Table 1 [40]. From the data obtained it can be concluded that the order of activity of these targets is **14 > 8c > 9a > 8a > 8b > 12 > 2**. The most activity compounds **14**, **8c**, **9a** and **8a** which are due to the presence of fluorine substituted thiobarbituric acids. These active compounds exhibited significant potency against gp41 6-HB formation with IC$_{50}$ values of 4.5 and 4.6 µM and against HIV-1 replication in the MT-2 cells with EC$_{50}$ values of 3.1 and 3.2 µM, respectively. Thus, providing a new starting point to develop highly potent small molecule HIV fusion inhibitors targeting gp41. On the other hand, compounds **14**, **8c**, **9a** and **8a** recorded a higher percent of protection (Table 1).

3.2.2. Inhibition of cyclin-dependent kinase2 (CDK2) for cell-tumor division

Various thiobarbituric acid derivatives exhibited anticancer activities [40,41]. A recent control on the cell tumor division depends on the use of polyfunctional heterocyclic nitrogen systems for inhibition of cyclin-dependent kinase 2 (CDK2) as tyrosine kinase inhibitors [42]. Thus, the present work aimed to prepare of new fluorine substituted thiobarbituric acid derivatives and their heterobicyclic nitrogen systems as a novel scaffold for the development of antiproliferative agents with possible pharmacological applications in oncology. The synthesized compounds were evaluated for their ability to inhibit acidity of CDK2 in a biochemical assay [43] with IC$_{50}$ values comparable to olomoucine as standard according to the reported methods. The obtained data were reported in Table 2. In view of the results obtained, the most active compounds bear a fluorine atom followed by a sulfa-drug moiety. In addition, we observed that a 4-fluorophenyl side chain at position 1 or 3 significantly decreases CDK2 inhibitory acidity. The activity of

the tested targets as **12 > 14 > 2 > 9a > 8a > 8b > 8c** in comparing with olomoucine as standard.

Table 2. Results CDK2 inhibition tests (IC$_{50}$ in μmol/dm) *.

Compound	IC$_{50}$ CDK2±SD (μM)
2	11.0±4.5
8a	15.1±5.3
8b	17.4±3.8
8c	>20
9a	14.1±1.8
12	4.5±2.8
14	5.2±1.73
Olomoucine	5.0±1.0

* SD: Standard deviation, Olomoucine value is included as a control.

4. Conclusion

Simple routs were explored to synthesize new fluorinated fused heterobicyclic systems containing a thiobarbituric acid moiety starting with fluorinated *N,N'*-diarylthiobarbituric acid, **2**. Some of new synthesized systems recorded good anti HIV-1 and cyclin dependent kinase 2. We hope that this approach may be a value to others seeking novel synthetic fragments with unique properties for medicinal chemistry.

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