

Synthesis of Barbituric and Thiobarbituric Acids Bearing 5,6-Diphenyl-1,2,4-Triazin-3-yl Moiety as CDK2 Inhibitors of Tumor Cells

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Abstract: Synthesis of several new diphenyl-1',2',4'-triazin-3'-yl barbituric acid are described. The method involves addition reaction of isocyanate and isothiocyanate and 3-amino-5,6-diphenyl-1,2,4-triazine (1) to give N^1, N^3 -disubstituted urea 2 and N^1, N^3 -disubstituted thioureas 3 and 4 respectively. Further, ring closure reactions with malonate ester give barbituric acid 5 and thiobarbituric acid 6 and 7. The Presence of the active methylene in the skeleton of compound 5-7 at C-5 are deduced by condensation with pyridine-4-carboxylaldehyde to give barbituric and thiobarbituric acids (8-10). Further fluoroacylation of compounds 5-7, afforded 1-(cyclohexyl/methyl/phenyl)-3-(5',6'-diphenyl-1',2',4'-triazin-3'-yl)-5-(trifluoroacetyl)-5H-barbituric/thiobarbituric acids (11-13). Synthesis compounds of the series 5-(trifluoroacetyl) barbituric acid (11) and 5-(trifluoroacetyl) thiobarbituric acids (12 and 13) were able to inhibit activity of CDK2 in a biochemical assay with IC50 values comparable to olomoucine. In addition, a pyridine side chain at C-5 (compound 9 and 10) significantly decreases CDK2 inhibitory activity.

Keywords: Barbituric, Thiobarbituric, 1,2,4-triazine, CDK₂, Malonate Ester, Trifluoroacylation

1. Introduction

The success of Imatinib mesylate as the first small molecule targeted kinase inhibitor for use in cancer therapy [1], are validated protein kinases as important drug targets in the treatment of human diseases [2]. The protein kinase family constitutes the largest gene-family for therapeutic development, and hence there is an urgent need to develop and discover compounds that can both serve as pharmacological probes and lead compounds for further drug development [3]. The condensed and substituted thiobarbituric acids possesses diverse pharmacological profile such as antimicrobial, selective cell adhesion inhibitors and DNA cleavage activities [4]. Additionally Barbiturate and thiobarbiturate derivatives attracted considerable attention owing to their various biological effects such as inhibiting collagenase-3 (MMP-3), recombinant cytochrome P450 enzymes and anti-inflammatory analgesic [5]. In focused the Polyfunctional heterocyclic nitrogen systems are essential for drug discovery

[6]. For example, pyrazolyl-1,2,4-triazines [5], 3-functionalized-5,6-diphenyl-1,2,4-triazines [6] and 3-amino-1,2,4-triazines [7]. In addition, functionalized bridgehead nitrogen heteroannulated 1,2,4-triazine systems works as pharmacological probes [10] while the pyrimidine nucleus and their derivatives exhibit a wide range of pharmacological, medicinal and biological properties [11].

Consequently, this investigation tends to synthesis barbituric and thiobarbituric acids as pyrimidine nucleus bearing a bioactive 5,6-diphenyl-1,2,4-triazin-3-yl moiety and their evaluate as CDK2 inhibitors of tumor cells.

2. Chemistry

3-Amino-5,6-diphenyl-1,2,4-triazine (1) [7] as starting material, is obtained by cyclocondensation of benzyl with aminoguanidine bicarbonate in reflux n-butanol. The Addition of cyclohexyl isocyanate, methyl isothiocyanate, and phenyl isothiocyanate to compound 1 in reflux EtOH, produced N^1, N^3 -disubstituted urea 2 and N^1, N^3 -disubstituted

thioureas 3 and 4 respectively (Figure 1).

To deduced the aim of this work, the compounds 2-4 on ring closure reactions with malonic acid in refluxing glacial acetic acid afforded the *N*¹-(cyclohexyl)-*N*³-(5',6'-diphenyl-

1',2',4'-triazin-3'-yl)barbituric acid (5) and/or *N*¹-(methyl/phenyl)-*N*³-(5',6'-diphenyl-1,2,4-triazin-3'-yl) thiobarbituric acids (6 and 7) respectively [12], Figure 1.

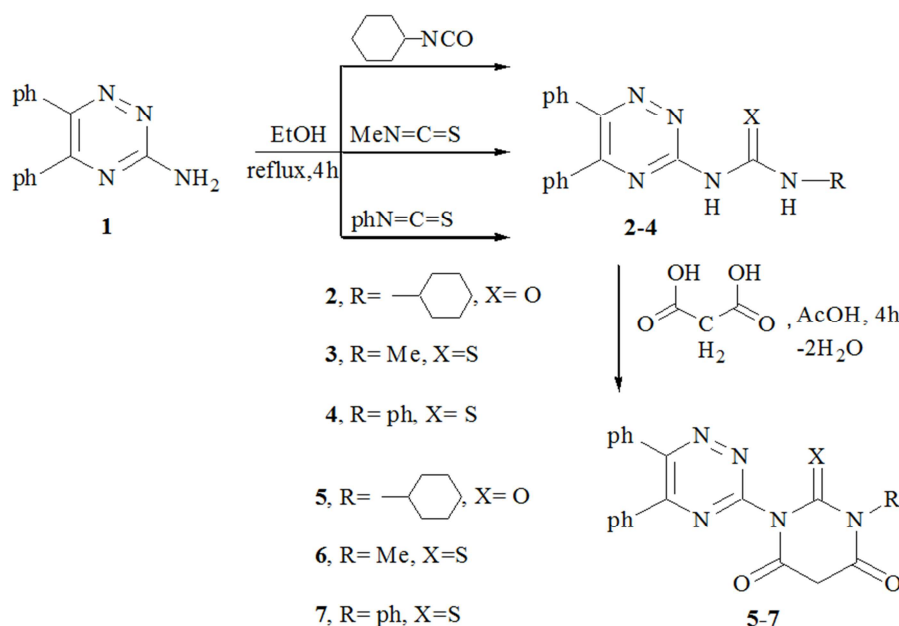


Figure 1. Ring closure reactions on compounds 2-4 in to give barbituric acid (5) and thiobarbituric acids (6 and 7).

The active methylene [13] in the skeleton of compound 5-7 at C-5 can be confirmed by condensation with pyridine-4-carboxylaldehyde to give 1-(cyclohexyl/methyl/phenyl)-3-(5,6-diphenyl-1',2',4'-triazin-3'-yl)-5-(pyridin-4-ene)barbituric and thiobarbituric acids (8-10) (Figure 2).

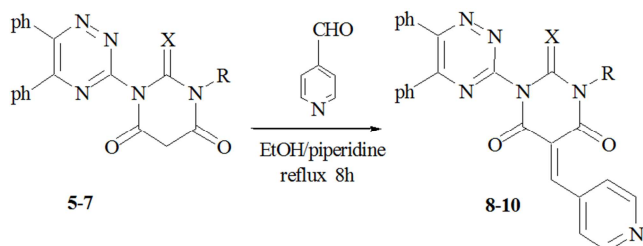


Figure 2. Synthesis of thiobarbituric acids (8-10).

The introducing of fluorine atoms to heterocyclic nitrogen systems, often improve and enhance the physical, chemical and medicinal properties [3, 4] Thus, fluoroacylation of compounds 5-7 by refluxing with hexafluoroacetic anhydride in THF, afforded 1-(cyclohexyl/methyl/phenyl)-3-(5',6'-diphenyl-1',2',4'-triazin-3'-yl)-5-(trifluoroacetyl)-5H-barbituric/thiobarbituric acids (11-13) (Figure 3).

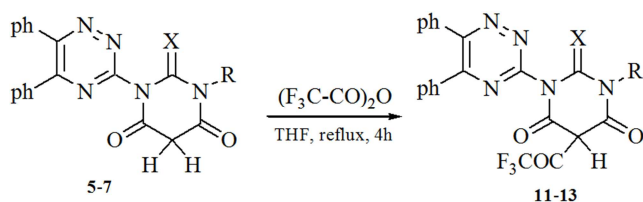


Figure 3. Synthesis of barbituric/thiobarbituric acids (11-13).

3. Results and Discussion

This work reports a simple synthesis strategy toward both 5,6-diphenyl-3-amino-1,2,4-triazine (1) and the substituted barbituric/thiobarbituric acids, Structures of the new targets obtained established from their correct elemental analysis and spectral measurements.

Thus, IR spectra of 1,3-disubstituted urea/thiourea (2 and 3) showed *peak* at 3180, 1630, 1385, 1195 cm⁻¹ attribute to NH, CO, acyclic NCSN, and C=S functional groups. While compound give peaks at 1190 (C=S), 3160 (NH), and 1330 cm⁻¹ (acyclic NCSN).

Structures of both substituted barbituric acids and thiobarbituric acids (5-7) can be deduced from spectral data. the UV spectrum of 7 recorded λ_{max} at 260 (nm, ε, 0.95), while that IR showed peaks at 3470 (OH), 1680 (C=O), 1441 (deformation of aliphatic CH₂), 1387 (cyclic NCSN), 1580, 1560 (C=N), 1180 (C=S), 860 and 810 cm⁻¹ (phenyl). The NMR spectrum of 7 showed a the hydroxy resonated proton as signals at δ 9.8, complicated aromatic protons at 7.96-7.77, 7.6-7.2 and active methylene two protons at 2.59-2.56 acids. Additionally, Mass fragmentation of compound 7 showed the molecular ion at m/e 451 (1.01) with the base peak at m/e 178 (100) attribute to diphenylacetylene radical [14].

According to the condensation of compound 6 with pyridin-4-carboxaldehyde the active methyl group (C-5) not showed as expected in the IR, ¹H NMR and ¹³C NMR spectra of compounds 8-10, ppm. Furthermore, IR spectrum showed only two carbonyl groups at ν 1720, 1700 cm⁻¹ and (C=S) at 1188 cm⁻¹

On the other hand, fluoroacetylation of compound 6 by reflux with hexafluoroacetic anhydride in THF afforded the mono (trifluoroacetyl) derivative 12. Structure of compound 12 confirmed by rang of spectrum analysis, IR spectrum showed broad hydroxyl peak of (OH) at 3450-3400, carboxylic C=O at 1700 cm^{-1} , while aliphatic CH at C-5 appears at 1414 cm^{-1} . thiobarbituric acid (C=S) at position-3 showed peaks at 1180 cm^{-1} . ^{13}C NMR of 12 recorded the presence of resonated carbon signals at δ 180, 166, 146, 142, 138, 132-122 and 40 ppm for C=S, C=O, C-F, C=N, C=C, CH_3 respectively, in addition to aromatic carbons of 1,2,4-triazine moiety.

Mass fragmentation of compound 12 showed m/e at lower percentage, which may be a less stability of the fluorinated systems, with a base peak at m/e 85 attribute to COCF_3 ions.

4. Experimental

Melting points were determined with an electrochemical Bibby Sturat Scientific melting point sample (UK). A Perkin Elmer Model RXI-FT IR system 55529 was used for Recording IR spectra of the prepared compounds (cm^{-1}). the ^1H and ^{13}C NMR spectra DMSO- d_6 (ppm), A Bruker advance DPX 400 MHZ model uses TMS an internal standard. A GC-MS-GP 1000 Ex model was used for recording the mass spectra of the compounds (MHZ). Electronic spectra were recorded in ethanol on Shimadzu UV and visible 310 IPC Spectrophotometer (nm). Elemental analysis was performed in micro analytical Center of Cairo University, Cairo, Egypt. 3-Amino-5,6-diphenyl-1,2,4-triazine (1) prepared according the reported method [7].

4.1. Synthesis of 1-(Cyclohexyl)-3-(5',6'-diphenyl-1,2,4-triazin-3'-yl) Urea (2)

A mixture of compound 1 (0.01 mol) and cyclohexyl isocyanate (0.01 mol) in abs. EtOH (50 ml) refluxed 2h, cooled. The solid was collected and crystallized from EtOH to give 2. Yield%; m.p. 167-168°C. IR (ν) cm^{-1} : 3180 (NH), 2980, 2888 (aliphatic CH_2), 1630-1620 (CONH), 1580 (C=N), 1487, 1441 (bending CH), 870, 850, 810 (phenyls). ^1H NMR (DMSO- d_6) δ ppm: 10.08 (s, 1H, b, NH), 9.15 (s, 1H, b, NH), 7.7-7.2 (m, 10H, aromatic); 2.15 (s, 1H, CH), 1.55, 1.50 (each m, 4- CH_2), 0.8 (s, 3H, CH_3). Anal. Calcd.; C, 70.77; H, 6.16; N, 18.76% for $\text{C}_{22}\text{H}_{23}\text{N}_5\text{O}$ (373). Found: C, 70.73; H, 6.16; N, 18.62%.

4.2. Synthesis of 1-(Methyl/phenyl)-3-(5',6'-diphenyl-1',2',4'-triazin-3'-yl) Thioureas (3 and 4)

A mixture of 1 (0.01 mol), methyl isothiocyanate and/or phenyl isothiocyanate (0.01 mol) in abs. EtOH (50 ml) refluxed 2h, cooled. The produced solid filtered off and crystallized from EtOH, to give 3 and 4 respectively.

3, Yield 79%; m.p. 180-182°C., Anal. Calcd.; C, 63.55; H, 4.67; N, 21.80; S, 9.96% for $\text{C}_{17}\text{H}_{15}\text{N}_5\text{S}$ (321). Found: C, 63.42; H, 4.58; N, 21.74; S, 10.01.

4, Yield 81%; m.p. 188-190°C. UV (EtOH) λ_{max} 240 nm,

IR (ν) cm^{-1} : 2880 (CH_2), 1610 (C=C), 1580 (C=N), 1350 (acyclic NCSN), 1190 (C=S), 850, 810, 790 (phenyls). ^1H NMR (DMSO- d_6) δ ppm: 10.34 (1H, b, NH), 9.34 (1H, b, NH), 7.67-7.2 (m, 10H, aromatic), 7.0-6.88 (m, 5H, phenyl protons). Anal. Calcd.; C, 68.92; H, 4.43; N, 18.27; S, 8.35% for $\text{C}_{22}\text{H}_{17}\text{N}_5\text{S}$ (383). Found: C, 68.86; H, 4.37; N, 18.07; S, 8.29%.

4.3. 1-(Cyclohexyl)-3-(5',6'-diphenyl-1',2',4'-triazin-3'-yl) Barbituric Acid (5)

Equimolar amounts of 2 and malonic acid in glacial AcOH (50 ml) refluxed for 4h, cooled then concentrated. The solid produced, filtered off and crystallized from dioxin to give 5, yield 65%, m.p. 180-182°C. IR (ν) cm^{-1} : 3470 (OH), 1700-1680 (2C=O), 1480, 1441 (bending CH), 850, 810 (phenyls). ^1H NMR (DMSO- d_6) δ ppm: 7.7-7.44 (m, 10H, aromatic), 3.52 (s, 1H, enolic HO-C"H), 2.59 (s, 1H, CH=C), 1.20 (s, 3H, CH_3). ^{13}C NMR (DMSO- d_6) δ ppm: 165.65, 159.63 and 158.02 (3C=O), 134.52 (C=N), 132-122 (aromatic carbons), 40 (CH_3). Anal. Calcd.; C, 68.02; H, 5.21; N, 15.87% for $\text{C}_{25}\text{H}_{23}\text{N}_5\text{O}_3$ (441). Found: C, 68.12; H, 5.18; N, 15.90.

4.4. 1-(Methyl/phenyl)-3-(5',6'-diphenyl-1,2,4-triazin-3'-yl) Thiobarbituric Acids (6 and 7)

A mixture of 3 and/or 4 (0.01 mol) and malonic acid (0.01 mol) in glacial AcOH (50 ml) refluxed 4h, cooled then concentrated. The solid obtained filtered off and crystallized from dioxin to give 6 and 7 respectively.

6: Yield 73%, m.p. 203-205°C. Anal. Calcd.; C, 61.69; H, 3.85; N, 17.99 for $\text{C}_{20}\text{H}_{15}\text{N}_5\text{SO}_2$ (389). Found: C, 61.73; H, 3.81; N, 18.09%. [15]

7: Yield%, m.p. 193-195°C. UV (EtOH) λ_{max} : 260 nm (ϵ , 0.95). IR (ν) cm^{-1} : 3470 (OH), 1710, 1680 (2C=O), 1610 (C=C), 1580 (C=N), 1488, 1440 (bending CH), 1330 (cyclic NCSN), 1180 (C=S), 880, 860, 810, 780 (phenyls). ^1H NMR (DMSO- d_6) δ ppm: 7.96, 7.77, 7.6-7.2; 7.01-6.8 (each m, 15H, aromatic), 9.8 (s, 1H, enolic OH-C"), 2.59 (s, CH=C). ^{13}C NMR (DMSO- d_6) δ ppm: 180.1 (C=S), 165, 159 (C=O), 142, 135 (C=N), 128-122 (aromatic carbons). M/S (Int.%): 451 (M^+ , 1.01); 178 (100), 135 (15), 84 (5.71), 70 (85.13), 56 (5.18). Anal. Calcd.; C, 66.51; H, 3.76; N, 15.52% for $\text{C}_{25}\text{H}_{17}\text{N}_5\text{SO}_2$ (451). Found: C, 66.56; H, 3.71; N, 15.48%.

4.5. 1-(Cyclohexyl)-3-(5',6'-diphenyl-1',2',4'-triazin-3'-yl)-5-(pyrid-4-ene) Barbituric Acid (8)

Equimolar amounts of 5 and pyridine-4-carboxaldehyde in EtOH (100 ml) with few drops of piperidine refluxed 8h, cooled, then poured onto ice-drops AcOH. The solid yielded filtered off and crystallized from dioxin to give 8, Yield 78%; m.p. 195-197°C. IR (ν) cm^{-1} : 3050 (aromatic CH), 1710, 1680, 1660 (3C=O), 1580 (C=N), 1488, 1441 (bending CH), 850, 810 (phenyls). ^1H NMR (DMSO- d_6) δ ppm: 9.23 (s, arylidene proton), 8.2, 8.0 (each dd, 2CH-pyridine), 7.8-7.66, 7.40-7.2, 7.0-6.69 (m, 18H, aromatic and pyridine). ^{13}C NMR (DMSO- d_6) δ ppm: 165.67, 160.91 (C=O), 138.4 (C=N), 133 (C=C), 130-122 (aromatic carbons), 40, 24 (aliphatic

carbons). Anal. Calcd.; C, 68.91; H, 4.96; N, 16.63% for $C_{29}H_{25}N_6O_3$ (505). Found: C, 67.88; H, 4.80; N, 15.59.

4.6. 1-(Methyl/phenyl)-3-(5',6'-diphenyl-1',2',4'-triazin-3'-yl)-5-(pyridi-4-ene)-Thiobarbituric Acids (9 and 10)

A mixture of **6** and **7** (0.01 mol) and pyridine-4-carboxaldehyde (0.01 mol) in EtOH (100 ml) and 2 ml of piperidine, refluxed for 8h, after cooled. The reaction mixture poured onto cold water 50 ml with 1 ml of AcOH. Collect the obtained solid by filtration and recrystallized from EtOH to give **9** and **10** respectively.

9, Yield 78%; m.p. 168-170°C. Anal. Calcd.; C, 64.51; H, 3.65; N, 18.06; S, 6.88% for $C_{25}H_{17}N_6SO_2$ (465). Found: C, 64.47; H, 3.45; N, 17.97; S, 6.83%.

10, Yield 61%; m.p. 180-182°C. IR (ν) cm^{-1} : 3060 (aromatic CH), 1720, 1700 (C=O), 1610 (C=C), 1590, 1560 (C=N), 1330 (cyclic NCS), 1170 (C=S), 910, 850, 810 (phenyls). 1H NMR (DMSO- d_6) δ ppm: 7.85 (s, 1H, CH=pyridine), 7.6, 7.7 (each d, d, 2CH-pyridine), 7.6-6.9, 6.7-6.55 (each m, 18H, aromatic & pyridine). ^{13}C NMR (DMSO- d_6) δ ppm: 181 (C=S), 165, 160 (C=O), 142 (C=N), 134.4 (CH=C arylidene), 132-122 (aromatic & pyridine carbons). Anal. Calcd.; C, 68.31; H, 3.60; N, 15.93; S, 6.07% for $C_{30}H_{19}N_6SO_2$ (527). Found: C, 68.28; H, 3.64; N, 15.88; S, 6.11%.

4.7. 1-(Cyclohexyl)-3-(5',6'-diphenyl-1',2',4'-triazin-3'-yl)-5-(trifluoroacetyl) Barbituric Acid (11)

A mixture of **5** (0.01 mol) and hexafluoroacetic anhydride (0.015 mol) in THF (100 ml) refluxed 2h, cooled. The resulted solid was collected by filtration and crystallized from dioxin to give **11**, yield 71%; m.p. 168-170°C. IR (ν) cm^{-1} : 3060 (aromatic CH), 1720, 1700, 1670 (C=O), 1610 (C=C), 1580 (C=N), 1480, 1441 (bending CH_2), 1230 (C-F), 910, 880, 810 (phenyls), 750 (C-F).

1H NMR (DMSO- d_6) δ ppm: 8.51 (s, 1H, OH), 7.6-7.4, 7.2-6.95 (m, 10H, aromatic), 2.58 (s, CH), 1.5, 1.25, 1.20 (each s, 3 CH_2). ^{13}C NMR (DMSO- d_6) δ ppm: 167.52, 166.37 (2C=O), 151 (C-OH), 146 (C-F), 142 (C=N), 132-127 (aromatic carbons), 40.44, 39.54, 25 (aliphatic carbons). Anal. Calcd.; C, 60.33; H, 4.09; N, 13.03; F, 10.61% for $C_{27}H_{22}N_5F_3O_4$ (537). Found: C, 60.03; H, 4.12; N, 12.96; F, 10.65%.

4.8. 1-(Methyl/phenyl)-3-(5',6'-diphenyl-1',2',4'-triazin-3'-yl)-5-(trifluoroacetyl) Thiobarbituric Acids (12 and 13)

A mixture of **6** or **7** (0.01 mol) and hexafluoroacetic anhydride (0.01 mol) in THF (100 ml) reflux for 2h, cooled. The solid obtained, filtered off and crystallized from dioxin to give **12** and **13** respectively.

12, Yield 62 %; m.p. 158-160°C. IR (ν) cm^{-1} : 3450 (OH), 3060 (aromatic CH), 2980, 2880 (aliphatic CH), 1700 (C=O), 1680 (C=O), 1610 (C=C), 1590 (C=N), 1350 (cyclic CH), 1240 (C-F), 1188 (C=S), 910, 850, 810 (phenyls), 780 (C-F). 1H NMR (DMSO- d_6) δ ppm: 8.8 (s, 1H, CH= cyclic), 7.8-7.66, 7.4-6.95 (each m, 10H, aromatic), 1.25 (s, 3H, CH_3).

^{13}C NMR (DMSO- d_6) δ ppm: 180 (C=S), 166 (C=O), 146 (C-F), 142 (C=N), 138 (C-N), 132-122 (aromatic carbons), 40 (CH_3 carbons). m/s (Int.%): 485 (487, M+2, 5.03): 178 (85.11), 113 (75.11), 85 (100), 69 (5.13). Anal. Calcd.; C, 54.43; H, 2.88; N, 14.43; F, 11.7; S, 6.58% for $C_{22}H_{14}N_5F_3SO_3$ (485). Found: C, 54.38; H, 2.88; N, 14.45; F, 11.67; S, 6.54%.

13, Yield 59%; m.p. 178-180°C. Anal. Calcd.; C, 59.23; H, 2.92; N, 12.79; F, 10.42; S, 8.5% for $C_{27}H_{16}N_5F_3SO_3$ (547). Found: C, 59.03; H, 2.96; N, 12.82; F, 10.37; S, 8.53%.

5. Inhibition of Cyclin-Dependent Kinase 2 (CDK2) for Cell Tumor Division

The purine-related pyrrolo[2,1-f][1,2,4]triazines have been identified as tyrosine kinase inhibitors, a well-established platform for modern anticancer chemotherapy [15]. Recent control on the cell tumor division depends on use of polyfunctional heterocyclic nitrogen systems as CDK2 for examples fluorine substituted thiobarbituric acid [16].

Recently, number of CDK inhibitors have been developed. Some compounds of the series were able to inhibit activity of CDK2 in a biochemical assay with IC50 values comparable to olomoucine [17]. The most active compounds with trifluoroacetyl at position 5, such as 5-(trifluoroacetyl)barbituric acid (**11**) and 5-(trifluoroacetyl)thiobarbituric acids (**12** and **13**) In addition we have observed that a pyridine side chain at C-5 significantly decreases CDK2 inhibitory activity (5-(pyridi-4-ene)-thiobarbituric acids compound **9** and **10**):). The data on CDK2 inhibition of [1,2,4]triazines derivatives summarized in (Table 1).

Generally, this investigation showed that Thiobarbituric acids **6** and **7** showed activity over than barbituric acid **5** and their thiourea derivatives **3** and **4**. While trifluoroacetyl-thiobarbituric acid **12** Record higher activity over the corresponding thiobarbituric acid **6**. Furthermore, compound **12** had a higher percentage of fluorine elements, which led to a higher hydrophobic, distribution, and H-bonding formation. Table 1.

Table 1. CDK₂ inhibition tests (IC₅₀ in $\mu mol dm^{-1}$).

Compound. No.	IC ₅₀ CDK ₂ ±SD (μMol)
2	>20
3	14.1±1.9
4	>20
5	11.2±5.3
6	5.50±4.5
7	10.15±3.8
8	15.2±1.7
9	16.1±1.8
10	18.5±2.8
11	4.8±1.7
12	4.2±1.0
13	4.5±1.0
Olomoucine	5.0±1.0

SD: standard deviation

Olomoucine value is included as control [17].

6. Conclusion

Fluorinated thiobarbituric and barbituric acids and their related systems, have been synthesis by simple effective methodology by the addition of isocyanate and isothiocyanate to 3-amino-1,2,4-triazine followed by ring closure reactions with malonic acid and finally condensation with fluoroacetylation. The novel synthesized systems is preliminary evaluated as CDK2 for cell tumor division, compounds with sulfur and trifluoroacetyl exhibit a higher activity over standard and other synthesis compounds.

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