

Full Research Paper

## Synthesis and Anti-tumor Activities of Novel [1,2,4]triazolo[1,5-a]pyrimidines

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**Abstract:** A series of novel [1,2,4]triazolo[1,5-a]pyrimidine derivatives has been designed and synthesized in order to find novel anti-tumor compounds. The structures of all the compounds were confirmed by IR, <sup>1</sup>H-NMR, MS and elemental analysis. Their anti-tumor activities against cancer cell lines (HT-1080 and Bel-7402) were tested by the MTT method *in vitro*. Among them, compound **19** displayed the best anti-tumor activity with IC<sub>50</sub> values of 12.3 μM and 6.1 μM against Bel-7402 and HT-1080 cell lines respectively.

**Keywords:** [1,2,4]triazolo[1,5-a]pyrimidines, Synthesis, antitumor activities

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### Introduction

Purine analogs are widely used against various diseases, particularly cancer. The clinical application of 6-mercaptopurine [1] and thioguanine [2] in cancer treatment and the development of potent purine based CDK inhibitors, such as Purvalanols [3, 4], Olomoucine [3] and Roscovitine [5], together with other findings based on the purine scaffold, have largely inspired and directed parallel developments in the chemistry and anti-tumor research of related heterocyclic analogs, including pyrrolo-pyrimidines [6], pyrazolo-pyrimidines [7, 8], imidazo-pyridines [9], triazolo-pyrimidines [10], pyrazolo-pyridazines [11] and imidazo-pyrazines [12].

[1,2,4]Triazolo[1,5-a]pyrimidines, a subtype of purine bioisosteric analogs, were also reported to possess potential anti-tumor activities, especially those bearing functional groups at C-5, C-6 or C-7 positions [13-15]. However, substitutions at the C-2 position seemed to be less attractive. Recently,

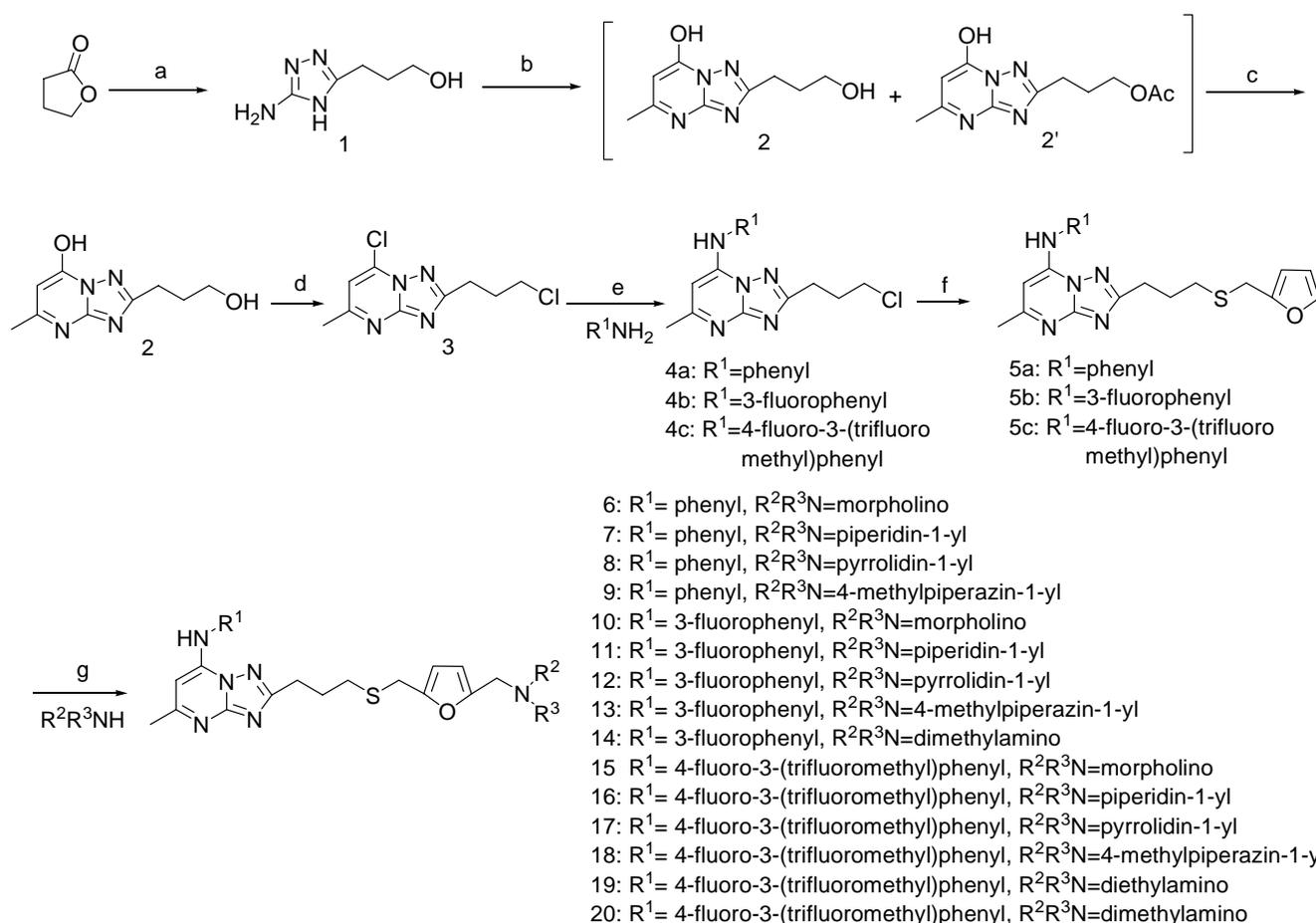
some [1,2,4]triazolo[1,5-a]pyrimidines bearing functional group at C-2 and C-7 positions, were disclosed for their good antiproliferative ability [16, 17], which greatly encouraged us to explore more potent analogs of such structures. Therefore, we carried out a series of modifications upon the [1,2,4]triazolo[1,5-a]pyrimidine scaffold by introducing functional groups into C-2 and C-7 positions. Herein, we report the synthesis and *in vitro* anti-tumor evaluation of a new series of 7-anilino-5-methyl-2-(3-((5-(substituted-aminomethyl)furan-2-yl)methylthio)propyl)[1,2,4]triazolo[1,5-a]pyrimidines (**6-20**).

## Results and Discussion

### Chemistry

The synthetic route for the target compounds is shown in **Scheme 1**.

**Scheme 1.** Synthesis of target compounds.



Reagents and conditions: a) aminoguanidine,  $\gamma$ -butyrolactone, Py, reflux, 10 h; b) ethyl acetoacetate, acetic acid, reflux, 30 h, c) methanolic ammonia, room temperature, 24 h; d) POCl<sub>3</sub>, reflux, 3 h; e) R<sup>1</sup>NH<sub>2</sub>, <sup>1</sup>PrOH, 50°C, 3 h; f) furan-2-ylmethanethiol, NaH, DMF, 50°C, 0.5 h; g) HCHO, R<sup>2</sup>R<sup>3</sup>NH, AcOH, 50°C, 4 h.

Commercially available  $\gamma$ -butyrolactone was first transformed into the substituted [1,2,4]triazole **1** with aminoguanidine carbonate in the presence of pyridine in 40% yield. Following the procedure reported by Okabe [18], condensation of **1** with ethyl acetoacetate was carried out in acetic acid at reflux to give a mixture of **2** and **2'**(the acetylated product of **2**), which further treated with methanolic

ammonia to give **2** in 88% yield. Subsequent treatment of **2** with phosphorus oxychloride afforded **3** in 94% yield. Displacement of the chloro group of **3** with various anilines provided the intermediate **4a-4c** in 87-93% yields.

Etherification of **4a-4c** with (furan-2-yl)methanethiol in the presence of sodium hydride provided intermediate **5a-5c**. Subsequent aminomethylation of **5a-5c** with various secondary amines and formaldehyde, followed by chromatographic purification gave the final products (**6-20**) in 45-80% yields.

#### Anticancer activities

All target compounds (**6-20**) were evaluated for their anti-tumor activity *in vitro* by the MTT method. The IC<sub>50</sub> values against Bel-7402 (Human Liver Cancer Cell Lines) and HT-1080 (Human Fibro Sarcoma Cell Lines) cell lines are summarized in **Table 1**.

**Table 1.** The anticancer activities of compounds **6-20**.

Compd.	IC <sub>50</sub> (μM)		Compd.	IC <sub>50</sub> (μM)	
	Bel-7402	HT-1080		Bel-7402	HT-1080
<b>6</b>	>300	>300	<b>14</b>	54.1	30.8
<b>7</b>	72.5	52.1	<b>15</b>	44.6	36.3
<b>8</b>	67.3	57.4	<b>16</b>	42.1	32.2
<b>9</b>	>300	237	<b>17</b>	13.9	28.4
<b>10</b>	>300	280	<b>18</b>	22.1	29.3
<b>11</b>	45.8	35.1	<b>19</b>	12.3	6.1
<b>12</b>	77.6	41.4	<b>20</b>	22.2	14.8
<b>13</b>	>300	261.9	cisplatin	35.5	22.7

**Table 1** shows that both substituents on the aniline ring and variations on 5"-furylmethyl of the side-chain have substantial influence on the anti-tumor activity. 3-Fluoro-phenylamino substituted series showed comparable or better anti-tumor activities than phenylamino substituted series (comparison of **7** and **11**, **8** and **12**). Moreover, introduction of 4-fluoro-3-(trifluoromethyl)phenylamino group into the C-7 position was found to be quite favorable for increasing anti-tumor activity (comparison of **8** and **17**, **14** and **20**). Among this series, compound **19** showed the best anti-tumor activity with IC<sub>50</sub> values of 12.3 μM and 6.1 μM against Bel-7402 and HT-1080 cell lines respectively, which was 4 times more potent than cisplatin. On the other hand, among the hydrophilic groups introduced into the 5"-furylmethyl of the side-chain at C-2 position of the scaffold, piperidinyl, pyrrolidinyl, diethylamino and dimethylamino groups rendered better anti-tumor activity, while morpholino, 4-methylpiperizinyl resulted in drastic decrease in anti-tumor potency (comparison of **6**, **9** and **7**, **8**). However, despite the negative effects of morpholino and 4-methylpiperizinyl substitutions, anti-tumor potency could be retained in the 4-fluoro-3-(trifluoromethyl)phenyl amino series as illustrated by the comparison of **6** and **15**, **13** and **18**, suggesting that the contribution of 4-fluoro-3-

(trifluoromethyl)phenyl amino groups to the potency might partly compensate the negative effect of morpholino and 4-methylpiperiziny substitution.

## Conclusions

In conclusion, a novel series of [1,2,4]triazolo[1,5-a]pyrimidines were synthesized and found to be active against tumor cell lines. Compounds with disubstituents on the aniline ring and piperidinyl, pyrrolidinyl, diethylamino or dimethylamino on the 5"-furylmethyl of the side-chain showed better anti-tumor activities than other series. Among this series, compound **19** showed the best anti-tumor activity and will be considered in a further study.

## Experimental Section

### General

Melting points were determined by the capillary tube method, and the thermometer was uncorrected. Mass spectra were obtained on an Agilent 1100 HPLC-MS instrument. <sup>1</sup>H-NMR spectra were run in DMSO-d<sub>6</sub>, CDCl<sub>3</sub>, with TMS at the internal standard, on a Bruker ARX-300 instrument operating at 300 MHz. IR spectra (KBr disks) were recorded on a Bruker IFS 55 instrument. Elemental analysis was performed with a Carlo-Erba 1106 Elemental analysis instrument.

### 5-amino-3-(3-hydroxypropyl)-4H-[1,2,4]triazole (**1**)

A mixture of aminoguanidine (65 g, 0.55 mol),  $\gamma$ -butyrolactone (43 g, 0.50 mol) and pyridine (900 mL) was heated to reflux for 10 h. The resultant mixture was concentrated and filtered to give a pale solid. The mass product was recrystallized from absolute ethanol (150 mL) to obtain **1** (28 g, 40%) as a white solid, m. p. 146-147 °C, (lit. 149-150 °C [19]). MS [MH<sup>+</sup>] (m/z): 142.1; <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) $\delta$ : 1.71 (pentad, 2H, CH<sub>2</sub>), 2.44 (t, 2H, *J* = 6.0 Hz, CH<sub>2</sub>), 3.41 (t, 2H, *J* = 6.2 Hz, CH<sub>2</sub>), 4.45 (s, 1H, OH), 5.55 (br s, 2H, NH<sub>2</sub>), 11.51 (br s, 1H, NH); Anal. calcd. for C<sub>5</sub>H<sub>10</sub>N<sub>4</sub>O: C 42.24, H 7.09, N 39.41; Found: C 42.01, H 7.01, N 39.23.

### 7-hydroxyl-2-(3-hydroxypropyl)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine (**2**)

A mixture of **1** (28 g, 0.20 mol), ethyl acetoacetate (30.8 g, 0.24 mol) and acetic acid (300 mL) was heated to reflux for 30 h and then concentrated, filtered to give a mixture of **2** and **2'** as a pale yellow solid. Then the solid was added into the saturated ammonia methanol (300 mL) and stirred at room temperature for 24 h. The mixture was evaporated and water was added, which was then acidified with dilute hydrochloride solution to pH 5-6, filtered and recrystallized from ethanol to give the product **2** (37 g, 88%), m. p. 204-206 °C. MS [MH<sup>+</sup>] (m/z): 208.1; <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>)  $\delta$ : 1.85 (pentad, 2H, CH<sub>2</sub>), 2.30 (s, 1H, CH<sub>3</sub>), 2.72 (t, 2H, *J* = 6.0 Hz, CH<sub>2</sub>), 3.45 (t, 2H, *J* = 6.1 Hz, CH<sub>2</sub>), 4.49 (br s, 1H, OH), 5.76 (s, 1H, C<sub>6</sub>-H), 12.98 (br s, 1H, C<sub>7</sub>-OH); Anal. calcd. for C<sub>9</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>: C 51.92, H 5.81, N 26.91; Found: C 51.86, H 5.68, N 26.79.

*7-chloro-2-(3-chloropropyl)-5-methyl-[1, 2, 4]triazolo[1,5-a]pyrimidine (3)*

A mixture of **2** (37 g, 0.18 mol) and phosphorus oxychloride (265 g, 1.70 mol) was heated to reflux for 3 h, and then was concentrated *in vacuo* to result a red oil, which was poured into water, and extracted with chloroform (250 mL×3). The organic layer was then washed with water three times, dried with anhydrous magnesium sulfate and concentrated to give **3** (41 g, 94%) as a yellow solid (LC purity: 96%, MS [MH<sup>+</sup>] (m/z): 245.2), which was directly used in next step without purification.

*General procedure for the synthesis of 7-anilino-5methyl-2-(3-chloroproyl)-[1,2,4]triazolo[1,5-a]pyrimidine (4a-4c)*

A mixture of R<sup>1</sup>NH<sub>2</sub> (44 mmol), **3** (10 g, 40 mmol) and isopropanol (100 mL) was heated at 50°C for 3 h. After cooling to room temperature and the following filtration, a yellow solid was obtained. Recrystallization of the solid from methanol gave **4a-4c** as slight yellow powder (87-93%).

*General procedure for the synthesis of 7-anilino-5-methyl-2-(3-(furan-2-ylmethylthio)propyl)-[1,2,4]triazolo [1,5-a]pyrimidine (5a-5c)*

Furan-2-ylmethanethiol (8.6 g, 75 mmol) was added dropwise into a suspension of NaH (1.8 g 75 mmol) and dry DMF (80 mL) at room temperature. After the addition, the mixture was stirred for 5 min, and then **4a-4c** (25 mmol) was added. The mixture was heated at 50°C for 30 min and was then poured into water. The brown oil which separated from water was triturated with diethyl ether, then filtered and recrystallized from ethyl acetate/cyclohexane to afford **5a-5c** as gray solid (80%-85%).

*General procedure for the synthesis of (6-20)*

Formaldehyde (0.6 g, 8 mmol) was added into the solution of R<sup>2</sup>R<sup>3</sup>NH (13 mmol) in acetic acid (20 mL). The mixture was stirred at 30°C for 10 min, and then **5a-5c** (5 mmol) was added. After stirring at 50°C for 4 h, the mixture was concentrated *in vacuo*. The residue was taken up in water (50 mL), basified with concentrated aqueous sodium hydroxide to pH 9-10, extracted with methylene dichloride, and then dried over magnesium sulfate. Evaporation of the solvent provided an oil residue, which was purified by chromatography to give the final products **6-20**.

*7-phenylamino-5-methyl-2-(3-((5-(morpholinomethyl)furan-2-yl)methylthio)propyl)-[1,2,4]triazolo [1,5-a]pyrimidine (6)*

Yield: 60%; m.p. 167-168 °C; MS [MH<sup>+</sup>] (m/z): 479.2; IR (KBr) cm<sup>-1</sup>: 3445.5 (ν<sub>NH</sub>), 2963.4 (ν<sub>CH3</sub>), 1609.3, 1576.3 (ν<sub>C=C</sub>, ν<sub>C=N</sub>), 1479.8 (δ<sub>CH2</sub>), 1328.5 (ν<sub>C-N</sub>). <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>)δ: 2.02 (pentad, 2H, CH<sub>2</sub>), 2.51 (s, 3H, CH<sub>3</sub>), 2.59 (m, 6H, 3×CH<sub>2</sub>), 2.88 (t, 2H, J = 7.2 Hz, CH<sub>2</sub>), 3.61 (br s, 4H, 2×CH<sub>2</sub>), 3.73 (s, 2H, CH<sub>2</sub>), 3.77 (s, 2H, CH<sub>2</sub>), 6.23 (d, 1H, J = 2.6 Hz, furyl-H), 6.27 (d, 1H, J = 2.7 Hz, furyl-H), 6.34 (s, 1H, C<sub>6</sub>-H), 7.29~7.48 (m, 5H, Ph-5×H); Anal. calcad. for C<sub>25</sub>H<sub>30</sub>N<sub>6</sub>O<sub>2</sub>S : C 62.74, H 6.32, N 17.56 Found: C 62.59 H 6.25, N 17.45.

7-phenylamino-5-methyl-2-(3-((5-(piperidin-1-ylmethyl)furan-2-yl)methylthio)propyl)-[1,2,4]triazolo[1,5-a]pyrimidine (7)

Yield: 64%; m.p. 169-170°C; MS [MH<sup>+</sup>] (m/z): 477.1; IR (KBr) cm<sup>-1</sup>: 3447.2 (ν<sub>NH</sub>), 2966.5 (ν<sub>CH3</sub>), 1609.1, 1575.9 (ν<sub>C=C</sub>, ν<sub>C=N</sub>), 1478.0 (δ<sub>CH2</sub>), 1329.6 (ν<sub>C-N</sub>). <sup>1</sup>H-NMR(CDCl<sub>3</sub>)δ: 1.42 (m, 2H, CH<sub>2</sub>), 1.64 (m, 4H, 2×CH<sub>2</sub>), 2.16 (pentad, 2H, CH<sub>2</sub>), 2.49 (br s, 4H, 2×CH<sub>2</sub>), 2.52 (s, 3H, CH<sub>3</sub>), 2.64 (t, 2H, J = 7.1 Hz, CH<sub>2</sub>), 2.99 (t, 2H, J = 7.3 Hz, CH<sub>2</sub>), 3.57 (s, 2H, CH<sub>2</sub>), 3.72 (s, 2H, CH<sub>2</sub>), 6.11 (d, 1H, J = 3.0 Hz, furyl-H), 6.14 (d, 1H, J = 3.0 Hz, furyl-H), 6.32 (s, 1H, C<sub>6</sub>-H), 7.35~7.50 (m, 5H, Ph-5×H); Anal. calcd. for C<sub>26</sub>H<sub>32</sub>N<sub>6</sub>OS : C 65.52, H 6.77, N 17.63 Found: C 65.44, H 6.63, N 17.60.

7-phenylamino-5-methyl-2-(3-((5-(pyrrolidin-1-ylmethyl)furan-2-yl)methylthio)propyl)-[1,2,4]triazolo[1,5-a]pyrimidine (8)

Yield: 64%; m.p. 162-164°C; MS [MH<sup>+</sup>] (m/z): 463.2; IR (KBr) cm<sup>-1</sup>: 3440.5 (ν<sub>NH</sub>), 2965.2 (ν<sub>CH3</sub>), 1611.5, 1576.1 (ν<sub>C=C</sub>, ν<sub>C=N</sub>), 1478.3 (δ<sub>CH2</sub>), 1329.8 (ν<sub>C-N</sub>). <sup>1</sup>H-NMR(CDCl<sub>3</sub>)δ: 1.82 (m, 4H, 2×CH<sub>2</sub>), 2.15 (pentad, 2H, CH<sub>2</sub>), 2.52 (s, 3H, CH<sub>3</sub>), 2.64 (t, 2H, J = 7.2 Hz, CH<sub>2</sub>), 2.69 (br s, 4H, 2×CH<sub>2</sub>), 2.99 (t, 2H, J = 7.3 Hz, CH<sub>2</sub>), 3.71 (s, 2H, CH<sub>2</sub>), 3.72 (s, 2H, CH<sub>2</sub>), 6.11 (d, 1H, J = 3.0 Hz, furyl-H), 6.17 (d, 1H, J = 2.9 Hz, furyl-H), 6.32 (s, 1H, C<sub>6</sub>-H), 7.35~7.50 (m, 5H, Ph-5×H); Anal. calcd. for C<sub>25</sub>H<sub>30</sub>N<sub>6</sub>OS : C 64.91, H 6.54, N 18.17 Found: C 64.79, H 6.43, N 18.11.

7-phenylamino-5-methyl-2-(3-((5-((4-methylpiperazin-1-yl)methyl)furan-2-yl)methylthio)propyl)-[1,2,4] triazolo[1,5-a]pyrimidine (9)

Yield: 73%; m.p. 176-179°C; MS [MH<sup>+</sup>] (m/z): 492.2; IR (KBr) cm<sup>-1</sup>: 3442.6 (ν<sub>NH</sub>), 2966.8 (ν<sub>CH3</sub>), 1609.3, 1576.8 (ν<sub>C=C</sub>, ν<sub>C=N</sub>), 1479.2 (δ<sub>CH2</sub>), 1329.0 (ν<sub>C-N</sub>). <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>)δ: 2.01 (pentad, 2H, CH<sub>2</sub>), 2.41 (s, 3H, CH<sub>3</sub>), 2.61 (t, 2H, J = 6.9 Hz, CH<sub>2</sub>), 2.74 (br s, 7H, CH<sub>3</sub>, 2×CH<sub>2</sub>), 3.17 (br s, 4H, 2×CH<sub>2</sub>), 3.72 (s, 2H, CH<sub>2</sub>), 3.77 (s, 2H, CH<sub>2</sub>), 6.22 (m, 2H, furyl-2×H), 6.36 (s, 1H, C<sub>6</sub>-H), 7.29~7.48 (m, 5H, Ph-5×H); Anal. calcd. for C<sub>26</sub>H<sub>33</sub>N<sub>7</sub>OS : C 63.52, H 6.77, N 19.94 Found: C 63.47, H 6.85, N 19.82.

7-(3-fluorophenylamino)-5-methyl-2-(3-((5-(morpholinomethyl)furan-2-yl)methylthio)propyl)-[1,2,4] triazolo[1,5-a]pyrimidine (10)

Yield: 80%; m.p. 173-175°C; MS [MH<sup>+</sup>] (m/z): 497.1; IR (KBr) cm<sup>-1</sup>: 3442.8 (ν<sub>NH</sub>), 2970.5 (ν<sub>CH3</sub>), 1608.0, 1575.2 (ν<sub>C=C</sub>, ν<sub>C=N</sub>), 1478.5 (δ<sub>CH2</sub>), 1329.4 (ν<sub>C-N</sub>). <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>)δ: 2.03 (pentad, 2H, CH<sub>2</sub>), 2.44 (s, 3H, CH<sub>3</sub>), 2.61 (t, 2H, J = 7.1 Hz, CH<sub>2</sub>), 2.70 (br s, 4H, 2×CH<sub>2</sub>), 2.90 (t, 2H, J = 7.3 Hz, CH<sub>2</sub>), 3.66 (br s, 4H, 2×CH<sub>2</sub>), 3.79 (s, 2H, CH<sub>2</sub>), 3.83 (s, 2H, CH<sub>2</sub>), 6.26 (d, 1H, J = 2.9 Hz, furyl-H), 6.33 (d, 1H, J = 2.8 Hz, furyl-H), 6.52 (s, 1H, C<sub>6</sub>-H), 7.13 (dd, 1H, J<sub>FH</sub>=8.4 Hz, J<sub>HH</sub>=7.7 Hz, Ph-4H), 7.34 (br d, 1H, J<sub>FH</sub>=7.7 Hz, Ph-2H), 7.34 (br d, 1H, J<sub>HH</sub>=7.7 Hz, Ph-6H), 7.50 (dd, 1H, J<sub>1</sub>=7.8 Hz, J<sub>2</sub>=7.7 Hz, Ph-5H); Anal. calcd. for C<sub>25</sub>H<sub>29</sub>FN<sub>6</sub>O<sub>2</sub>S : C 55.28, H 5.89, N 16.92 Found: C 55.21, H 5.78, N 16.79.

7-(3-fluorophenylamino)-5-methyl-2-(3-((5-(piperidin-1-ylmethyl)furan-2-yl)methylthio)propyl)-[1,2,4] triazolo[1,5-a]pyrimidine (**11**)

Yield: 68%; m.p. 170-172 °C; MS [MH<sup>+</sup>] (*m/z*): 495.1; IR (KBr) cm<sup>-1</sup>: 3444.5 (ν<sub>NH</sub>), 2963.5 (ν<sub>CH3</sub>), 1609.5, 1576.5 (ν<sub>C=C</sub>, ν<sub>C=N</sub>), 1479.8 (δ<sub>CH2</sub>), 1329.1 (ν<sub>C-N</sub>). <sup>1</sup>H-NMR(DMSO-*d*<sub>6</sub>)δ: 1.48 (br s, 2H, CH<sub>2</sub>), 1.71 (br s, 2H, 2×CH<sub>2</sub>), 2.02 (pentad, 2H, CH<sub>2</sub>), 2.45 (s, 3H, CH<sub>3</sub>), 2.63 (t, 2H, *J* = 7 Hz, CH<sub>2</sub>), 2.91 (t, 2H, *J* = 7.1 Hz, CH<sub>2</sub>), 3.03 (br s, 4H, 2×CH<sub>2</sub>), 3.82 (s, 2H, CH<sub>2</sub>), 4.26 (s, 2H, CH<sub>2</sub>), 6.35 (br s, 1H, furyl-H), 6.53 (br s, 2H, C<sub>6</sub>-H, furyl-H), 7.14 (dd, 1H, *J*<sub>FH</sub>=8.5 Hz, *J*<sub>HH</sub>=7.7 Hz, Ph-4H), 7.34 (br d, 1H, *J*<sub>FH</sub>=7.9 Hz, Ph-2H), 7.34 (br d, 1H, *J*<sub>HH</sub>=7.9 Hz, Ph-6H), 7.52 (dd, 1H, *J*<sub>1</sub>=7.7 Hz, *J*<sub>2</sub>=7.7 Hz, Ph-5H); Anal. calcad. for C<sub>26</sub>H<sub>31</sub>FN<sub>6</sub>OS : C 63.13, H 6.32, N 16.99 Found: C 63.05, H 6.21, N 16.88.

7-(3-fluorophenylamino)-5-methyl-2-(3-((5-(pyrrolidin-1-ylmethyl)furan-2-yl)methylthio)propyl)-[1,2,4] triazolo[1,5-a]pyrimidine (**12**)

Yield: 65%; m.p. 166-168 °C; MS [MH<sup>+</sup>] (*m/z*): 481.1; IR (KBr) cm<sup>-1</sup>: 3442.8 (ν<sub>NH</sub>), 2968.5 (ν<sub>CH3</sub>), 1610.2, 1574.2 (ν<sub>C=C</sub>, ν<sub>C=N</sub>), 1478.2 (δ<sub>CH2</sub>), 1328.9 (ν<sub>C-N</sub>). <sup>1</sup>H-NMR(CDCl<sub>3</sub>)δ: 1.82 (m, 4H, 2×CH<sub>2</sub>), 2.14 (pentad, 2H, CH<sub>2</sub>), 2.55 (s, 3H, CH<sub>3</sub>), 2.64 (t, 2H, *J* = 7.2 Hz, CH<sub>2</sub>), 2.69 (br s, 4H, 2×CH<sub>2</sub>), 2.99 (t, 2H, *J* = 7.2 Hz, CH<sub>2</sub>), 3.71 (s, 4H, 2×CH<sub>2</sub>), 6.11 (br s, 1H, furyl-H), 6.16 (br s, 1H, furyl-H), 6.38 (s, 1H, C<sub>6</sub>-H), 7.03 (dd, 1H, *J*<sub>FH</sub>=8.1 Hz, *J*<sub>HH</sub>=7.0 Hz, Ph-4H), 7.14 (br d, 1H, *J*<sub>FH</sub>=7.1 Hz, Ph-2H), 7.14 (br d, 1H, *J*<sub>HH</sub>=7.1 Hz, Ph-6H), 7.45 (dd, 1H, *J*<sub>1</sub>=7.2 Hz, *J*<sub>2</sub>=7.0 Hz, Ph-5H); Anal. calcad. for C<sub>25</sub>H<sub>29</sub>FN<sub>6</sub>OS : C 62.48, H 6.08, N 17.49 Found: C 62.38, H 5.99, N 17.41.

7-(3-fluorophenylamino)-5-methyl-2-(3-((5-((4-methylpiperazin-1-yl)methyl)furan-2-yl)methylthio)propyl)-[1,2,4]triazolo[1,5-a]pyrimidine (**13**)

Yield: 77%; m.p. 179-180 °C; MS [MH<sup>+</sup>] (*m/z*): 510.2; IR (KBr) cm<sup>-1</sup>: 3445.1 (ν<sub>NH</sub>), 2967.8 (ν<sub>CH3</sub>), 1608.5, 1575.9 (ν<sub>C=C</sub>, ν<sub>C=N</sub>), 1479.5 (δ<sub>CH2</sub>), 1329.1 (ν<sub>C-N</sub>). <sup>1</sup>H-NMR(DMSO-*d*<sub>6</sub>)δ: 2.02 (pentad, 2H, CH<sub>2</sub>), 2.43 (s, 3H, CH<sub>3</sub>), 2.57~2.62 (m, 6H, 3×CH<sub>2</sub>), 2.73 (s, 3H, CH<sub>3</sub>), 2.89 (t, 2H, *J* = 6.9 Hz, CH<sub>2</sub>), 3.16 (br s, 4H, 2×CH<sub>2</sub>), 3.56 (s, 2H, CH<sub>2</sub>), 3.76 (s, 2H, CH<sub>2</sub>), 6.22 (m, 2H, furyl-2×H), 6.51 (s, 1H, C<sub>6</sub>-H), 7.12 (dd, 1H, *J*<sub>FH</sub>=8.6 Hz, *J*<sub>HH</sub>=7.5 Hz, Ph-4H), 7.33 (br d, 1H, *J*<sub>FH</sub>=7.8 Hz, Ph-2H), 7.33 (br d, 1H, *J*<sub>HH</sub>=7.8 Hz, Ph-6H), 7.51 (dd, 1H, *J*<sub>1</sub>=7.5 Hz, *J*<sub>2</sub>=7.5 Hz, Ph-5H); Anal. calcad. for C<sub>26</sub>H<sub>32</sub>FN<sub>7</sub>OS : C 61.27, H 6.33, N 19.24 Found: C 61.15, H 6.25, N 19.12.

7-(3-fluorophenylamino)-5-methyl-2-(3-((5-((dimethylamino)methyl)furan-2-yl)methylthio)propyl)-[1,2,4]triazolo[1,5-a]pyrimidine (**14**)

Yield: 52%; m.p. 156-157 °C; MS [MH<sup>+</sup>] (*m/z*): 455.2; IR (KBr) cm<sup>-1</sup>: 3443.5 (ν<sub>NH</sub>), 2964.5 (ν<sub>CH3</sub>), 1608.2, 1575.4 (ν<sub>C=C</sub>, ν<sub>C=N</sub>), 1479.8 (δ<sub>CH2</sub>), 1329.5 (ν<sub>C-N</sub>). <sup>1</sup>H-NMR(CDCl<sub>3</sub>)δ: 2.15 (pentad, 2H, CH<sub>2</sub>), 2.30 (s, 6H, 2×CH<sub>3</sub>), 2.55 (s, 3H, CH<sub>3</sub>), 2.64 (t, 2H, *J* = 7.1 Hz, CH<sub>2</sub>), 2.99 (t, 2H, *J* = 7.2 Hz, CH<sub>2</sub>), 3.51 (s, 2H, CH<sub>2</sub>), 3.72 (s, 2H, CH<sub>2</sub>), 6.13 (br s, 2H, furyl-2×H), 6.40 (s, 1H, C<sub>6</sub>-H), (dd, 1H, *J*<sub>FH</sub>=8.3 Hz, *J*<sub>HH</sub>=7.1 Hz, Ph-4H), 7.15 (br d, 1H, *J*<sub>FH</sub>=7.3 Hz, Ph-2H), 7.15 (br d, 1H, *J*<sub>HH</sub>=7.3 Hz, Ph-6H), 7.45 (dd, 1H, *J*<sub>1</sub>=7.2 Hz, *J*<sub>2</sub>=7.1 Hz, Ph-5H); Anal. calcad. for C<sub>23</sub>H<sub>27</sub>FN<sub>6</sub>OS : C 60.77, H 5.99, N 18.49 Found: C 60.69, H 5.78, N 18.38.

7-(4-fluoro-3-(trifluoromethyl)phenylamino)-5-methyl-2-(3-((5-(morpholinomethyl)furan-2-yl)methylthio)propyl)-[1,2,4]triazolo[1,5-a]pyrimidine (**15**)

Yield: 75%; m.p. 190-192 °C; MS [MH<sup>+</sup>] (*m/z*): 565.1; IR (KBr) cm<sup>-1</sup>: 3446.5 (ν<sub>NH</sub>), 2870.3 (ν<sub>CH3</sub>), 1622.3, 1581.2, 1505.3 (ν<sub>C=C</sub>, ν<sub>C=N</sub>), 1478.1 (δ<sub>CH2</sub>), 1323.5 (ν<sub>C-N</sub>). <sup>1</sup>H-NMR(DMSO-*d*<sub>6</sub>)δ: 2.02 (pentad, 2H, CH<sub>2</sub>), 2.42 (s, 3H, CH<sub>3</sub>), 2.61 (t, 2H, *J* = 7.2 Hz, CH<sub>2</sub>), 2.75 (br s, 4H, 2×CH<sub>2</sub>), 2.90 (t, 2H, *J* = 7.1 Hz, CH<sub>2</sub>), 3.11 (br s, 4H, 2×CH<sub>2</sub>), 3.65 (br s, 2H, CH<sub>2</sub>), 3.79 (br s, 2H, CH<sub>2</sub>), 6.26 (d, 1H, *J* = 3.0 Hz, furyl-H), 6.33 (d, 1H, *J* = 2.9 Hz, furyl-H), 6.41 (s, 1H, C<sub>6</sub>-H), 7.64 (dd, 1H, *J*<sub>FH</sub> = 10.0 Hz, *J*<sub>HH</sub> = 9.5 Hz, Ph-5H), 7.83 (m, 2H, Ph-2, 6-2×H); Anal. calcd. for C<sub>26</sub>H<sub>28</sub>F<sub>4</sub>N<sub>6</sub>O<sub>2</sub>S : C 55.31, H 5.00, N 14.88 Found: C 55.19, H 4.79, N 14.72.

7-(4-fluoro-3-(trifluoromethyl)phenylamino)-5-methyl-2-(3-((5-(piperidin-1-ylmethyl)furan-2-yl)methylthio)propyl)-[1,2,4]triazolo[1,5-a]pyrimidine (**16**)

Yield: 54%; m.p. 182-183 °C; MS [MH<sup>+</sup>] (*m/z*): 563.1; IR (KBr) cm<sup>-1</sup>: 3443.6 (ν<sub>NH</sub>), 2953.7 (ν<sub>CH3</sub>), 1620.4, 1575.8, 1505.3 (ν<sub>C=C</sub>, ν<sub>C=N</sub>), 1476.7 (δ<sub>CH2</sub>), 1323.0 (ν<sub>C-N</sub>). <sup>1</sup>H-NMR(DMSO-*d*<sub>6</sub>)δ: 1.44 (m, 2H, CH<sub>2</sub>), 1.66 (m, 4H, 2×CH<sub>2</sub>), 2.02 (pentad, 2H, CH<sub>2</sub>), 2.41 (s, 3H, CH<sub>3</sub>), 2.61 (t, 2H, *J* = 6.9 Hz, CH<sub>2</sub>), 2.89 (t, 2H, *J* = 7.1 Hz, CH<sub>2</sub>), 3.00 (br s, 4H, 2×CH<sub>2</sub>), 3.79 (s, 2H, CH<sub>2</sub>), 4.09 (s, 2H, CH<sub>2</sub>), 6.30 (br s, 1H, furyl-H), 6.40 (s, 1H, C<sub>6</sub>-H), 6.47 (br s, 1H, furyl-H), 7.63 (dd, 1H, *J*<sub>FH</sub> = 9.9 Hz, *J*<sub>HH</sub> = 9.0 Hz, Ph-5H), 7.79~7.83 (m, 2H, Ph-2, 6-2×H); Anal. calcd. for C<sub>27</sub>H<sub>30</sub>F<sub>4</sub>N<sub>6</sub>OS : C 57.64, H 5.37, N 14.94 Found: C 57.49, H 5.15, N 14.87.

7-(4-fluoro-3-(trifluoromethyl)phenylamino)-5-methyl-2-(3-((5-(pyrrolidin-1-ylmethyl)furan-2-yl)methylthio)propyl)-[1,2,4]triazolo[1,5-a]pyrimidine (**17**)

Yield: 54%; m.p. 179-180 °C; MS [MH<sup>+</sup>] (*m/z*): 549.1; IR (KBr) cm<sup>-1</sup>: 3445.1 (ν<sub>NH</sub>), 2953.7 (ν<sub>CH3</sub>), 1620.4, 1505.3 (ν<sub>C=C</sub>, ν<sub>C=N</sub>), 1479.5 (δ<sub>CH2</sub>), 1323.0 (ν<sub>C-N</sub>). <sup>1</sup>H-NMR(CDCl<sub>3</sub>)δ: 1.81 (m, 4H, 2×CH<sub>2</sub>), 2.13 (pentad, 2H, CH<sub>2</sub>), 2.53 (s, 3H, CH<sub>3</sub>), 2.62 (t, 2H, *J* = 7.2 Hz, CH<sub>2</sub>), 2.67 (br s, 4H, 2×CH<sub>2</sub>), 2.99 (t, 2H, *J* = 7.3 Hz, CH<sub>2</sub>), 3.71 (s, 2H, CH<sub>2</sub>), 3.72 (s, 2H, CH<sub>2</sub>), 6.10 (d, 1H, *J* = 3.1 Hz, furyl-H), 6.14 (d, 1H, *J* = 3.0 Hz, furyl-H), 6.16 (s, 1H, C<sub>6</sub>-H), 7.36 (dd, 1H, *J*<sub>FH</sub> = 9.2 Hz, *J*<sub>HH</sub> = 9.0 Hz, Ph-5H), 7.61 (m, 2H, Ph-2, 6-2×H); Anal. calcd. for C<sub>26</sub>H<sub>28</sub>F<sub>4</sub>N<sub>6</sub>OS : C 56.92, H 5.14, N 15.32 Found: C 56.85, H 5.21, N 15.18.

7-(4-fluoro-3-(trifluoromethyl)phenylamino)-5-methyl-2-(3-((5-((4-methylpiperazin-1-yl)methyl)furan-2-yl)methylthio)propyl)-[1,2,4]triazolo[1,5-a]pyrimidine (**18**)

Yield: 79%; m.p. 179-180 °C; MS [MH<sup>+</sup>] (*m/z*): 578.0; IR (KBr) cm<sup>-1</sup>: 3444.7 (ν<sub>NH</sub>), 2965.7 (ν<sub>CH3</sub>), 1610.2, 1575.8 (ν<sub>C=C</sub>, ν<sub>C=N</sub>), 1478.7 (δ<sub>CH2</sub>), 1329.5 (ν<sub>C-N</sub>). <sup>1</sup>H-NMR(DMSO-*d*<sub>6</sub>)δ: 2.02 (pentad, 2H, CH<sub>2</sub>), 2.41 (s, 3H, CH<sub>3</sub>), 2.59 (t, 2H, *J* = 7.1 Hz, CH<sub>2</sub>), 2.72 (br s, 7H, CH<sub>3</sub>, 2×CH<sub>2</sub>), 2.89 (t, 2H, *J* = 7.1 Hz, CH<sub>2</sub>), 3.15 (br s, 4H, 2×CH<sub>2</sub>), 3.55 (s, 2H, CH<sub>2</sub>), 3.76 (s, 2H, CH<sub>2</sub>), 6.21 (m, 2H, furyl-2×H), 6.40 (s, 1H, C<sub>6</sub>-H), 7.63 (dd, 1H, *J*<sub>FH</sub> = 9.9 Hz, *J*<sub>HH</sub> = 9.2 Hz, Ph-5H), 7.83 (m, 2H, Ph-2, 6-2×H); Anal. calcd. for C<sub>27</sub>H<sub>31</sub>F<sub>4</sub>N<sub>7</sub>OS : C 56.14, H 5.41, N 16.97 Found: C 56.21, H 5.29, N 16.86.

7-(4-fluoro-3-(trifluoromethyl)phenylamino)-5-methyl-2-(3-((5-((diethylamino)methyl)furan-2-yl)methylthio)propyl)-[1,2,4]triazolo[1,5-a]pyrimidine (**19**)

Yield: 45%; m.p. 172-174 °C; MS [MH<sup>+</sup>] (*m/z*): 551.2; IR (KBr) cm<sup>-1</sup>: 3445.2 (ν<sub>NH</sub>), 2970.1 (ν<sub>CH3</sub>), 1575.6, (ν<sub>C=C</sub>, ν<sub>C=N</sub>), 1479.5 (δ<sub>CH2</sub>), 1329.5 (ν<sub>C-N</sub>). <sup>1</sup>H-NMR(CDCl<sub>3</sub>)δ: 1.11 (t, 6H, *J* = 6.9 Hz, 2×CH<sub>3</sub>), 2.15 (pentad, 2H, CH<sub>2</sub>), 2.54 (s, 3H, CH<sub>3</sub>), 2.61 (m, 6H, 3×CH<sub>2</sub>), 2.99 (t, 2H, *J* = 7.4 Hz, CH<sub>2</sub>), 3.72 (s, 4H, 2×CH<sub>2</sub>), 6.12 (m, 2H, furyl-2H), 6.18 (s, 1H, C<sub>6</sub>-H), 7.36 (dd, 1H, *J*<sub>FH</sub>=9.0 Hz, *J*<sub>HH</sub>=9.0 Hz, Ph-5H), 7.64 (m, 2H, Ph-2, 6-2×H); Anal. calcad. for C<sub>26</sub>H<sub>30</sub>F<sub>4</sub>N<sub>6</sub>OS : C 56.71, H 5.49, N 15.26 Found: C 56.57, H 5.39, N 15.12.

7-(4-fluoro-3-(trifluoromethyl)phenylamino)-5-methyl-2-(3-((5-((dimethylamino)methyl)furan-2-yl)methylthio)propyl)-[1,2,4]triazolo[1,5-a]pyrimidine (**20**)

Yield: 47%; m.p. 166-168 °C; MS [MH<sup>+</sup>] (*m/z*): 523.1; IR (KBr) cm<sup>-1</sup>: 3443.9 (ν<sub>NH</sub>), 2966.3 (ν<sub>CH3</sub>), 1609.5, 1575.3 (ν<sub>C=C</sub>, ν<sub>C=N</sub>), 1479.8 (δ<sub>CH2</sub>), 1328.2 (ν<sub>C-N</sub>). <sup>1</sup>H-NMR(CDCl<sub>3</sub>)δ: 2.14 (pentad, 2H, CH<sub>2</sub>), 2.33 (s, 6H, 2×CH<sub>3</sub>), 2.54 (s, 3H, CH<sub>3</sub>), 2.63 (t, 2H, *J* = 7.1 Hz, CH<sub>2</sub>), 2.99 (t, 2H, *J* = 7.2 Hz, CH<sub>2</sub>), 3.56 (s, 2H, CH<sub>2</sub>), 3.72 (s, 2H, CH<sub>2</sub>), 6.13 (br s, 1H, furyl-H), 6.17 (br s, 2H, furyl-H, C<sub>6</sub>-H), 7.36 (dd, 1H, *J*<sub>FH</sub>=9.0 Hz, *J*<sub>HH</sub>=8.7 Hz, Ph-5H), 7.64 (m, 2H, Ph-2, 6-2×H); Anal. calcad. for C<sub>24</sub>H<sub>26</sub>F<sub>4</sub>N<sub>6</sub>OS : C 55.16, H 5.01, N 16.08 Found: C 55.03, H 4.92, N 16.15.

### Pharmacology

The anticancer activities of compounds **6-20** were evaluated *in vitro* on Bel-7402 (Human Liver Cancer cell lines) and HT-1080 (Human Fibro Sarcoma cell lines) by measuring cell viability by the MTT method, with cisplatin as the positive control. The cells were seeded in RPM I 1640 medium (100 μL) in a 96-well plate at a concentration of 4000 cells per well. After culturing for 12 h at 37 °C and 5% CO<sub>2</sub>, cells were incubated with various concentrations of the samples for 24 h. MTT was added at a terminal concentration of 5 μg/mL and incubated with the cells for 4 h. The formazan crystals were dissolved in DMSO (100 μL) in each well and the optical density was measured at 492 nm (for the absorbance of MTT formazan) and 630 nm (for the reference wavelength). The IC<sub>50</sub> was calculated using the Bacus Laboratories Incorporated Slide Scanner (Bliss) software. Each compound was tested in triplicate at every concentration.

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*Sample Availability:* Samples of the compounds mentioned above are available from authors

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