Synthesis and Cytotoxicity Studies of Novel [1,2,4]Triazolo[1,5-*a*]pyrimidine-7-amines

Xin ZHAI, Yan-Fang ZHAO, Ya-Jing LIU, Yong ZHANG, Feng-Qiang XUN, Jun LIU, and Ping GONG*

Key Lab of New Drugs Design and Discovery of Liaoning Province, School of Pharmaceutical Engineering, Shenyang Pharmaceutical University; 110016, Shenyang, P. R. China.

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A series of novel *N*-anilino-5-methyl-2-(3-(5-(alkylaminomethyl)furan-2-yl-methylthio)propyl)-[1,2,4]triazolo-[1,5-*a*]pyrimidine-7-amine derivatives were synthesized and evaluated for their *in vitro* cytotoxicity against two cancer cell lines, Bel-7402 and HT-1080. Compounds 9, 14, 19 and 23 possessed marked cytotoxicity, especially 23 (with IC_{50} values of 15.0 μM and 7.8 μM against Bel-7402 and HT-1080 cell lines, respectively), which had emerged as lead compound. The activity was found to depend strongly on substitution pattern of the side chains at C-2 position, and 4-triflouromethylanilino substituent at C-7 position was an option for anticancer potency.

Key words [1,2,4]triazolo[1,5-*a*]pyrimidine-7-amine; synthesis; cytotoxicity

Cancer is a disease of striking significance in the world today. It represents the second leading cause of human mortality after cardiovascular diseases. In order to develop more effective and reliable anticancer agents, a large number of compounds bearing nitrogen-containing fused heterocyclic skeletons, such as 4-anilinoquinazolines, pyrazolopyrimidines, triazolopyrimidines, pyrrolopyrimidines, pyrazolopyridazines and imidazopyrazines, have been discovered particularly and many of them exhibited excellent anticancer activity.[1—5)]

Recently, [1,2,4]triazolo[1,5-*a*]pyrimidines have aroused increasing attentions from chemical and biological view points since they were proved to be the promising anticancer agents with a unique mechanism of promoting tubulin polymerization[1,6)] as well as the mechanism of cyclin-dependent kinases-2 inhibition.[7)] It was not until recently that some *N*-anilino-[1,2,4]triazolo[1,5-*a*]pyrimidine-7-amine analogs bearing functional groups at C-2 position were reported for their good cytotoxicity,[8,9)] which have largely inspired us and directed parallel developments in the chemistry and cytotoxicity studies of these related derivatives.[10)] With an aim to produce [1,2,4]triazolo[1,5-*a*]pyrimidine-7-amine derivatives endowed with improved solubility and better biological interactions, a series of new molecules containing nitrogen atoms in the terminal of side chain at C-2 position on the scaffold were designed and synthesized. Further modifications were performed by introducing various alkylaminomethyl functional groups into C-5 position of furan ring in the side chain and substituted anilines into C-7 position in the [1,2,4]triazolo[1,5-*a*]pyrimidine core.

In this paper, we would like to report the synthesis and cytotoxicity of a series of novel *N*-anilino-5-methyl-2-(3-(5-(alkylaminomethyl)furan-2-yl-methylthio)propyl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-7-amines represented by the general structure of **7**—**24** in Fig. 1.

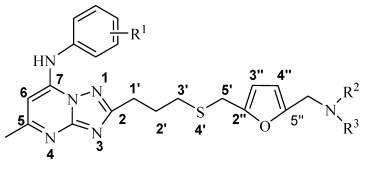


Fig. 1. Structure of **7**—**24**

Results and Discussion

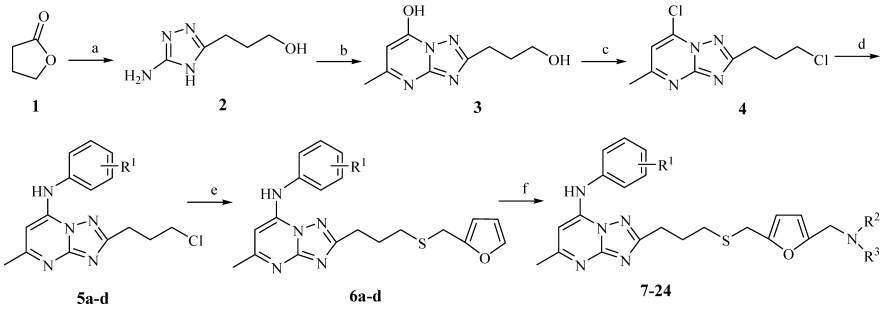
Chemistry The title [1,2,4]triazolo[1,5-*a*]pyrimidine-7-amine derivatives **7**—**24** were synthesized as shown in Chart 1. Commercially available γ-butyrolactone was treated with aminoguanidine carbonate in pyridine to give the 5-amino-3-(3-hydroxypropyl)-4*H*-[1,2,4]-triazole **2** in 40% yield exclusively. As described in literature,[11)] cyclization of **2** with ethyl acetoacetate was carried out in acetic acid at reflux to afford the 3′-hydroxy acetylized intermediate, which was converted to hydroxylate **3** by further reaction with ammonia in methanol in 88% yield. Subsequent treatment of **3** with excess phosphorus oxychloride afforded chloro derivative **4**, a key synthon for further elaboration, in 94% yield. Coupling reaction of **4** with various anilines provided the intermediates **5a**—**d** in 87—93% yields after recrystallization. By etherification of **5a**—**d** with (furan-2-yl)methanethiol in the presence of an excess amount of sodium hydride in dried DMF, the key intermediates **6a**—**d** were obtained.

To further investigate the influence on cytotoxicity of polar chains that facilitate the solubility and the biological interactions, we introduced various Mannich bases into the C-5 position of furan ring in the side chain by reaction of compounds **6a**—**d** with appropriate secondary amines and formaldehyde, followed by column chromatographic purification to afford the desired compounds **7**—**24** in 45—80% yields.

Cytotoxicity and Discussion Cytotoxicity of the synthesized compounds **7**—**24** against Bel-7402 (Human Liver Cancer) and HT-1080 (Human Fibro Sarcoma) cell lines were determined by MTT assay. Cisplatin as positive control, and the results expressed as IC_{50} are summarized in Table 1.

As shown in Table 1, most of the evaluated compounds exhibited good cytotoxicity, and compounds **9**, **14**, **19** and **23**, bearing pyrrolidinylmethyl groups at C-5 position on furyl moieties, possessed even better *in vitro* cytotoxicity against both two tumor cell lines than cisplatin. Among all the tested compounds, **23** was of particular interest because of its marked activity (IC_{50} values of 15.0 μM and 7.8 μM against Bel-7402 and HT-1080 cell lines, respectively) and had emerged as lead compound.

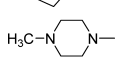
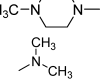
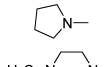
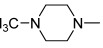
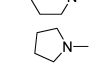
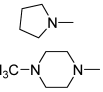
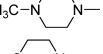
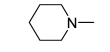
* To whom correspondence should be addressed. e-mail: gongpinggp@126.com



Reagents and conditions: (a) aminoguanidine, pyridine, reflux, 10 h; (b) i) ethyl acetoacetate, acetic acid, reflux, 30 h; ii) methanol, ammonia, r.t., 24 h; (c) $POCl_3$, reflux, 3 h; (d) R^1-substituted aniline, i-PrOH, 50 °C, 3 h; (e) (furan-2-yl)methanethiol, NaH, DMF, 50 °C, 0.5 h; (f) HCHO, R^2R^3NH, AcOH, 50 °C, 4 h.

Chart 1. Synthesis of Target Compounds **7**—**24**

Table 1. The Substituents and Cytotoxicity of Compounds **7**—**24**

Compd.	R^1	NR^2R^3	IC_{50} (μM)	
			Bel-7402	HT-1080
7	3-Cl		56.0	48.6
8	3-Cl		28.3	23.1
9	3-Cl		29.0	13.1
10	3-Cl		71.2	29.8
11	3-Cl		30.3	25.6
12	3-Cl, 4-F		56.7	71.2
13	3-Cl, 4-F		27.3	27.0
14	3-Cl, 4-F		33.5	18.3
15	3-Cl, 4-F		34.7	25.8
16	3-Cl, 4-F		43.6	20.9
17	4-OCF_3		>300	182.9
18	4-OCF_3		35.6	20.1
19	4-OCF_3		19.3	9.0
20	4-OCF_3		42.6	29.2
21	4-CF_3		40.0	104.1
22	4-CF_3		22.3	12.0
23	4-CF_3		15.0	7.8
24	4-CF_3		35.7	30.1
Cisplatin			35	22

The data indicated that 3-(5-(alkylaminomethyl)ffuran-2-yl-methylthio)propyl side chain at C-2 position on [1,2,4]triazolo[1,5-*a*]pyrimidine scaffold had a very important effect on anti-tumor activity, and variations of the terminal substituents at C-5 position of furan ring would change the activity dramatically. Generally, pyrrolidinyl was the most potent substituent which produced the compounds with excellent activity, as demonstrated by **9**, **14**, **19** and **23**. In addition, piperidinyl and dimethylamino also had good contributions to the anti-tumor activity, while morpholinyl and 4-methylpiperizinyl resulted in dramatic decrease or abolishment in anti-tumor potency. A case in point is that compound **17** with morpholinylmethyl group at C-5 position of furan ring almost abolished the activity, whereas **19** bearing pyrrolidinylmethyl substituent provided a 2-fold increase in potency against two tumor cell lines relative to the positive control. On the other hands, 4-triflouromethylanilino substituent at C-7 position on the skeleton was an option for anticancer potency, as **21**—**24** showed more potent cytotoxicity superior to the corresponding compounds bearing 3-chloroanilino, 3-chloro-4-fluoroanilino and 4-trifluoromethoxyanilino substituents at C-7 position. Furthermore, all of the compounds, except for **12** and **21**, were more potent on the HT-1080 cells than on the Bel-7402 cells (about 2-fold in the case of **9**, **10**, **14**, **16**, **19**, **20**, **23**).

Conclusion

We reported the synthesis and evaluation of cytotoxic activity of novel [1,2,4]triazolo[1,5-*a*]pyrimidine-7-amine derivatives. Among the tested compounds, **23** is considered promising lead for further structural modifications. The activity was found to depend strongly on substitution pattern of the side chains at C-2 position, so eventually the activity of the compounds could be tailored by further structural modifications. The results of this study will provide useful information for the design of novel molecules as cytotoxic agents.

Experimental

Melting points were determined by the capillary tube method and were uncorrected. Infrared spectra were obtained from KBr pellets on a Bruker IFS 55 instrument. ^{1}H-NMR spectra were recorded at 300 MHz on a Bruker ARX-300 instrument and chemical shifts are reported in parts per million (δ) downfield from TMS as the internal standard. Mass spectra were carrided out with an Agilent 1100 HPLC-MS instrument. Elemental analyses were performed with a Carlo-Erba 1106 analyzer. All reagents and solvents were commercially available unless otherwise indicated.

5-Amino-3-(3-hydroxypropyl)-4*H*-[1,2,4]triazole (2) A mixture of aminoguanidine (65 g, 0.55 mol) and γ-butyrolactone (43 g, 0.50 mol) in pyridine (900 ml) was stirred for 10 h at reflux. The solvent was evaporated under vacuum and the resultant mixture was filtered to give a pale solid. The mass product was recrystallized from absolute ethanol (150 ml) and dried to give 28 g (40%) of **2** as a white solid, mp 147—148 °C (lit. 149—150 °C[12]). ^{1}H-NMR (DMSO-d_6) δ: 1.71 (2H, m, $C_{2'}$-CH_2), 2.44 (2H, t, J=6.0 Hz, $C_{1'}$-CH_2), 3.41 (2H, t, J=6.2 Hz, $C_{3'}$-CH_2), 4.45 (1H, s, OH), 5.55 (2H, br s, NH_2), 11.51 (1H, br s, NH). MS *m/z*: 142.1 (M^+); *Anal.* Calcd for $C_5H_{10}N_4O$: 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 (3) A mixture of **2** (28 g, 0.20 mol) and ethyl acetoacetate (30.8 g, 0.24 mol) in acetic acid (300 ml) was stirred for 30 h at reflux. Acetic acid was evaporated under vacuum and the resultant mixture was filtered. The resulting off-white solid was then added into the saturated ammonia methanol (300 ml) and stirred at room temperature for 24 h. The mixture was evaporated and water (400 ml) was added, which was then acidified with dilute hy-

drochloride solution to pH 5—6. The resulting precipitate was filtered and recrystallized from ethanol to give the product **3** (37 g, 88%), mp 204—206 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.85 (2H, m, $C_{2'}$-CH_2), 2.30 (3H, s, CH_3), 2.72 (2H, t, J=6.0 Hz, $C_{1'}$-CH_2), 3.45 (2H, t, J=6.1 Hz, $C_{3'}$-CH_2), 4.49 (1H, br s, OH), 5.76 (1H, s, C_6-H), 12.98 (1H, br s, C_7-OH). MS *m/z*: 208.1 (M^+); *Anal.* Calcd for $C_9H_{12}N_4O_2$: 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 (4) A mixture of **3** (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 vacuum 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 **4** (41 g, 94%) as a yellow solid (LC purity: 96%, MS *m/z*: 245.2 (M^+)), which was directly used in next step without purification.

General Procedure for the Preparation of the *N*-Anilino-2-(3-chloropropyl)-5-methyl-[1,2,4]triazolo-[1,5-*a*]pyrimidin-7-amines A mixture of R^1-substituted anilines (44 mmol) and **4** (10 g, 40 mmol) in isopropanol (100 ml) was stirred for 3 h at 50 °C. After cooling to room temperature, the formed precipitates was filtered, washed with water, dried and crystallized from methanol to give **5a**—**d** (87—93%) as pale powder.

***N*-(3-Chlorophenyl)-2-(3-chloropropyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (5a)** Prepared from **4** and 3-chlorophenyl amine, 87% yield. mp 168—169 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.92 (2H, m, $C_{2'}$-CH_2), 2.38 (3H, s, CH_3), 2.67 (2H, t, J=6.1 Hz, $C_{1'}$-CH_2), 3.22 (2H, t, J=6.1 Hz, $C_{3'}$-CH_2), 4.19 (1H, br s, NH), 6.34 (1H, s, C_6-H), 7.24 (1H, m, Ph-C_2-H), 7.37—7.42 (3H, m, Ph-$C_{4,5,6}$-3H). MS *m/z*: 336.2 (M^+); *Anal.* Calcd for $C_{15}H_{15}Cl_2N_5$: C, 53.58; H, 4.50; N, 20.83; Found: C, 53.52; H, 4.47; N, 20.77.

***N*-(3-Chloro-4-fluorophenyl)-2-(3-chloropropyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (5b)** Prepared from **4** and 3-chloro-4-fluorophenyl amine, 89% yield. mp 175—176 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.94 (2H, m, $C_{2'}$-CH_2), 2.38 (3H, s, CH_3), 2.67 (2H, t, J=6.0 Hz, $C_{1'}$-CH_2), 3.23 (2H, t, J=6.2 Hz, $C_{3'}$-CH_2), 4.23 (1H, br s, NH), 6.36 (1H, s, C_6-H), 7.43—7.51 (2H, m, Ph-$C_{2,6}$-2H), 7.66 (1H, m, Ph-C_5-H). MS *m/z*: 354.1 (M^+); *Anal.* Calcd for $C_{15}H_{14}Cl_2FN_5$: C, 50.86; H, 3.98; N, 19.77; Found: C, 50.82; H, 3.90; N, 19.69.

***N*-(4-(Trifluoromethoxy)phenyl)-2-(3-chloropropyl)-5-methyl-[1,2,4]-triazolo[1,5-*a*]pyrimidin-7-amine (5c)** Prepared from **4** and 4-(trifluoromethoxy) phenyl amine, 93% yield. mp 154—155 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.94 (2H, m, $C_{2'}$-CH_2), 2.38 (3H, s, CH_3), 2.67 (2H, t, J=6.1 Hz, $C_{1'}$-CH_2) , 3.23 (2H, t, J=6.2 Hz, $C_{3'}$-CH_2), 4.16 (1H, br s, NH), 6.36 (1H, s, C_6-H), 7.35 (2H, d, J=8.7 Hz, Ph-$C_{2,6}$-2H), 7.52 (2H, d, J=8.7 Hz, Ph-$C_{3,5}$-2H). MS *m/z*: 385.9 (M^+); *Anal.* Calcd for $C_{16}H_{15}ClF_3N_5O$: C, 49.81; H, 3.92; N, 18.15; Found: C, 49.78; H, 3.85; N, 18.10.

***N*-(4-(Trifluoromethyl)phenyl)-2-(3-chloropropyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (5d)** Prepared from **4** and 4-(trifluoromethyl) phenyl amine, 91% yield. mp 147—148 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.95 (2H, m, $C_{2'}$-CH_2), 2.40 (3H, s, CH_3), 2.69 (2H, t, J=6.1 Hz, $C_{1'}$-CH_2), 3.23 (2H, t, J=6.2 Hz, $C_{2'}$-CH_2), 4.23 (1H, br s, NH), 6.43 (1H, s, C_6-H), 7.46 (2H, d, J=8.7 Hz, Ph-$C_{2,6}$-2H), 7.57 (2H, d, J=8.7 Hz, Ph-$C_{3,5}$-2H). MS *m/z*: 370.0 (M^+); *Anal.* Calcd for $C_{16}H_{15}ClF_3N_5$: C, 51.97; H, 4.09; N, 18.94; Found: C, 51.93; H, 4.01; N, 18.91.

General Procedure for the Preparation of *N*-Anilino-2-(3-(ffuran-2-yl-methylthio)propyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amines Furan-2-ylmethanethiol (8.6 g, 75 mmol) was added dropwise into a suspension of NaH (1.8 g 75 mmol) in dried DMF (80 ml) at room temperature. After the addition, the mixture was stirred for 5 min, and then **5a**—**d** (25 mmol) was added in one portion. The mixture was heated at 50 °C for 30 min and then poured into water. The brown oil which separated from water was triturated with diethyl ether. The resulting precipitate was collected by filtration, washed well with water and further purified by recrystallization from ethyl acetate/cyclohexane to afford **6a**—**d** as gray solid (80—85%).

***N*-(3-Chlorophenyl)-2-(3-(ffuran-2-yl-methylthio)propyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (6a)** Prepared from **5a**, 81% yield. mp 148—150 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.99 (2H, m, $C_{2'}$-CH_2), 2.41 (3H, s, CH_3), 2.61 (2H, t, J=7.1 Hz, $C_{1'}$-CH_2), 2.88 (2H, t, J=7.1 Hz, $C_{3'}$-CH_2), 3.72 (2H, s, $C_{5'}$-CH_2), 4.18 (1H, br s, NH), 6.04 (1H, d, J=2.7 Hz, $C_{3''}$-H), 6.18 (1H, t, $C_{4''}$-H), 6.44 (1H, s, C_6-H), 7.11 (1H, d, J=1.9 Hz, $C_{5''}$-H), 7.26 (1H, m, Ph-C_2-H), 7.39—7.44 (3H, m, Ph-$C_{4,5,6}$-3H). MS *m/z*: 414.0 (M^+); *Anal.* Calcd for $C_{20}H_{20}ClN_5OS$: C, 58.03; H, 4.87; N, 16.92; Found: C, 58.00; H, 4.82; N, 16.88.

***N*-(3-Chloro-4-fluorophenyl)-2-(3-(ffuran-2-yl-methylthio)propyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (6b)** Prepared from **5b**, 82% yield. mp 155—157 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.99 (2H, m, $C_{2'}$-CH_2), 2.42 (3H, s, CH_3), 2.61 (2H, t, J=7.0 Hz, $C_{1'}$-CH_2), 2.88 (2H, t, J=7.2 Hz, $C_{3'}$-CH_2), 3.77 (2H, s, $C_{5'}$-CH_2), 4.12 (1H, br s, NH), 6.02 (1H, d, J=3.8 Hz, $C_{3''}$-H), 6.14 (1H, t, $C_{4''}$-H), 6.32 (1H, s, C_6-H), 7.08 (1H, d, J=2.0 Hz, $C_{5''}$-H), 7.41—7.50 (2H, m, Ph-$C_{2,6}$-2H), 7.64 (1H, m, Ph-C_5-H). MS *m/z*: 431.9 (M^+); *Anal.* Calcd for $C_{20}H_{19}ClFN_5OS$: C, 55.62; H, 4.43; N, 16.21; Found: C, 55.58; H, 4.38; N, 16.19.

***N*-(4-(Trifluoromethoxy)phenyl)-2-(3-(ffuran-2-yl-methylthio)propyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (6c)** Prepared from **5c**, 85% yield. mp 145—147 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.99 (2H, m, $C_{2'}$-CH_2), 2.42 (3H, s, CH_3), 2.62 (2H, t, J=6.9 Hz, $C_{1'}$-CH_2), 2.90 (2H, t, J=7.1 Hz, $C_{3'}$-CH_2), 3.73 (2H, s, $C_{5'}$-CH_2), 4.31 (1H, br s, NH), 6.07 (1H, d, J=3.7 Hz, $C_{3''}$-H), 6.15 (1H, t, $C_{4''}$-H), 6.41 (1H, s, C_6-H), 7.13 (1H, d, J=2.0 Hz, $C_{5''}$-H), 7.43 (2H, d, J=8.7 Hz, Ph-$C_{2,6}$-2H), 7.55 (2H, d, J=8.7 Hz, Ph-$C_{3,5}$-2H). MS *m/z*: 463.6 (M^+); *Anal.* Calcd for $C_{21}H_{20}F_3N_5O_2S$: C, 54.42; H, 4.35; N, 15.11; Found: C, 54.25; H, 4.28; N, 15.04.

***N*-(4-(Trifluoromethyl)phenyl)-2-(3-(ffuran-2-yl-methylthio)propyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (6d)** Prepared from **5d**, 81% yield. mp 157—159 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.01 (2H, m, $C_{2'}$-CH_2), 2.44 (3H, s, CH_3), 2.61 (2H, t, J=6.9 Hz, $C_{1'}$-CH_2), 2.91 (2H, t, J=7.1 Hz, $C_{3'}$-CH_2), 3.77 (2H, s, $C_{5'}$-CH_2), 4.37 (1H, br s, NH), 6.02 (1H, d, J=3.7 Hz, $C_{3''}$-H), 6.14 (1H, t, $C_{4''}$-H), 6.47 (1H, s, C_6-H), 7.21 (1H, d, J=2.1 Hz, $C_{5''}$-H), 7.64 (2H, d, J=8.7 Hz, Ph-$C_{2,6}$-2H), 7.80 (2H, d, J=8.7 Hz, Ph-$C_{3,5}$-2H). MS *m/z*: 447.8 (M^+); *Anal.* Calcd for $C_{21}H_{20}F_3N_5OS$: C, 56.37; H, 4.50; N, 15.65; Found: C, 56.32; H, 4.48; N, 15.60.

General Procedure for the Preparation of *N*-Anilino-5-methyl-2-(3-((5-(alkyl aminomethyl)furan-2-yl)methylthio)propyl)-[1,2,4]triazolo-[1,5-*a*]pyrimidine-7-amines Formaldehyde (0.6 g, 8 mmol) was added into acetic acid (20 ml) containing an appropriate amine (R^2R^3NH, 13 mmol). The mixture was stirred at 30 °C for 10 min, and then **6a**—**d** (5 mmol) was added. After stirring at 50 °C for 4 h, the mixture was concentrated in vacuum. The residue was treated with 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 column chromatography to give the final products **7**—**24** as off-white powder.

***N*-(3-Chlorophenyl)-5-methyl-2-(3-((5-(morpholinomethyl)furan-2-yl)methylthio)propyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (7)** Prepared from **6a** and morpholine, 73% yield. mp 170—172 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.02 (2H, m, $C_{2''}$-CH_2), 2.42 (3H, s, CH_3), 2.60 (2H, t, J=6.9 Hz, $C_{1'}$-CH_2), 2.67 (4H, br s, morpholino-$C_{2,6}$-2CH_2), 2.89 (2H, t, J=7.1 Hz, $C_{3'}$-CH_2), 3.64 (4H, br s, morpholino-$C_{3,5}$-2CH_2), 3.78 (2H, s, $C_{5'}$-CH_2), 3.85 (2H, s, NCH_2), 6.25 (1H, d, J=2.8 Hz, $C_{3''}$-H), 6.32 (1H, d, J=2.8 Hz, $C_{4''}$-H), 6.44 (1H, s, C_6-H), 7.34 (1H, m, Ph-C_2-H), 7.46—7.52 (3H, m, Ph-$C_{4,5,6}$-3H). IR (KBr) cm^{-1}: 3445.2, 2968.3, 1608.4, 1566.9, 1478.7, 1325.8. MS *m/z*: 513.2 (M^+). *Anal.* Calcad for $C_{25}H_{29}ClN_6O_2S$: C, 58.53; H, 5.70; N, 16.38. Found: C, 58.42; H, 5.59; N, 16.33.

***N*-(3-Chlorophenyl)-5-methyl-2-(3-((5-(piperidin-1-ylmethyl)furan-2-yl)methylthio)propyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (8)** Prepared from **6a** and piperidine, 65% yield. mp 166—168 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.44 (2H, m, piperidinyl-C_4-CH_2), 1.68 (4H, br s, piperidinyl-$C_{3,5}$-2CH_2), 2.02 (2H, m, $C_{2''}$-CH_2), 2.42 (3H, s, CH_3), 2.61 (2H, t, J=6.9 Hz, $C_{1'}$-CH_2), 2.89 (2H, t, J=7.1 Hz, $C_{3'}$-CH_2), 2.99 (4H, br s, piperidinyl-$C_{2,6}$-2CH_2), 3.80 (2H, s, $C_{5'}$-CH_2), 4.19 (2H, s, NCH_2), 6.32 (1H, br s, $C_{3''}$-H), 6.45 (1H, s, C_6-H), 6.50 (1H, br s, $C_{4''}$-H), 7.34 (1H, m, Ph-C_2-H), 7.46—7.52 (3H, m, Ph-$C_{4,5,6}$-3H). IR (KBr) cm^{-1}: 3445.7, 2948.3, 1620.4, 1533.9, 1479.0, 1329.1. MS *m/z*: 511.3 (M^+). *Anal.* Calcd for $C_{26}H_{31}ClN_6OS$: C, 61.10; H, 6.11; N, 16.44. Found: C, 61.05; H, 6.15; N, 16.29.

***N*-(3-Chlorophenyl)-5-methyl-2-(3-((5-(pyrrolidin-1-ylmethyl)furan-2-yl)methylthio)propyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (9)** Prepared from **6a** and pyrrolidine, 69% yield. mp 179—180 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.83 (4H, m, pyrrodinyl-$C_{3,4}$-2CH_2), 2.14 (2H, m, $C_{2'}$-CH_2), 2.55 (3H, s, CH_3), 2.63 (2H, t, J=7.1 Hz, $C_{1'}$-CH_2), 2.71 (4H, br s, pyrrodinyl-$C_{2,5}$-2CH_2), 2.99 (2H, t, J=6.8 Hz, $C_{3'}$-CH_2), 3.72 (4H, br s, $C_{5'}$-CH_2, NCH_2), 6.11 (1H, br s, $C_{3''}$-H), 6.17 (1H, br s, $C_{4''}$-H), 6.34 (1H, s, C_6-H), 7.28 (1H, m, Ph-C_2-H), 7.39—7.43 (3H, m, Ph-$C_{4,5,6}$-3H). IR (KBr) cm^{-1}: 3443.6, 2963.8, 1609.5, 1575.9, 1479.2, 1329.1. MS *m/z*: 497.2 (M^+). *Anal.* Calcd for $C_{25}H_{29}ClN_6OS$: C, 60.41; H, 5.88; N, 16.91. Found: C, 60.35; H, 5.75; N, 16.86.

***N*-(3-Chlorophenyl)-5-methyl-2-(3-((5-((4-methylpiperazin-1-yl)methyl)furan-2-yl)methylthio)propyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-**

7-amine (10) Prepared from **6a** and 4-methylpiperazine, 82% yield. mp 201—202 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.02 (2H, m, $C_{2'}$-CH_2), 2.42 (3H, s, NCH_3), 2.57—2.63 (6H, m, $C_{1'}$-CH_2, piperazinyl-$C_{3,5}$-$2CH_2$), 2.72 (3H, s, C_5-CH_3), 2.89 (2H, t, J=7.2 Hz, $C_{3'}$-CH_2), 3.16 (4H, br s, piperazinyl-$C_{2,6}$-$2CH_2$), 3.55 (2H, s, $C_{5'}$-CH_2), 3.76 (2H, s, NCH_2), 6.21 (2H, m, $C_{3'',4''}$-H), 6.45 (1H, s, C_6-H), 7.34 (1H, m, Ph-C_2-H), 7.46—7.52 (3H, m, Ph-$C_{4,5,6}$-3H); IR (KBr) cm^{-1}: 3446.2, 2960.6, 1621.8, 1567.4, 1515.6, 1468.8, 1329.5. MS *m/z*: 526.4 (M^+). *Anal.* Calcd for $C_{26}H_{32}ClN_7OS$: C, 59.36; H, 6.13; N, 18.64. Found: C, 59.29; H, 6.05; N, 18.59.

***N*-(3-Chlorophenyl)-2-(3-((5-((dimethylamino)methyl)furan-2-yl)methylthio)propyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (11)** Prepared from **6a** and dimethylamine, 55% yield. mp 163—164 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (2H, m, $C_{2'}$-CH_2), 2.38 (6H, s, $N(CH_3)_2$), 2.55 (3H, s, C_5-CH_3), 2.64 (2H, t, J=7.1 Hz, $C_{1'}$-CH_2), 2.99 (2H, t, J=7.2 Hz, $C_{3'}$-CH_2), 3.63 (2H, s, $C_{5'}$-CH_2), 3.73 (2H, s, NCH_2), 6.14 (1H, br s, $C_{3''}$-H), 6.22 (1H, br s, $C_{4''}$-H), 6.36 (1H, s, C_6-H), 7.28 (1H, m, Ph-C_2-H), 7.39—7.43 (3H, m, Ph-$C_{4,5,6}$-3H); IR (KBr) cm^{-1}: 3443.5, 2925.9, 1609.8, 1566.9, 1478.5, 1328.3. MS *m/z*: 471.1 (M^+). *Anal.* Calcd for $C_{23}H_{27}ClN_6OS$: C, 58.65; H, 5.78; N, 17.84. Found: C, 58.46; H, 5.83; N, 17.75.

***N*-(3-Chloro-4-fluorophenyl)-5-methyl-2-(3-((5-(morpholinomethyl)-furan-2-yl)methylthio)propyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (12)** Prepared from **6b** and morpholine, 72% yield. mp 182—183 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.02 (2H, m, $C_{2'}$-CH_2), 2.41 (3H, s, CH_3), 2.60 (2H, br s, $C_{1'}$-CH_2), 2.88 (2H, br s, $C_{3'}$-CH_2), 2.91 (4H, br s, morpholino-$C_{2,6}$-$2CH_2$), 3.72 (4H, br s, morpholino-$C_{3,5}$-$2CH_2$), 3.80 (2H, s, $C_{5'}$-CH_2), 4.10 (2H, s, NCH_2), 6.31 (1H, br s, $C_{3''}$-H), 6.36 (1H, br s, $C_{4''}$-H), 6.46 (1H, s, C_6-H), 7.52 (2H, m, Ph-$C_{2,6}$-2H), 7.63 (1H, m, Ph-C_5-H); IR (KBr) cm^{-1}: 3445.2, 2925.7, 1576.5 1496.0, 1478.5, 1328.6. MS *m/z*: 531.5 (M^+). *Anal.* Calcd for $C_{25}H_{28}ClFN_6O_2S$: C, 56.54; H, 5.31; N, 15.83. Found: C, 56.35; H, 5.23; N, 15.69.

***N*-(3-Chloro-4-fluorophenyl)-5-methyl-2-(3-((5-(piperidin-1-ylmethyl)-furan-2-yl)methylthio)propyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (13)** Prepared from **6b** and piperidine, 75% yield. mp 180—182 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (2H, m, piperidinyl-C_4-CH_2), 1.67 (4H, m, piperidinyl-$C_{3,5}$-$2CH_2$), 2.02 (2H, m, $C_{2'}$-CH_2), 2.41 (3H, s, CH_3), 2.61 (2H, t, J=6.9 Hz, $C_{1'}$-CH_2), 2.89 (2H, t, J=7.2 Hz, $C_{3'}$-CH_2), 2.95 (4H, br s, piperidinyl-$C_{2,6}$-$2CH_2$), 3.80 (2H, s, $C_{5'}$-CH_2), 4.15 (2H, s, NCH_2), 6.30 (1H, d, J=3.3 Hz, $C_{3''}$-H), 6.36 (1H, s, C_6-H), 6.48 (1H, d, J=3.3 Hz, $C_{4''}$-H), 7.45—7.53 (2H, m, Ph-$C_{2,6}$-2H), 7.68 (1H, m, Ph-C_5-H). IR (KBr) cm^{-1}: 3443.5, 2947.7, 1623.7, 1575.9, 1494.1, 1478.5, 1320.9. MS *m/z*: 529.5 (M^+). *Anal.* Calcd for $C_{26}H_{30}ClFN_6OS$: C, 59.02; H, 5.72; N, 15.88. Found: C, 58.86; H, 5.62; N, 15.75.

***N*-(3-Chloro-4-fluorophenyl)-5-methyl-2-(3-((5-(pyrrolidin-1-yl-methyl)furan-2-yl)methylthio)propyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (14)** Prepared from **6b** and pyrrolidine, 75% yield. mp 175—178 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.89 (4H, m, pyrrodinyl-$C_{3,4}$-$2CH_2$), 2.02 (2H, m, $C_{2'}$-CH_2), 2.41 (3H, s, CH_3), 2.61 (2H, t, J=6.9 Hz, $C_{1'}$-CH_2), 2.89 (2H, t, J=7.1 Hz, $C_{3'}$-CH_2), 3.20 (4H, br s, pyrrodinyl-$C_{2,3}$-$2CH_2$), 3.81 (2H, s, $C_{5'}$-CH_2), 4.35 (2H, s, NCH_2), 6.33 (1H, s, J=2.9 Hz, $C_{3''}$-H), 6.36 (1H, s, C_6-H), 6.52 (1H, s, J=2.8 Hz, $C_{4''}$-H), 7.48—7.54 (2H, m, Ph-$C_{2,6}$-2H), 7.67 (1H, m, Ph-C_5-H). IR (KBr) cm^{-1}: 3446.1, 2966.8, 1609.4, 1573.7, 1479.6, 1327.8. MS *m/z*: 515.4 (M^+). *Anal.* Calcd for $C_{25}H_{28}ClFN_6OS$: C, 58.30; H, 5.48; N, 16.32. Found: C, 58.18; H, 5.40; N, 16.21.

***N*-(3-Chloro-4-fluorophenyl)-5-methyl-2-(3-((5-((4-methylpiperazin-1-yl)methyl)furan-2-yl)methylthio)propyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (15)** Prepared from **6b** and 4-methylpiperazine, 80% yield. mp 195—196 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.01 (2H, m, $C_{2'}$-CH_2), 2.41 (3H, s, C_5-CH_3), 2.59 (2H, t, J=6.9 Hz, $C_{1'}$-CH_2), 2.72 (7H, br s, NCH_3, piperazinyl-$C_{3,5}$-$2CH_2$), 2.88 (2H, t, J=7.2 Hz, $C_{3'}$-CH_2), 3.13 (4H, br s, piperazinyl-$C_{2,6}$-$2CH_2$), 3.55 (2H, s, $C_{5'}$-CH_2), 3.76 (2H, s, NCH_2), 6.20 (1H, d, J=3.0 Hz, $C_{3''}$-H), 6.22 (1H, d, J=3.3 Hz, $C_{4''}$-H), 6.36 (1H, s, C_6-H), 7.45—7.53 (2H, m, Ph-$C_{2,6}$-2H), 7.67 (1H, m, Ph-C_5-H). IR (KBr) cm^{-1}: 3442.9, 3008.2, 1574.5, 1495.3, 1478.2, 1328.2. MS *m/z*: 544.5 (M^+). *Anal.* Calcd for $C_{26}H_{31}ClFN_7OS$: C, 57.39; H, 5.74; N, 18.02. Found: C, 57.25; H, 5.62; N, 17.95.

***N*-(3-Chloro-4-fluorophenyl)-2-(3-((5-((dimethylamino)methyl)furan-2-yl)methylthio)propyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (16)** Prepared from **6b** and dimethylamine, 70% yield. mp 170—172 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.02 (2H, m, $C_{2'}$-CH_2), 2.41 (3H, s, C_5-CH_3), 2.61 (2H, t, J=6.9 Hz, $C_{1'}$-CH_2), 2.69 (6H, s, $N(CH_3)_2$), 2.89 (2H, t, J=7.2 Hz, $C_{3'}$-CH_2), 3.81 (2H, s, $C_{5'}$-CH_2), 4.28 (2H, s, NCH_2), 6.34 (1H, d, J=2.9 Hz, $C_{3''}$-H), 6.36 (1H, s, C_6-H), 6.56 (1H, d, J=3.0 Hz, $C_{4''}$-H), 7.47—7.56 (2H, m, Ph-$C_{2,6}$-2H), 7.67 (1H, m, Ph-C_5-H). IR (KBr) cm^{-1}: 3446.5, 2925.2, 1576.4, 1496.3, 1430.1. MS *m/z*: 489.1 (M^+). *Anal.* Calcd for $C_{23}H_{26}ClFN_6OS$: C, 56.49; H, 5.36; N, 17.19. Found: C, 56.38; H, 5.25; N, 17.12.

5-Methyl-2-(3-((5-(morpholinomethyl)furan-2-yl)methylthio)propyl)-*N*-(4-(trifluoromethoxy)phenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (17) Prepared from **6c** and morpholine, 57% yield. mp 185—187 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.02 (2H, m, $C_{2'}$-CH_2), 2.41 (3H, s, CH_3), 2.60 (6H, br s, $C_{1'}$-CH_2, morpholino-$C_{2,6}$-$2CH_2$), 2.89 (2H, t, J=7.2 Hz, $C_{3'}$-CH_2), 3.60 (4H, br s, morpholino-$C_{3,5}$-$2CH_2$), 3.72 (2H, s, $C_{5'}$-CH_2), 3.77 (2H, s, NCH_2), 6.18—6.28 (2H, m, $C_{3'',4''}$-2H), 6.41 (1H, s, C_6-H), 7.46 (2H, d, J=8.7 Hz, Ph-$C_{2,6}$-2H), 7.57 (2H, m, J=8.7 Hz, Ph-$C_{3,5}$-2H). IR (KBr) cm^{-1}: 3447.5, 2963.8, 1610.5, 1575.4, 1478.8, 1329.0. MS *m/z*: 563.2 (M^+). *Anal.* Calcd for $C_{26}H_{29}F_3N_6O_3S$: C, 55.51; H, 5.20; N, 14.94; Found: C, 55.47; H, 5.18; N, 14.89.

5-Methyl-2-(3-((5-(piperidin-1-ylmethyl)furan-2-yl)methylthio)-propyl)-*N*-(4-(trifluoromethoxy)phenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (18) Prepared from **6c** and piperidine, 49% yield. mp 177—179 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.43 (2H, m, piperidinyl-C_4-CH_2), 1.65 (4H, br s, piperidinyl-$C_{3,5}$-$2CH_2$), 2.02 (2H, m, $C_{2'}$-CH_2), 2.41 (3H, s, CH_3), 2.61 (2H, t, J=6.9 Hz, $C_{1'}$-CH_2), 2.89 (2H, t, J=7.1 Hz, $C_{3'}$-CH_2), 2.99 (4H, br s, piperidinyl-$C_{3,5}$-$2CH_2$), 3.78 (2H, s, $C_{5'}$-CH_2), 4.06 (2H, s, NCH_2), 6.29 (1H, d, J=2.9 Hz, $C_{3''}$-H), 6.42 (2H, br s, $C_{4''}$-H, C_6-H), 7.46 (2H, d, J=8.6 Hz, Ph-$C_{2,6}$-2H), 7.57 (2H, m, J=8.7 Hz, Ph-$C_{3,5}$-2H); IR (KBr) cm^{-1}: 3441.5, 2963.2, 1608.9, 1575.8, 1479.5, 1329.2. MS *m/z*: 561.2 (M^+). *Anal.* Calcd for $C_{27}H_{31}F_3N_6O_2S$: C, 57.84; H, 5.57; N, 14.99; Found: C, 57.78; H, 5.51; N, 14.94.

5-Methyl-2-(3-((5-(pyrrolidin-1-ylmethyl)furan-2-yl)methylthio)-propyl)-*N*-(4-(trifluoromethoxy)phenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (19) Prepared from **6c** and pyrrolidine, 45% yield. mp 170—172 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.89 (4H, m, pyrrodinyl-$C_{3,4}$-$2CH_2$), 2.02 (2H, m, $C_{2'}$-CH_2), 2.42 (3H, s, CH_3), 2.62 (2H, t, J=7.1 Hz, $C_{1'}$-CH_2), 2.89 (2H, t, J=7.2 Hz, $C_{3'}$-CH_2), 3.20 (4H, br s, pyrrodinyl-$C_{2,5}$-$2CH_2$), 3.78 (2H, s, $C_{5'}$-CH_2), 3.89 (2H, s, NCH_2), 6.30 (1H, s, $C_{3''}$-H), 6.42 (1H, s, C_6-H), 6.53 (1H, s, $C_{4''}$-H), 7.46 (2H, d, J=8.5 Hz, Ph-$C_{2,6}$-2H), 7.57 (2H, m, J=8.7 Hz, Ph-$C_{3,5}$-2H); IR (KBr) cm^{-1}: 3444.2, 2964.6, 1609.6, 1573.6, 1478.6, 1328.1. MS *m/z*: 547.2 (M^+). *Anal.* Calcd for $C_{26}H_{29}F_3N_6O_2S$: C, 57.13; H, 5.35; N, 15.37; Found: C, 57.08; H, 5.30; N, 15.32.

5-Methyl-2-(3-((5-((4-methylpiperazin-1-yl)methyl)furan-2-yl)-methylthio)propyl)-*N*-(4-(trifluoromethoxy)phenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (20) Prepared from **6c** and 4-methylpiperazine, 67% yield. mp 189—191 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.02 (2H, m, $C_{2'}$-CH_2), 2.41 (3H, s, CH_3), 2.60 (2H, t, J=7.1 Hz, $C_{1'}$-CH_2), 2.72 (7H, br s, piperazinyl-$C_{3,5}$-$2CH_2$, NCH_3), 2.89 (2H, t, J=7.1 Hz, $C_{3'}$-CH_2), 3.14 (4H, br s, piperazinyl-$C_{2,6}$-$2CH_2$), 3.55 (2H, s, $C_{5'}$-CH_2), 3.76 (2H, s, NCH_2), 6.21 (2H, br s, $C_{3'',4''}$-2H), 6.42 (1H, s, C_6-H), 7.46 (2H, d, J=8.5 Hz, Ph-$C_{2,6}$-2H), 7.57 (2H, m, J=8.8 Hz, Ph-$C_{3,5}$-2H); IR (KBr) cm^{-1}: 3441.4, 2961.5, 1608.5, 1575.4, 1477.8, 1329.2. MS *m/z*: 576.1 (M^+). *Anal.* Calcd for $C_{27}H_{32}F_3N_7O_2S$: C, 56.33; H, 5.60; N, 17.03; Found: C, 56.27; H, 5.54; N, 16.94.

5-Methyl-2-(3-((5-(morpholinomethyl)furan-2-yl)methylthio)propyl)-*N*-(4-(trifluoromethyl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (21) Prepared from **6d** and morpholine, 59% yield. mp 180—182 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.02 (2H, m, $C_{2'}$-CH_2), 2.44 (3H, s, CH_3), 2.59 (2H, br s, $C_{1'}$-CH_2), 2.63 (4H, br s, morpholino-$C_{2,6}$-$2CH_2$), 2.88 (2H, t, J=7.2 Hz, $C_{3'}$-CH_2), 3.61 (4H, br s, morpholino-$C_{3,5}$-$2CH_2$), 3.72 (2H, s, $C_{5'}$-CH_2), 4.06 (2H, s, NCH_2), 6.25—6.28 (2H, m, $C_{3'',4''}$-2H), 6.63 (1H, s, C_6-H), 7.67 (2H, d, J=8.3 Hz, Ph-$C_{2,6}$-2H), 7.82 (2H, d, J=8.5 Hz, Ph-$C_{3,5}$-2H). IR (KBr) cm^{-1}: 3446.6, 2963.5, 1609.5, 1574.8, 1479.5, 1328.4. MS *m/z*: 547.3 (M^+). *Anal.* Calcd for $C_{26}H_{29}F_3N_6O_2S$: C, 57.13; H, 5.35; N, 15.37; Found: C, 57.10; H, 5.33; N, 15.32.

5-Methyl-2-(3-((5-(piperidin-1-ylmethyl)furan-2-yl)methylthio)-propyl)-*N*-(4-(trifluoromethyl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (22) Prepared from **6d** and piperidine, 51% yield. mp 173—174 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.46 (2H, m, piperidinyl-C_4-CH_2), 1.69 (4H, m, piperidinyl-$C_{3,5}$-$2CH_2$), 2.03 (2H, m, $C_{2'}$-CH_2), 2.50 (3H, s, CH_3), 2.61 (2H, t, J=7.3 Hz, $C_{1'}$-CH_2), 2.90 (2H, t, J=7.1 Hz, $C_{3'}$-CH_2), 3.00 (4H, br s, piperidinyl-$C_{2,6}$-$2CH_2$), 3.80 (2H, s, $C_{5'}$-CH_2), 4.23 (2H, s, NCH_2), 6.33 (1H, br s, $C_{3''}$-H), 6.51 (1H, br s, $C_{4''}$-H), 6.63 (1H, s, C_6-H), 7.68 (2H, d, J=8.3 Hz, Ph-$C_{2,6}$-2H), 7.82 (2H, d, J=8.5 Hz, Ph-$C_{3,5}$-2H). IR (KBr) cm^{-1}: 3443.9, 2963.9, 1608.6, 1575.3, 1477.5, 1328.4. MS *m/z*: 545.2 (M^+). *Anal.* Calcd for $C_{27}H_{31}F_3N_6OS$: C, 59.54; H, 5.74; N, 15.43; Found: C, 59.49; H, 5.70; N, 15.38.

5-Methyl-2-(3-((5-(pyrrolidin-1-ylmethyl)furan-2-yl)methylthio)-propyl)-*N*-(4-(trifluoromethoxy)phenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (23) Prepared from **6d** and pyrrolidine, 58% yield. mp 163—

165 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.89 (4H, br s, pyrrodinyl-$C_{3,4}$-$2CH_2$), 2.02 (2H, m, $C_{2'}$-CH_2), 2.42 (3H, s, CH_3), 2.61 (2H, t, J=7.5 Hz, $C_{1'}$-CH_2), 2.9 (2H, t, J=7.2 Hz, $C_{3'}$-CH_2), 3.21 (4H, br s, pyrrodinyl-$C_{2,5}$-$2CH_2$), 3.81 (2H, s, $C_{5'}$-CH_2), 4.36 (2H, s, NCH_2), 6.33 (1H, d, J=3.0 Hz, $C_{3''}$-H), 6.47 (1H, s, C_6-H), 6.53 (1H, d, J=3.0 Hz, $C_{4''}$-H), 7.68 (2H, d, J=8.3 Hz, Ph-$C_{2,6}$-2H), 7.82 (2H, d, J=8.5 Hz, Ph-$C_{3,5}$-2H). IR (KBr) cm^{-1}: 3445.1, 2975.2, 1608.3, 1574.3, 1476.1, 1328.5. MS *m*/*z*: 531.1 (M^+). *Anal.* Calcd for $C_{26}H_{29}F_3N_6OS$: C, 58.85; H, 5.51; N, 15.84; Found: C, 58.81; H, 5.47; N, 15.79.

5-Methyl-2-(3-((5-((4-methylpiperazin-1-yl)methyl)furan-2-yl)-methylthio)propyl)-*N*-(4-(trifluoromethoxy)phenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (24) Prepared from **6d** and 4-methylpiperazine, 65% yield. mp 188—189 °C; ^{1}H-NMR (DMSO-d_6) δ: 2.02 (2H, m, $C_{2'}$-CH_2), 2.44 (3H, s, C_5-CH_3), 2.59 (2H, t, J=7.2 Hz, $C_{1'}$-CH_2), 2.72 (7H, br s, piperazinyl-$C_{3,5}$-$2CH_2$, NCH_3), 2.90 (2H, t, J=7.2 Hz, $C_{3'}$-CH_2), 3.15 (4H, br s, piperazinyl-$C_{2,6}$-$2CH_2$), 3.55 (2H, s, $C_{5'}$-CH_2), 3.76 (2H, s, NCH_2), 6.21 (2H, br s, $C_{3'',4''}$-2H), 6.63 (1H, s, C_6-H), 7.68 (2H, d, J=8.1 Hz, Ph-$C_{2,6}$-2H), 7.82 (2H, d, J=8.4 Hz, Ph-$C_{3,5}$-2H); IR (KBr) cm^{-1}: 3445.7, 2969.4, 1609.7, 1576.8, 1479.8, 1329.0. MS *m*/*z*: 559.9 (M^+). *Anal.* Calcd for $C_{27}H_{32}F_3N_7OS$: C, 57.95; H, 5.76; N, 17.52; Found: C, 57.91; H, 5.72; N, 15.49.

Evaluation of Biological Activity The anti-tumor activities of compounds **7**—**24** were evaluated with Bel-7402 (Human Liver Cancer Cell Lines) and HT-1080 (Human Fibro Sarcoma Cell Lines) by the MTT method *in vitro*, with cisplatin as the positive control. The cancer cell lines (Bel-7402 and HT-1080) were cultured in minimum essential medium (MEM) supplement with 10% fetal bovine serum (FBS).

Approximately 4×10^3 cells, suspended in MEM medium, were plated onto each well of a 96-well plate and incubated in 5% CO_2 at 37 °C for 24 h. The test compounds at indicated final concentrations were added to the culture medium and the cell cultures were continued for 72 h. Fresh MTT was added to each well at a terminal concentration of 5 μg/ml and incubated with cells at 37 °C for 4 h. The formazan crystals were dissolved in 100 μl DMSO each well, and the absorbency at 492 nm (for absorbance of MTT formazan) and 630 nm (for the reference wavelength) was measured with the ELISA reader.

The cytotoxicity effect was expressed as the IC_{50}, which was calculated by Bliss.

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