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## Synthesis and biological evaluation of a series of 2-((1-substituted-1H-1,2,3-triazol-4-yl)methylthio)-6-(naphthalen-1-ylm ethyl)pyrimidin-4(3H)-one as potential HIV-1 inhibitors

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**Abstract:** A series of novel S-DABO derivatives with the substituted 1,2,3-triazole moiety on the C-2 side chain were synthesized by using the simple and efficient CuAAC reaction, and biologically evaluated as inhibitors of HIV-1. Among them, the most active HIV-1 inhibitors was compound 4-((4-((4-(2,6-dichlorobenzyl)-5-methyl-6-oxo-1,6-dihydropyrimidin-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzenesulfonamide (**B5b7**), which exhibited similar HIV-1 inhibitory potency (EC<sub>50</sub> = 3.22 µM) compared with 3TC (EC<sub>50</sub> = 2.24 µM). None of these compounds demonstrated inhibition against HIV-2 replication. The

preliminary structure-activity relationship (SAR) of these new derivatives was discussed briefly.

**Keywords:** HIV, NNRTIS, Pyrimidine, Click chemistry, Antiviral activity, Drug design, SAR

### 1. Introduction

Human immunodeficiency virus type-1 (HIV-1) non-nucleoside reverse transcriptase inhibitors (NNRTIs) were the major components of highly active antiretroviral therapy (HAART), a major problem is that the long-term efficacy of NNRTIs is limited by the rapid emergence of drug-resistant HIV-1 strains. Thus, in recent years, the discovery of novel NNRTIs chemical entities with improved drug resistance profiles was considered to be a very active research field [1-3].

Dihydro-alkoxy-benzyl-oxopyrimidines (DABOs) were one of the most representative classes of HIV-1 NNRTIs developed in the past two decades. Up to now, three generations of DABO analogues have been investigated on the base of the C-2 substitutent features, i.e.: dihydro-alkyloxy-benzyl-oxopyrimidines

(*O*-DABOs), dihydro-alkylthio- benzyl-oxopyrimidines (*S*-DABOs) and dihydro-alkylamino-difluorobenzyloxopyrimidines (*N*-DABOs) (**Figure 1**) [4].

Among DABO derivatives, *S*-DABOs were the most prominent anti-HIV agents, with the C-2 alkylthio chain being extremely important for exhibition of anti-HIV-1 activity. The NHC=O fragment at N3/C4 position of the pyrimidine is a critical factor for the binding because the key hydrogen bonds were formed between N3-H and the carbonyl group of Lys101 [5]. The optimal moieties at positions 5 of the pyrimidine nucleus were dependent on the nature of the C-2 side chain. Both arylcarbonylmethyl and benzyl substituent of *S*-DABOs at the C-2 site of the pyrimidine core exert their potent anti-HIV-1 effects by the interaction with the side chain of Pro236 [6]. Various chemical modifications of C-6 position had been carried out in the lab of Artico [7]. When the benzyl group at C-6 of the pyrimidine ring was replaced by 1/2-naphthylmethyl or halogenated benzyl moieties, a set of compounds demonstrated favorable potencies against wild-type (WT) HIV-1 in the low-micromolar range. The introduction of the hydrophobic C-6 side chain of *S*-DABOs might be more favorable to improve a putative  $\pi$ -stacking interaction between the aryl ring of the ligand and Tyr188 or Tyr181 of RT [8].

Figure 1. The structures of DABOs families.

**Figure 2.** The newly designed S-DABOs with the substituted triazole moiety on the C2 side chain.

Recent work in our lab on S-DABOs reported that assembly of a phenylaminocarbonylmethylthio moiety at the C2 site of the pyrimidinecore has led to a set of novel lead compounds with promising antiviral potencies against HIV-1 (**Figure 2**) [9a,b]. Among them, **MY-4b3** was identified as the most potent molecule ( $EC_{50} = 0.18 \mu M$ ,  $CC_{50} > 243.56 \mu M$ , SI >1326). Moreover, a novel C-2 thioethanone S-DABO derivative **JZ-6c1** ( $EC_{50}=0.24 \mu M$ ) was reported to demonstrate the improved

or comparable HIV-1 potency compared with NVP (EC<sub>50</sub>=0.21  $\mu$ M) and DLV (EC<sub>50</sub>=0.32  $\mu$ M) [10]. As the C-2 side chain of *S*-DABOs pointed toward the solvent exposed region and accommodated substantial modifications of the inhibitor, we postulated that the introduction of the thioacetanilide and thioethanone group to the C-2 side chain might be more favorable to improve specific protein-inhibitor interactions, and further exploration of the plasticity of this part of the pocket may lead to the discovery of new S-DABOs with improved pharmacokinetic properties without a significant loss of binding affinity. These interesting clues prompted us to further explore the structure-activity relationships (SARs) of the C-2 side chain in S-DABOs.

In recent years, the 1,2,3-triazole structural motif, the product obtained from the Cu(I)-catalyzed, alkyne-azide 1,3-dipolar cycloaddition (CuAAC) reaction, has emerged as attractive and desirable scaffolds in the development of potential drug molecules in medicinal chemistry in this regard considering the fact that the triazole is a safe bioequivalent surrogate for the amide bond, which demonstrates high dipole and enhanced hydrogen bonding interactions compared to the amide. Because of their chemical features, these triazoles were proposed to be aggressive pharmacophores that participate in drug-receptor interactions while maintaining an excellent chemical and metabolic profile [11].

Based on the existing SARs of C2-functionalized S-DABOs [12], we proposed that the structural modification of S-DABOs by incorporating the substituted triazole moiety to the corresponding site of C-2 side chain could enhance the interactions between RT and the inhibitors. In order to examine our proposal and generate more potent NNRTIs, in the present work, a series of novel S-DABO derivatives with the substituted 1,2,3-triazole moiety on the C-2 side chain were designed, synthesized by using the simple and efficient CuAAC reaction, and evaluated for their anti-HIV activities (Figure 2).

### 2. Results and discussions

### 2.1. Chemistry

The synthetic route of the newly designed compounds is described in **Scheme 1**. The key intermediate  $\beta$ -ketoesters (A2a, A2b, B2a, B2b) were prepared with a simple method previously used by us [10] through the reaction of 2-(naphthalen-1-yl)acetic acid (A1) or 2-(2,6-dichlorophenyl)acetic acid (B1) with N,N'-carbonyldiimidazole (CDI) followed by treatment with potassium 3-ethoxy-3-oxopropanoate (a) or potassium 3-ethoxy-2-methyl-3-oxopropanoate (b) in the presence of anhydrous MgCl<sub>2</sub> and Et<sub>3</sub>N. Next, the cyclization reaction of  $\beta$ -ketoesters (A2a, A2b, B2a, B2b) with thiourea in the presence of EtONa (in refluxing EtOH) afforded the substituted uracils (A3a, A3b, B3a, B3b). Treatment of these uracils with 3-bromoprop-1-yne in the presence of  $K_2CO_3$  in anhydrous DMF gave the key alkyne intermadeties (A4a, A4b, B4a, B4b). Then, the synthesis of these triazole linked S-DABOs (A5a1-A5a7, A5b1-A5b7, B5a1-B5a7 and B5b1-B5b7) was accomplished using the copper catalyzed azido-alkyne cycloaddition (CuAAC) reaction in the mild conditions. The substituted benzyl azides were easily synthesized by the reaction of substituted benzyl halide with sodium azide at room temperature. Finally, the iodination of compounds A5a1-A5a7 and B5a1-B5a7 occurred subsequently to prepare compounds A6a1-A6a7 and B6a1-B6a7, respectively, using  $PbO_2$  and  $I_2$  in HOAc. Both analytical and spectral data of all the title derivatives are in full agreement with the proposed structures.

Scheme 1. Reagents and Conditions: (i) (a)  $MgCl_2$ ,  $Et_3N$ ,  $CH_3CN$ , rt, 2h; (b) CDI, rt, overnight then reflux, 2 h; (ii) thiourea, EtONa, EtOH, reflux, 6h; (iii)  $HC\equiv CCH_2Br$ ,  $K_2CO_3$ , DMF; (iv) (substituted) $Ar^1$ - $CH_2N_3$ , VcNa, CuSO\_4.5H\_2O, H\_2O, tertiary butanol, 65°C; (v) HOAc, PbO\_2, I\_2.

### 2.2. Anti-HIV activity evaluation

The newly synthesized S-DABO derivatives were evaluated for their cytotoxicity and anti-HIV activities in MT-4 cell cultures infected by HIV-1 IIIB strain (WT), HIV-1

mutant strain RES056 (K103N/Y181C double mutanted RT) and HIV-2 strain ROD, respectively. The FDA-approved drugs nevirapine (NVP), lamivudine (3TC), azidothymidine (AZT), Didanosine (DDI), delavirdine (DLV), efavirenz (EFV) and etravirine (ETV, TMC125) were chosen as reference drugs. Comparisons of the antiviral inhibitory concentration (EC<sub>50</sub>), cytotoxic concentration (CC<sub>50</sub>), and SI (selectivity, given by the CC<sub>50</sub>/EC<sub>50</sub> ratio) values for diverse compounds were depicted in **Table 1** and **Table 2**.

### Table 1.

5-Hydrogen/methyl/iodo-6-(naphthalen-1-ylmethyl)-2-((1-(arylmethyl)-1H-1,2,3-triazol-4-yl)methylthio)pyrimidin-4(3H)-one.

**Table 2.** 5-Hydrogen/methyl/iodo-6-(2,6-dichlorobenzyl)-2-((1-(arylmethyl)-1H-1,2,3-triazol-4-yl)methylthio)pyrimidin-4(3H)-one.

The results revealed that six target compounds (**B5b1**, **B5B3-B5b7**) had remarkable activities against WT HIV-1, with EC<sub>50</sub> values in the low micromolecular range, which was better than that of DDI (EC<sub>50</sub> = 23.20  $\mu$ M). Even so, they were less active in comparison with the previously reported C-2 substituted S-DABO derivatives and other reference drugs [9,10]. The most active compound 4-((4-((4-(2,6-dichlorobenzyl)-5-methyl-6-oxo-1,6-dihydropyrimidin-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzenesulfonamide (**B5b7**) showed activity with EC<sub>50</sub> value of 3.22  $\mu$ M comparable to that of 3TC (EC<sub>50</sub> = 2.24  $\mu$ M). In addition, these S-DABOs analogues did not proved active HIV-2 and HIV-1 mutant strain RES056. Taking together, these data we can assume that the novel S-DABOs most probably act as genuine NNRTIs.

In terms of SARs, it became immediately apparent that substitution at C-6 of the pyrimidine ring were detrimental, since the 2,6-dichlorobenzyl subseries was

generally more active than the corresponding naphthalen-1-ylmethyl subseries. Only compound **A5b7** in naphthalen-1-ylmethyl series demonstrated weak HIV inhibitory effect.

As with the SAR of previous S-DABOs, the presence of suitable substituents at the C-5 position of uracil ring closely correlated with the antiviral activity. Optimal anti-HIV-1 activity was obtained with compounds bearing a methyl moiety at the C-5 site (**B5b1-B5b7**). There was still one compound (**B5a1**) in C-5 unsubstituted subseries (**B5a1-B5a7**) with EC<sub>50</sub> value in double-digit mrcromolar level. Whereas, when a iodine atom was introduced to this position, the bioactivity was completely impaired.

Moreover, this study also suggested that the nature of the substituent on the 4-position of the phenyl ring (terminal of C-2 side chain) significantly influenced on the antiviral activity of these novel S-DABOs. Notably, among compounds **B5b1-B5b7**, SO<sub>2</sub>NH<sub>2</sub> (**B5b7**) appeared to be the most favorable group, closely followed in the sequence 4-COMe > 4-OMe > 4-CN > 4-CONH<sub>2</sub> > 4-H > 4-F. It is interesting to note that, in many types of NNRTIs, the optimum activity was often found with substituents containing hydrophilic SO<sub>2</sub>NH<sub>2</sub>, indicating its nature can better accommodate the chemical environment in this region of RT and provide potential interactions with amino acids. This conclusion was consistent with those previously observed results in the arylazolyl(azinyl)thioacetanilides series [13,14].

### 3. Conclusion

As part of a project devoted to structural optimization of the S-DABOs NNRTIS and to the further elucidation of the SARs around this scaffold, a new series of S-DABO analogues, characterized by the same central scaffold and a variously functionalized 1,2,3-triazole linked side chain at C-2 position of the pyrimidone ring, were prepared and assessed for their anti-HIV activity and cytotoxicity *in vitro*.

Generally, some of the synthesized compounds displayed remarkable anti-HIV-1 (WT) activity in low micromolar level. The best compound of this series was compound **B5b7**, which exhibited potent activity with  $EC_{50}$  value of 3.22  $\mu$ M comparable to that of 3TC ( $EC_{50} = 2.24 \mu$ M). Preliminary SAR studies provided some insights for discovery of more potent NNRTIS.

### 4. Experimental Section

### 4.1 Chemistry

All melting points were determined on a micro melting point apparatus and are uncorrected. <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra were obtained on a Bruker Avance-400NMR-spectrometer in the indicated solvents. Chemical shifts are expressed in  $\delta$  units and TMS as internal reference. Mass spectra were taken on a LC Autos ampler Device: Standard G1313A instrument. TLC was performed on Silica Gel GF254 for TLC (Merck) and spots were visualized by iodine vapours or by irradiation with UV light ( $\lambda$ = 254 nm). Flash column chromatography was performed on column packed with Silica Gel60 (230-400 mesh). Solvents were reagent grade, when necessary, were purified and dried by standard methods. Concentration of the reaction solutions involved the use of rotary evaporator at reduced pressure.

### 4.1.1 General procedure for the preparation of substituted benzyl azides

Different substituted benzyl halide (1 mmol) were dissolved in anhydrous DMF (10 mL), followed by addition of sodium azide (1.2 mmol). The reaction mixture was stirred at room temperature overnight. Then 50 mL water was poured into the mixture, the mixture was extracted with ethyl acetate (3×10 mL). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give the corresponding substituted benzyl azides as crude products.

4.1.2 General procedure for the preparation of

5-hydrogen/methyl/iodo-6-(naphthalen-1-ylmethyl)-2-((1-(arylmethyl)-1H-1,2,3-tri azol-4-yl)methylthio)pyrimidin-4(3H)-ones.

## General procedure for the preparation of ethyl 4-(naphthalen-1-yl)-3-oxobutanoate (A2a) or ethyl 2-methyl-4-(naphthalen-1-yl)-3-oxobutanoate (A2b)

A mixture solution of starting material potassium 3-ethoxy-3-oxopropanoate (a) or potassium 3-ethoxy-2-methyl-3-oxopropanoate (**b**) (75.2 mmol), MgCl<sub>2</sub> (9.0 g, 94.5 mmol), Et<sub>3</sub>N (12.1 g, 120 mmol) in 150 mL anhydrous CH<sub>3</sub>CN were stirred at room temperature for 2 hours. Then this solution were added to another mixture solution of 2-(naphthalen-1-yl)acetic acid (7.0 g, 37.6 mmol) and CDI (7.3 g, 45 mmol) in 100 mL anhydrous CH<sub>3</sub>CN. The reaction mixture was stirred overnight at room temperature and then heated to reflux for 2h. After the mixture was cooled, a solution of 3N HCl (100 mL) was added slowly while the temperature was kept below 20°C, and the resulting clear mixtures were stirred for another 20 minutes. The organic layer was separated and concentrated, and the residue was treated with EtOAc (80 mL). The aqueous layer was extracted with EtOAc (3×100 mL), and the combined organic layers were washed with saturated NaHCO<sub>3</sub> (3×100 mL) and brine (3×100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give the crude product ethyl 4-(naphthalen-1-yl)-3-oxobutanoate (A2a) or ethyl 2-methyl-4-(naphthalen-1-yl)-3-oxobutanoate (A2b) as yellow oil, respectively, which were directly used in the next step without further purification.

General procedure for the preparation of 6-(naphthalen-1-ylmethyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (A3a) or 5-methyl-6-(naphthalen-1-ylmethyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (A3b) Sodium metal (0.92 g, 40mmol) was dissolved in absolute ethanol (20 mL), then thiourea (2.28 g, 30mmol) and the intermediate A2a or A2b (10 mmol) was added

successively. The reaction mixture was heated in reflux for 6 hours, then was evaporated to dryness under reduced pressure. The residue was re-dissolved in H<sub>2</sub>O (50 mL). The solution was acidified with 3M HCl solution to pH 4. The resulting precipitate was filtered, washed with H<sub>2</sub>O and Et<sub>2</sub>O successively, and dried to give the crude product **A3a** or **A3b** as white solid, which was directly used in the following step without further purification.

### 6-(naphthalen-1-ylmethyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one(A3a)

<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ: 12.60 (1H, s, NH), 12.42 (1H, s, NH), 7.95-7.98 (2H, m, aromatic), 7.89 (1H, d, *J* = 8.00 Hz), 7.48-7.58 (4H, m, aromatic), 5.13 (1H, s, CO-CH), 4.23(2H, s, Ph-CH<sub>2</sub>). ESI-MS: m/z 269.4 (M+1), 291.3 (M+Na). C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>OS (268.07).

### 5-methyl-6-(naphthalen-1-ylmethyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one

### (A3b)

<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ: 12.62 (1H, s, NH), 12.43 (1H, s, NH), 7.95-7.99 (2H, m, aromatic), 7.88 (1H, d, *J* = 8.00 Hz), 7.47-7.58 (4H, m, aromatic), 4.28(2H, s, Ph-CH<sub>2</sub>), 1.39(3H, s, CH<sub>3</sub>). ESI-MS: m/z 283.3 (M+1), 305.4 (M+Na). C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>OS (282.08).

### General procedure for the preparation of

6-(naphthalen-1-ylmethyl)-2-(prop-2-ynylthio)pyrimidin-4(3H)-one (A4a) or 5-methyl-6-(naphthalen-1-ylmethyl)-2-(prop-2-ynylthio)pyrimidin-4(3H)-one (A4b)

A mixture solution of intermediate **A3a** or **A3b** (7mmol), K<sub>2</sub>CO<sub>3</sub> (7mmol, 0.96 g) in 30 mL anhydrous DMF was stirred at room temperature for 30 min. Then propargyl bromide (6.3 mmol, 0.74 g) in 5 mL anhydrous DMF were dropwise added into the solution in 4 hours. TLC analysis indicated that the reaction was finished in 15h. Then 100 mL ice water was poured into the mixture. The formed solid was filtrated, washed with water. Then the crude product was recrystallized in MeOH to get the desired product **A4a** or **A4b** as yellow solid.

### 6-(naphthalen-1-ylmethyl)-2-(prop-2-ynylthio)pyrimidin-4(3H)-one(A4a)

<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ: 12.74 (1H, s, NH), 7.95-7.98 (2H, m, aromatic), 7.91 (1H, d, *J* = 8.00 Hz), 7.48-7.59 (4H, m, aromatic), 5.13 (1H, s, CO-CH), 4.23(2H, s, Ph-CH<sub>2</sub>), 3.96(2H, s, S-CH<sub>2</sub>), 3.08(1H, s, C=CH). ESI-MS: m/z 307.3 (M+1), 329.4 (M+Na). C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>OS (306.08).

### 5-methyl-6-(naphthalen-1-ylmethyl)-2-(prop-2-ynylthio)pyrimidin-4(3H)-one (A4b)

<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ: 12.74 (1H, s, NH), 7.96-7.98 (2H, m, aromatic), 7.89 (1H, d, *J* = 8.00 Hz), 7.48-7.57 (4H, m, aromatic), 4.20 (2H, s, Ph-CH<sub>2</sub>), 3.91(2H, s, S-CH<sub>2</sub>), 3.07(1H, s, C=CH), 1.39 (3H, s, CH<sub>3</sub>). ESI-MS: m/z 321.3 (M+1), 343.5 (M+Na). C<sub>19</sub>H<sub>16</sub>N<sub>2</sub>OS (320.10).

## General procedure for the preparation of 6-(naphthalen-1-ylmethyl)-2-((1-(arylmethyl)-1H-1,2,3-triazol-4-yl)methylthio)pyri midin-4(3H)-one (A5a1-A5a7) or 5-methyl-6-(naphthalen-1-ylmethyl)-2-((1-(arylmethyl)-1H-1,2,3-triazol-4-yl)methyl thio)pyrimidin-4(3H)-one (A5b1-A5b7)

To a mixture of intermediate **A4a** or **A4b** (0.65 mmol) and substituted benzyl azide (0.65 mmol) in water and tertiary butanol (v/v= 1:1, 15 mL), the water solution (1N) of sodiumascorbate (0.04 g, 0.195 mmol) was added, followed by the addition of copper (II) sulfate pentahydrate (0.065 mmol, 0.017g) in water (7.5 % solution). The heterogeneous mixture was stirred vigorously at 65°C for 8 hours. The formed solid was filtrated and washed with water. Then the crude product was recrystallized in MeOH to give the products

6-(naphthalen-1-ylmethyl)-2-((1-(arylmethyl)-1H-1,2,3-triazol-4-yl)methylthio)pyrimi din-4(3H)-one (**A5a1-A5a7**) or

5-methyl-6-(naphthalen-1-ylmethyl)-2-((1-(arylmethyl)-1H-1,2,3-triazol-4-yl)methylth io)pyrimidin-4(3H)-one (**A5b1-A5b7**) as white or light yellow solids.

## General procedure for the preparation of 5-iodo-6-(naphthalen-1-ylmethyl)-2-((1-(arylmethyl)-1H-1,2,3-triazol-4-yl)methylthi o)pyrimidin-4(3H)-one (A5c1-A5c7)

To a solution of **A5a1-A5a7** (0.5 mmol) in HOAc (5 mL) was added the PbO<sub>2</sub> (0.30 mmol) and I<sub>2</sub> (0.30 mmol), and the mixture were stirred at room temperature. After completion of the reaction according to TLC analysis, the mixture was poured into H<sub>2</sub>O (50 mL). The resulting solid was then filtered, washed with water, and purified by silica gel column chromatography to afford the final products **A5c1-A5c7**.

## 2-(((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-6-(naphthalen-1-ylmethyl) pyrimidin-4(3H)-one (A5a1)

Recrystallized from methanol as a light yellow crystal, yield 72.1%, mp:195-197°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ : 12.54 (1H, s, NH), 8.11 (1H, dd, *J* = 5.60, 3.24 Hz), 7.82 (1H, d, *J* = 7.60 Hz), 7.66 (1H, s, triazole-H), 7.44-7.51 (4H, m, aromatic), 7.30 (2H, dd, *J* = 8.52, 5.72 Hz), 7.19 (2H, t, *J* = 8.88 Hz), 5.92 (1H, s, CO-CH), 5.47 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.31 (2H, s, Ph-CH<sub>2</sub>), 4.30 (2H, s, S-CH<sub>2</sub>). ESI-MS:m/z 458.4 (M+1), 480.3 (M+Na). C<sub>25</sub>H<sub>20</sub>FN<sub>5</sub>OS (457.52).

## 2-(((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)thio)-6-(naphthalen-1-ylmethyl)pyrimidin -4(3H)-one (A5a2)

Recrystallized from methanol as a white crystal, yield 63.7%, mp:190-192°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ : 12.54 (1H, s, NH), 8.11 (1H, dd, *J* = 5.92, 3.16 Hz), 7.91 (1H, dd, *J* = 6.08, 3.24 Hz), 7.81 (1H, d, *J* = 7.68 Hz), 7.64 (1H, s, triazole-H), 7.43-7.51 (4H, m, aromatic), 7.30-7.37 (3H, m, aromatic), 7.21 (2H, d, *J* = 6.84 Hz), 5.92 (1H, s, CO-CH), 5.47 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.31 (2H, s, Ph-CH<sub>2</sub>), 4.29 (2H, s, S-CH<sub>2</sub>). ESI-MS:m/z 440.4 (M+1), 462.4(M+Na). C<sub>25</sub>H<sub>21</sub>N<sub>5</sub>OS (439.53).

## 2-(((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-6-(naphthalen-1-ylmeth yl)pyrimidin-4(3H)-one (A5a3)

Recrystallized from methanol as a white crystal, yield 70.2%, mp:193-195°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ :12.56 (1H, s, NH), 8.11 (1H, dd, *J* = 5.68, 3.00 Hz), 7.92 (1H, dd, *J* = 6.08, 3.24 Hz), 7.83 (1H, d, *J* = 7.84 Hz), 7.60 (1H, s, triazole-H), 7.44-7.51 (4H, m, aromatic), 7.20 (2H, d, *J* = 8.40 Hz), 6.89 (2H, d, *J* = 8.48 Hz),5.93 (1H, s, CO-CH), 5.39 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.30 (2H, s, Ph-CH<sub>2</sub>), 4.29 (2H, s, S-CH<sub>2</sub>), 3.73 (3H, s, OCH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ : 159.6, 134.4, 133.9, 132.1, 129.9, 128.9, 128.5, 128.3, 127.8, 126.6, 126.2, 126.1, 124.9, 123.5, 114.5, 55.6, 52.7, 24.8. ESI-MS: m/z 470.4 (M+1), 492.3 (M+Na). C<sub>26</sub>H<sub>23</sub>N<sub>5</sub>O<sub>2</sub>S (469.56).

### 4-((4-(((4-(naphthalen-1-ylmethyl)-6-oxo-1,6-dihydropyrimidin-2-yl)thio)methyl)-1H -1,2,3-triazol-1-yl)methyl)benzamide (A5a4)

Recrystallized from methanol as a white crystal, yield 75.4%, mp:250-252°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ: 12.54 (1H, s, NH), 8.11 (1H, d, *J* = 4.52 Hz), 7.80-7.98 (5H, m, aromatic), 7.67 (1H, s, triazole-H), 7.40-7.50 (5H, m, aromatic), 7.27 (2H, d, *J* = 7.80 Hz), 5.94 (1H, s, CO-CH), 5.55 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.33 (2H, s, Ph-CH<sub>2</sub>), 4.30 (2H, s, S-CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm) δ: 167.9, 139.4, 134.6, 134.4, 133.9, 132.1, 128.9, 128.4, 128.3, 127.9, 127.8, 126.6, 126.2, 126.1, 124.9, 124.0, 52.8, 24.9. ESI-MS: m/z 483.3 (M+1), 505.3(M+Na). C<sub>26</sub>H<sub>22</sub>N<sub>6</sub>O<sub>2</sub>S (482.56).

## 2-((4-(((4-(naphthalen-1-ylmethyl)-6-oxo-1,6-dihydropyrimidin-2-yl)thio)methyl)-1H -1,2,3-triazol-1-yl)methyl)benzonitrile (A5a5)

Recrystallized from methanol as a white crystal, yield 67.2%, mp: 170-173°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ : 12.59 (1H, s, NH), 8.11 (1H, dd, *J* = 8.92, 3.16 Hz), 7.92 (2H, dd, *J* = 12.40, 7.16 Hz), 7.77-7.82 (2H, m, aromatic), 7.70(1H, t, *J* = 7.48 Hz), 7.56 (1H, t, *J* = 7.52 Hz), 7.44-7.50 (4H, m, aromatic), 7.22 (1H, d, *J* = 7.76 Hz), 5.91 (1H, s, CO-CH), 5.71 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.33 (2H, s, Ph-CH<sub>2</sub>), 4.31 (2H, s, S-CH<sub>2</sub>). ESI-MS: m/z 465.3 (M+1), 487.3 (M+Na). C<sub>26</sub>H<sub>20</sub>N<sub>6</sub>OS (464.54).

## 2-(((1-(2-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-6-(naphthalen-1-ylmethyl )pyrimidin-4(3H)-one (A5a6)

Recrystallized from methanol as a white crystal, yield 62.1%, mp:101-104°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ :12.54 (1H, s, NH), 8.10 (1H, dd, *J* = 9.56, 3.44 Hz), 7.88 (1H, d, *J* = 3.32 Hz), 7.79 (1H, dd, *J* = 8.60, 1.20 Hz), 7.58 (1H, s, triazole-H), 7.42-7.52 (4H, m, aromatic), 7.24 (1H, td, *J* = 7.44, 0.72 Hz), 7.16 (1H, td, *J* = 7.48, 2.32 Hz), 6.93 (1H, d, *J* = 7.56 Hz), 5.92 (1H, s, CO-CH), 5.53 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.31 (2H, s, Ph-CH<sub>2</sub>), 4.28 (2H, s, S-CH<sub>2</sub>), 2.27 (3H, s, Ph-CH<sub>3</sub>). ESI-MS: m/z 454.3 (M+1), 476.3 (M+Na). C<sub>26</sub>H<sub>23</sub>N<sub>5</sub>OS (453.56).

## 4-((4-(((4-(naphthalen-1-ylmethyl)-6-oxo-1,6-dihydropyrimidin-2-yl)thio)methyl)-1H -1,2,3-triazol-1-yl)methyl)benzenesulfonamide (A5a7)

Recrystallized from methanol as a white crystal, yield 79.3%, mp:140-142°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ : 12.49 (1H, s, NH), 8.13 (1H, dd, *J* = 9.48, 3.64 Hz), 7.91 (1H, dd, *J* = 5.52, 2.04 Hz), 7.80-7.83 (4H, m, aromatic), 7.67 (1H, s, triazole-H), 7.30-7.52 (5H, m, aromatic), 5.93 (1H, s, CO-CH), 5.56 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.32 (2H, s, Ph-CH<sub>2</sub>), 4.30 (2H, s, S-CH<sub>2</sub>). ESI-MS: m/z 519.3 (M+1), 541.3 (M+Na). C<sub>25</sub>H<sub>22</sub>N<sub>6</sub>O<sub>3</sub>S<sub>2</sub> (518.61).

## 2-(((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5-methyl-6-(naphthalen-1ylmethyl)pyrimidin-4(3H)-one (A5b1)

Recrystallized from methanol as a light yellow crystal, yield 75.6%, mp: 207-210°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ : 12.52 (1H, s, NH), 8.13 (1H, dd, *J* = 5.96, 2.48 Hz), 7.88 (1H, dd, *J* = 6.68, 3.96 Hz), 7.75 (1H, d, *J* = 8.16 Hz), 7.49 (2H, td, *J* = 6.04, 2.32 Hz), 7.38 (1H, t, *J* = 7.24 Hz), 7.15-7.29 (6H, m, aromatic), 5.38 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.36 (2H, s, Ph-CH<sub>2</sub>), 4.02 (2H, s, S-CH<sub>2</sub>), 2.03 (3H, s, pyrimidone-CH<sub>3</sub>). ESI-MS: m/z 472.4 (M+1), 494.5 (M+Na). C<sub>26</sub>H<sub>22</sub>FN<sub>5</sub>OS (471.55).

## 2-(((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)thio)-5-methyl-6-(naphthalen-1-ylmethyl) pyrimidin-4(3H)-one (A5b2)

Recrystallized from methanol as a white crystal, yield 61.0%, mp:175-177°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ: 12.61 (1H, s, NH), 8.13 (1H, dd, *J* = 9.12, 1.80 Hz), 7.87 (1H, dd, *J* = 7.00, 2.92 Hz), 7.73 (1H, d, *J* = 8.16 Hz), 7.47-7.51 (2H, m, aromatic), 7.25-7.39 (6H, m, aromatic), 7.16 (2H, dd, *J* = 7.64, 2.20 Hz), 5.38 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.36 (2H, s, Ph-CH<sub>2</sub>), 4.04 (2H, s, S-CH<sub>2</sub>), 2.04 (3H, s, pyrimidone-CH<sub>3</sub>). ESI-MS: m/z 454.4 (M+1), 476.4 (M+Na). C<sub>26</sub>H<sub>23</sub>N<sub>5</sub>OS (453.56).

## 2-(((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5-methyl-6-(naphthalen -1-ylmethyl)pyrimidin-4(3H)-one (A5b3)

Recrystallized from methanol as a white crystal, yield 72.4%, mp:164-166°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ: 12.56 (1H, s, NH), 8.15 (1H, dd, *J* = 9.16, 2.28 Hz), 7.89 (1H, dd, *J* = 6.68, 3.92 Hz), 7.76 (1H, d, *J* = 8.16 Hz), 7.50 (2H, td, *J* = 6.04, 2.32 Hz), 7.39 (1H, t, *J* = 7.32 Hz), 7.26 (1H, d, *J* = 5.12 Hz), 7.12 (1H, d, *J* = 8.60 Hz), 6.87 (2H, d, *J* = 8.64 Hz), 5.30 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.34 (2H, s, Ph-CH<sub>2</sub>), 4.04 (2H, s, S-CH<sub>2</sub>), 3.73 (3H, s, O-CH<sub>3</sub>), 2.02 (3H, s, pyrimidone-CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm) δ: 159.5, 144.0, 135.0, 133.8, 132.4, 129.8, 128.8, 128.2, 127.3, 127.1, 126.4, 126.2, 126.0, 124.8, 123.1, 114.5, 55.6, 52.7, 37.7, 24.5, 11.0. ESI-MS: : m/z 484.5 (M+1), 506.5(M+Na). C<sub>27</sub>H<sub>25</sub>N<sub>5</sub>O<sub>2</sub>S (483.58).

## 4-((4-(((5-methyl-4-(naphthalen-1-ylmethyl)-6-oxo-1,6-dihydropyrimidin-2-yl)thio) methyl)-1H-1,2,3-triazol-1-yl)methyl)benzamide (A5b4)

Recrystallized from methanol as a white crystal, yield 63.2%, mp: 238-240°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ: 12.54 (1H, s, NH), 8.12 (1H, d, *J* = 7.56 Hz), 7.95 (1H, s), 7.83-7.88 (3H, m, aromatic), 7.73 (1H, d, *J* = 8.12 Hz), 7.48 (2H, td, *J* = 5.04, 1.64 Hz), 7.37 (2H, t, *J* =7.36 Hz), 7.27-7.30 (2H, m, aromatic), 7.20 (2H, d, *J* = 8.16 Hz), 5.45 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.35 (2H, s, Ph-CH<sub>2</sub>), 4.05 (2H, s, S-CH<sub>2</sub>), 2.02 (3H, s, pyrimidone-CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ :167.8, 144.1, 139.4, 134.9,

134.5, 133.7, 132.4, 128.8, 128.3, 127.9, 127.3, 127.2, 126.4, 126.1, 125.9, 124.8, 123.6, 52.7, 37.6, 24.4, 11.0. ESI-MS: m/z 497.5 (M+1), 519.4(M+Na). C<sub>27</sub>H<sub>24</sub>N<sub>6</sub>O<sub>2</sub>S (496.58).

## 2-((4-(((5-methyl-4-(naphthalen-1-ylmethyl)-6-oxo-1,6-dihydropyrimidin-2-yl)thio) methyl)-1H-1,2,3-triazol-1-yl)methyl)benzonitrile (A5b5)

Recrystallized from methanol as a yellow crystal, yield 71.0%, mp: 130-132°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ :12.62 (1H, s, NH), 8.12 (1H, dd, *J* = 8.92, 3.16 Hz), 7.92 (2H, dd, *J* = 10.60, 7.16 Hz), 7.62-7.82 (2H, m, aromatic), 7.70 (1H, t, *J* = 7.62 Hz), 7.52 (1H, t, *J* = 7.52 Hz), 7.42-7.53 (2H, m, aromatic), 7.20 (1H, d, *J* = 7.76 Hz), 7.14 (1H, d, *J* = 7.76 Hz), 5.61 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.36 (2H, s, Ph-CH<sub>2</sub>), 4.06 (2H, s, S-CH<sub>2</sub>), 2.04 (3H, s, pyrimidone-CH<sub>3</sub>). ESI-MS: m/z 479.4 (M+1), 501.4 (M+Na). C<sub>27</sub>H<sub>22</sub>N<sub>6</sub>OS (478.57).

### 5-methyl-2-(((1-(2-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-6-(naphthalen-1 -ylmethyl)pyrimidin-4(3H)-one (A5b6)

Recrystallized from methanol as a white crystal, yield 72.4%, mp:145-147°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ : 12.54 (1H, s, NH), 8.10 (1H, d, *J* = 7.92 Hz), 7.84 (1H, dd, *J* = 7.28, 1.72 Hz), 7.71 (1H, d, *J* = 8.16 Hz), 7.49 (2H, td, *J* = 7.68, 1.40 Hz), 7.35 (1H, t, *J* = 7.28 Hz), 7.21-7.27 (4H, m, aromatic), 7.12 (1H, td, *J* = 7.48, 1.60 Hz), 6.84 (1H, d, *J* = 7.52 Hz), 5.40 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.33 (2H, s, Ph-CH<sub>2</sub>), 4.04 (2H, s, S-CH<sub>2</sub>), 2.23 (3H, s, Ph-CH<sub>3</sub>), 2.02 (3H, s, pyrimidone-CH<sub>3</sub>). ESI-MS: m/z 468.4 (M+1) , 470.5 (M+3), 484.6 (M+Na). C<sub>27</sub>H<sub>25</sub>N<sub>5</sub>OS (467.59).

## 4-((4-(((5-methyl-4-(naphthalen-1-ylmethyl)-6-oxo-1,6-dihydropyrimidin-2-yl)thio) methyl)-1H-1,2,3-triazol-1-yl)methyl)benzenesulfonamide (A5b7)

Recrystallized from methanol as a white crystal, yield 78.2%, mp:160-162°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ: 12.56 (1H, s, NH), 8.13 (1H, d, *J* = 7.72 Hz), 7.86 (1H, dd, *J* = 7.28, 1.92 Hz), 7.79 (2H, d, *J* = 8.28 Hz), 7.73 (1H, d, *J* = 8.12 Hz), 7.49 (2H, td, *J* = 5.72, 1.64 Hz), 7.29-7.41 (7H, m, aromatic), 5.48 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.37 (2H,

s, Ph-CH<sub>2</sub>), 4.06 (2H, s, S-CH<sub>2</sub>), 2.04 (3H, s, pyrimidone-CH<sub>3</sub>). ESI-MS: m/z 533.5 (M+1), 555.3 (M+Na). C<sub>26</sub>H<sub>24</sub>N<sub>6</sub>O<sub>3</sub>S<sub>2</sub>(532.64).

## 2-(((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5-iodo-6-(naphthalen-1-yl methyl)pyrimidin-4(3H)-one (A5c1)

Recrystallized from methanol as a white crystal, yield 70.3%, mp:131-133°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ : 13.06 (1H, s, NH), 8.06 (1H, d, *J* = 8.80 Hz), 7.88 (1H, d, *J* = 6.92 Hz), 7.77 (1H, d, *J* = 8.16 Hz), 7.36-7.52 (4H, m, aromatic), 7.16-7.26 (5H, m, aromatic), 5.37 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.55(2H, s, Ph-CH<sub>2</sub>), 3.98 (2H, s, S-CH<sub>2</sub>). ESI-MS: m/z 584.1 (M+1), 606.3 (M+Na). C<sub>25</sub>H<sub>19</sub>FIN<sub>5</sub>OS (583.42).

### 2-(((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)thio)-5-iodo-6-(naphthalen-1-ylmethyl)py rimidin-4(3H)-one (A5c2)

Recrystallized from methanol as a light yellow crystal, yield 67.5%, mp: 120-122°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ : 13.01 (1H, s, NH), 8.05 (1H, d, *J* = 7.60 Hz), 7.88 (1H, dd, *J* = 7.20, 1.92 Hz), 7.75 (1H, d, *J* = 8.04 Hz), 7.49 (2H, td, *J* = 7.16, 1.48 Hz), 7.16-7.39 (6H, m, aromatic), 7.14 (2H, dd, *J* = 7.76, 5.72 Hz), 5.37 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.54 (2H, s, Ph-CH<sub>2</sub>), 3.98 (2H, s, S-CH<sub>2</sub>). ESI-MS: m/z 566.3 (M+1), 588.2 (M+Na). C<sub>25</sub>H<sub>20</sub>IN<sub>5</sub>OS (565.43).

### 5-iodo-2-(((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-6-(naphthalen-1ylmethyl)pyrimidin-4(3H)-one (A5c3)

Recrystallized from methanol as a white crystal, yield 63.4%, mp:192-195°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ:13.05 (1H, s, NH), 8.08 (1H, dd, *J* = 9.00, 1.68 Hz), 7.90 (1H, dd, *J* = 7.04, 2.92 Hz), 7.78 (1H, d, *J* = 8.08 Hz), 7.52 (2H, td, *J* = 6.80, 1.76 Hz), 7.33-7.41 (2H, m, aromatic), 7.18 (1H, s), 7.12 (2H, d, *J* = 8.60 Hz), 5.28 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.55 (2H, s, Ph-CH<sub>2</sub>), 3.98 (2H, s, S-CH<sub>2</sub>), 3.73 (3H, s, O-CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm) δ: 159.6, 143.4, 134.3, 133.8, 132.3, 129.8, 128.9, 128.2, 127.6, 127.4, 126.6, 126.2, 126.0, 124.7, 123.2, 114.5, 55.6, 52.7, 44.1, 24.8. ESI-MS: m/z 596.3 (M+1), 618.4 (M+Na). C<sub>26</sub>H<sub>22</sub>IN<sub>5</sub>O<sub>2</sub>S (595.45).

## 4-((4-(((5-iodo-4-(naphthalen-1-ylmethyl)-6-oxo-1,6-dihydropyrimidin-2-yl)thio)met hyl)-1H-1,2,3-triazol-1-yl)methyl)benzamide (A5c4)

Recrystallized from methanol as a light yellow crystal, yield 70.2%, mp:201-203°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ :13.085 (1H, s, NH), 8.068 (1H, d, *J* = 8.00 Hz), 7.98 (1H, s), 7.85-7.89 (3H, m, aromatic), 7.76 (1H, dd, *J* = 9.00, 2.16 Hz), 7.52 (2H, td, *J* = 6.64, 5.56 Hz), 7.36-7.40 (3H, m, aromatic), 7.20-7.25 (3H, m, aromatic), 5.44 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.55 (2H, s, Ph-CH<sub>2</sub>), 4.00 (2H, s, S-CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ : 167.8, 143.6, 139.3, 134.5, 134.3, 133.7, 132.3, 128.9, 128.3, 127.9, 127.6, 127.4, 126.6, 126.2, 125.9, 124.7, 123.7, 52.7, 44.1, 24.7. ESI-MS: m/z 609.2 (M+1), 631.4 (M+Na). C<sub>26</sub>H<sub>21</sub>IN<sub>6</sub>O<sub>2</sub>S (608.45).

## 2-((4-(((5-iodo-4-(naphthalen-1-ylmethyl)-6-oxo-1,6-dihydropyrimidin-2-yl)thio)met hyl)-1H-1,2,3-triazol-1-yl)methyl)benzonitrile (A5c5)

Recrystallized from methanol as a brown crystal, yield 63.5%, mp:148-151°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ :13.06 (1H, s, NH), 8.07 (1H, d, *J* = 8.24 Hz), 7.86-7.93 (2H, m, aromatic), 7.67-7.76 (2H, m, aromatic), 7.47-7.58 (4H, m, aromatic), 7.19-7.38 (2H, m, aromatic), 7.16 (1H, dd, *J* = 14.00, 7.68 Hz), 5.61 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.52 (2H, s, Ph-CH<sub>2</sub>), 4.00 (2H, s, S-CH<sub>2</sub>). ESI-MS: m/z 591.3 (M+1) , 613.2 (M+Na). C<sub>26</sub>H<sub>19</sub>IN<sub>6</sub>OS (590.44).

# 5-iodo-2-(((1-(2-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-6-(naphthalen-1-yl methyl)pyrimidin-4(3H)-one (A5c6)

Recrystallized from methanol as a brown crystal, yield 72.3%, mp:190-192°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ :13.06 (1H, s, NH), 8.10 (1H, d, *J* = 7.92 Hz), 7.84 (1H, dd, *J* = 7.08, 2.12 Hz), 7.71 (1H, d, *J* = 8.08 Hz), 7.48 (2H, td, *J* = 5.24, 2.52 Hz), 7.34 (1H, t, *J* = 7.40 Hz), 7.21-7.23 (4H, m, aromatic), 7.12 (1H, td, *J* = 7.32, 2.08 Hz), 6.87 (1H, d, *J* = 7.44 Hz), 5.42 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.34 (2H, s, Ph-CH<sub>2</sub>), 3.98 (2H, s, S-CH<sub>2</sub>), 2.25 (3H, s, Ph-CH<sub>3</sub>). ESI-MS: m/z 580.3 (M+1), 602.3 (M+Na). C<sub>26</sub>H<sub>22</sub>IN<sub>5</sub>OS (579.46).

## 4-((4-(((5-iodo-4-(naphthalen-1-ylmethyl)-6-oxo-1,6-dihydropyrimidin-2-yl)thio)met hyl)-1H-1,2,3-triazol-1-yl)methyl)benzenesulfonamide (A5c7)

Recrystallized from methanol as a light yellow crystal, yield 77.2%, mp:194-197°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ : 12.14 (1H, s, NH), 8.12 (1H, d, *J* = 7.52 Hz), 7.87 (1H, dd, *J* = 9.32, 2.28 Hz), 7.78 (2H, d, *J* = 8.28 Hz), 7.73 (1H, d, *J* = 8.16 Hz), 7.48 (2H, td, *J* = 5.88, 1.80 Hz), 7.29-7.41 (7H, m, aromatic), 5.50 (2H, s, Ph-CH<sub>2</sub>-triazole), 4.43 (2H, s, Ph-CH<sub>2</sub>), 4.03 (2H, s, S-CH<sub>2</sub>). ESI-MS: m/z 645.3 (M+1), 645.3 (M+3), 667.2 (M+Na). C<sub>25</sub>H<sub>21</sub>IN<sub>6</sub>O<sub>3</sub>S<sub>2</sub> (644.51).

4.1.3 General procedure for the preparation of 5-hydrogen/methyl/iodo-6-(2,6 -dichlorobenzyl)-2-((1-(arylmethyl)-1H-1,2,3-triazol-4-yl)methylthio)pyrimidin-4(3H )-one(B5a1-B5a7; B5b1-B5b7; B5c1-B5c7).

5-Hydrogen/methyl/iodo-6-(2,6-dichlorobenzyl)-2-((1-(arylmethyl)-1H-1,2,3-triazol-4 -yl)methylthio)pyrimidin-4(3H)-ones were accomplished efficiently using the well-established synthetic protocols described in **Section 4.1.2**.

### ethyl 4-(2,6-dichlorophenyl)-3-oxobutanoate (B2a)

<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ: 7.32 (2H, d, *J* = 8.00 Hz, 3,5-PhH), 7.16 (1H, t, *J* = 8.00 Hz, 4-PhH), 4.20-4.25 (4H, m), 3.56 (2H, s,CO-CH<sub>2</sub>-CO), 1.30 (3H, t, *J* = 8.00 Hz, CH<sub>3</sub>). C<sub>12</sub>H<sub>12</sub>Cl<sub>2</sub>O<sub>3</sub>

### ethyl 4-(2,6-dichlorophenyl)-2-methyl-3-oxobutanoate (B2b)

<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ: 7.32 (2H, d, *J* = 8.00 Hz, 3,5-PhH), 7.16 (1H, t, *J* = 8.00 Hz, 4-PhH), 4.20-4.26 (4H, m), 3.51 (1H, q, *J* = 8.00 Hz, CO-CH-CO), 1.30 (3H, t, *J* = 8.00 Hz, O-CH<sub>2</sub>-CH<sub>3</sub>), 0.91 (3H, d, *J* = 8.00 Hz, CH-CH<sub>3</sub>). C<sub>13</sub>H<sub>14</sub>Cl<sub>2</sub>O<sub>3</sub>

### 6-(2,6-dichlorobenzyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (B3a)

<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ: 12.47 (1H, s, NH), 12.34 (1H, s, NH), 7.51 (2H, d, *J* = 8.00 Hz, 3,5-PhH), 7.34 (1H, t, *J* = 8.00 Hz, 4-PhH), 5.78 (1H, s, CO-CH), 4.15(2H,

s, Ph-CH<sub>2</sub>). ESI-MS: m/z 287.3 (M+1), 289.5 (M+3), 291.3 (M+5), 309.5 (M+Na). C<sub>11</sub>H<sub>8</sub>Cl<sub>2</sub>N<sub>2</sub>OS (285.97).

### 6-(2,6-dichlorobenzyl)-5-methyl-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (B3b)

<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ: 12.47 (1H, s, NH), 12.32 (1H, s, NH), 7.50 (2H, d, J = 8.00 Hz, 3,5-PhH), 7.34 (1H, t, J = 8.00 Hz, 4-PhH), 4.20(2H, s, Ph-CH<sub>2</sub>), 1.37 (3H, s, CH<sub>3</sub>). ESI-MS: m/z 301.3 (M+1), 303.4 (M+3), 305.3 (M+5), 323.3 (M+Na). C<sub>12</sub>H<sub>10</sub>Cl<sub>2</sub>N<sub>2</sub>OS (299.99).

### 6-(2,6-dichlorobenzyl)-2-(prop-2-yn-1-ylthio)pyrimidin-4(1H)-one(B4a)

<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ: 12.73 (1H, s, NH), 7.51 (2H, d, *J* = 8.00 Hz, 3,5-PhH), 7.34 (1H, t, *J* = 8.00 Hz, 4-PhH), 5.78 (1H, s, CO-CH), 4.15(2H, s, Ph-CH<sub>2</sub>), 3.88(2H, s, S-CH<sub>2</sub>), 3.09(1H, s, C=CH). ESI-MS: m/z 325.3 (M+1), 327.3 (M+3), 329.4 (M+5), 347.2 (M+Na). C<sub>14</sub>H<sub>10</sub>Cl<sub>2</sub>N<sub>2</sub>OS (323.99).

### 6-(2,6-dichlorobenzyl)-5-methyl-2-(prop-2-yn-1-ylthio)pyrimidin-4(1H)-one (B4b)

<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ: 12.75 (1H, s, NH), 7.50 (2H, d, *J* = 8.00 Hz, 3,5-PhH), 7.34 (1H, t, *J* = 8.00 Hz, 4-PhH), 4.20 (2H, s, Ph-CH<sub>2</sub>), 3.91 (2H, s, S-CH<sub>2</sub>), 3.08(1H, s, C=CH), 1.37(3H, s, CH<sub>3</sub>). ESI-MS: m/z 339.3 (M+1), 341.5 (M+3), 343.4 (M+5), 361.5 (M+Na). C<sub>15</sub>H<sub>12</sub>Cl<sub>2</sub>N<sub>2</sub>OS (338.00).

### 2-(((1-(4-acetylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-6-(2,6-dichlorobenzyl)pyri midin-4(3H)-one (B5a1)

Recrystallized from methanol as a white crystal, yield 82.3%, mp: 198-200°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ : 12.63 (1H, s, NH), 7.94 (2H, d, *J* = 8.2Hz, C<sub>3</sub>,C<sub>5</sub>-Ph''-H), 7.66 (1H, s, triazole-H), 7.46 (2H, d, *J* = 8.0 Hz, C<sub>2</sub>,C<sub>6</sub>-Ph'-H), 7.38 (2H, d, *J* = 8.2 Hz, C<sub>3</sub>,C<sub>4</sub>-Ph'-H), 7.30 (1H, t, *J* = 7.8 Hz, C<sub>4</sub>-Ph''-H), 5.74 (1H, s, pyrimidin-H), 5.63 (2H, s, triazole-CH<sub>2</sub>), 4.35 (2H, s, S-CH<sub>2</sub>), 4.15 (2H, s, Ph-CH<sub>2</sub>), 2.56 (3H, s, CO-CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ : 197.93, 172.46, 164.11, 143.84, 141.45, 136.94,

135.99, 133.56, 130.16, 129.12, 128.93, 128.41, 124.02, 52.80, 38.39, 24.85, 21.51. ESI-MS: m/z 500.2 (M+1), 522.2 (M+Na). C<sub>23</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>5</sub>O<sub>2</sub>S (499.06).

### 6-(2,6-dichlorobenzyl)-2-(((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)pyri midin-4(3H)-one (B5a2)

Recrystallized from methanol as a white crystal, yield 84.5%,mp: 189-191°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ :12.62 (1H, s, NH), 7.76 (1H, s, triazole-H), 7.46 (2H, d, *J* = 8.0Hz, C<sub>3</sub>,C<sub>5</sub>-Ph''-H), 7.29-7.37 (3H, m, aromatic), 7.18 (1H, t, *J* = 7.8 Hz), 5.74 (1H, s, pyrimidone-H), 5.53 (2H, s, triazole-CH<sub>2</sub>), 4.34 (2H, s, S-CH<sub>2</sub>), 4.14 (2H, s, Ph-CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ : 163.57, 161.14, 143.84, 136.01, 133.61, 132.63, 130.61 (d, *J* = 8.0 Hz, C<sub>3</sub>,C<sub>5</sub>-Ph''), 130.11, 128.90, 123.71, 116.15, 115.93, 52.49, 38.45, 24.89.ESI-MS: m/z476.2 (M+1), 498.3 (M+Na). C<sub>21</sub>H<sub>16</sub>Cl<sub>2</sub>FN<sub>5</sub>OS (475.04).

## 2-(((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)thio)-6-(2,6-dichlorobenzyl)pyrimidin-4(3 H)-one (B5a3)

Recrystallized from methanol as a white crystal, yield 80.5%,mp: 218-221°C.<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ :12.64 (1H, s, NH), 7.74 (1H, s, triazole-H), 7.45 (2H, d, *J* = 8.0Hz, C<sub>3</sub>,C<sub>5</sub>-Ph''-H), 7.26-7.39(6H, m, aromatic), 5.75 (1H, s, pyrimidone-H), 5.53 (2H, s, triazole-CH<sub>2</sub>), 4.33 (2H, s, S-CH<sub>2</sub>), 4.15 ( 2H, s, Ph-CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ : 143.72, 136.41, 136.01, 133.59, 130.14, 129.21, 128.92, 128.60, 128.31, 123.74, 53.26, 38.42, 24.86. ESI-MS: m/z 458.4 (M+1), 480.3 (M+Na). C<sub>21</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>5</sub>OS (457.05).

## 4-((4-(((4-(2,6-dichlorobenzyl)-6-oxo-1,6-dihydropyrimidin-2-yl)thio)methyl)-1H-1,2, 3-triazol-1-yl)methyl)benzamide (B5a4)

Recrystallized from methanol as a white crystal, yield 79.6%, mp: 248-250°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ :12.65 (1H, s, NH), 7.97 (1H, s, triazole-H), 7.86 (2H, d, J = 8.1Hz, C<sub>3</sub>,C<sub>5</sub>-Ph'-H), 7.78 (1H, s), 7.45 (2H, d, J = 8.0Hz, C<sub>3</sub>,C<sub>5</sub>-Ph''-H), 7.28-7.38 (4H, m, aromatic), 5.77 (1H, s, pyrimidone-H), 5.60 (2H, s, triazole-CH<sub>2</sub>), 4.35 (2H, s, S-CH<sub>2</sub>), 4.16 (2H, s, Ph-CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ : 167.89, 164.39,

162.76, 143.81, 139.41, 136.01, 134.56, 133.61, 130.10, 128.90, 128.38, 128.05, 123.93, 52.87, 38.42, 24.87. ESI-MS: m/z 501.3 (M+1), 523.4 (M+Na). C<sub>22</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>6</sub>O<sub>2</sub>S (500.06).

## 6-(2,6-dichlorobenzyl)-2-(((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)p yrimidin-4(3H)-one (B5a5)

Recrystallized from methanol as a white crystal, yield 84.1%,mp: 174-176°C.<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ :12.57 (1H, s, NH), 7.70 (1H, s, triazole-H),7.46 (2H, d, *J* = 7.9Hz, C<sub>3</sub>,C<sub>5</sub>-Ph''-H), 7.28 (1H, t, *J* = 7.8 Hz, C<sub>4</sub>-Ph''-H), 7.24 (2H, d, *J* = 7.6Hz, C<sub>2</sub>,C<sub>6</sub>-Ph'-H), 6.91 (2H, d, *J* = 7.7Hz, C<sub>3</sub>,C<sub>5</sub>-Ph'-H), 5.73 (1H, s, pyrimidone-H), 5.44 (2H, s, triazole-CH<sub>2</sub>), 4.32 (2H, s, S-CH<sub>2</sub>), 4.11 (2H, s, Ph-CH<sub>2</sub>), 3.73 (3H, s, O-CH<sub>3</sub>).<sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ : 159.62, 136.02, 133.62, 130.13, 130.02, 128.90, 114.57, 55.59, 52.84, 38.45, 24.23. ESI-MS: m/z 488.3 (M+1), 510.3 (M+Na). C<sub>22</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>5</sub>O<sub>2</sub>S (487.06).

## 4-((4-(((4-(2,6-dichlorobenzyl)-6-oxo-1,6-dihydropyrimidin-2-yl)thio)methyl)-1H-1,2, 3-triazol-1-yl)methyl)benzonitrile (B5a6)

Recrystallized from methanol as a white crystal, yield 76.8%,mp: 215-217°C.<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ :12.60 (1H, s, NH), 7.84 (2H, d, *J* = 8.2Hz, C<sub>3</sub>,C<sub>5</sub>-Ph''-H), 7.82 (1H, s, triazole-H), 7.46 (2H, d, *J* = 8.0Hz, C<sub>3</sub>,C<sub>5</sub>-Ph'-H), 7.40 (2H, d, *J* = 8.1Hz, C<sub>2</sub>,C<sub>6</sub>-Ph'-H), 7.28 (1H, t, *J* = 7.9 Hz, C<sub>4</sub>-Ph''-H), 5.75 (1H, s, pyrimidone-H), 5.66 (2H, s, triazole-CH<sub>2</sub>), 4.35 (2H, s, S-CH<sub>2</sub>), 4.15 (2H, s, Ph-CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ : 170.79, 143,94, 141.91, 135.99, 133.58, 133.19, 130.14, 129.04, 128.92, 124.20, 118.98, 111.40, 52.62, 38.42, 24.84.ESI-MS: m/z 483.2 (M+1), 505.2 (M+Na)C<sub>22</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>6</sub>OS (482.05).

## 4-((4-(((4-(2,6-dichlorobenzyl)-6-oxo-1,6-dihydropyrimidin-2-yl)thio)methyl)-1H-1,2, 3-triazol-1-yl)methyl)benzenesulfonamide (B5a7)

Recrystallized from methanol as a white crystal, yield 83.2%, mp: 229-231°C.<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ :12.67 (1H, s, NH), 7.81 (2H, d, *J* = 8.2Hz, C<sub>3</sub>,C<sub>5</sub>-Ph'-H),

7.80 (1H, s, triazole-H), 7.34-7.48 (6H, m, aromatic), 7.28 (1H, t, *J* = 8.0 Hz, C<sub>4</sub>-Ph''-H), 5.76 (1H, s, pyrimidone-H), 5.62 (2H, s, triazole-CH<sub>2</sub>), 4.34 (2H, s, S-CH<sub>2</sub>), 4.16 (2H, s, Ph-CH<sub>2</sub>).<sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm) δ:163.25, 144.32, 143.84, 140.17, 136.01, 133.61, 130.13, 128.92, 128.75, 126.58, 124.00, 52.66, 38.43, 24.86. ESI-MS: m/z537.2 (M+1), 559.2 (M+Na). C<sub>21</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>6</sub>O<sub>3</sub>S<sub>2</sub> (536.03).

## 2-(((1-(4-acetylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-6-(2,6-dichlorobenzyl)-5-m ethylpyrimidin-4(3H)-one(B5b1)

Recrystallized from methanol as a white crystal, yield 85.3%,mp: 207-209°C.<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ:12.52 (1H, s, NH), 7.95 (2H, d, *J* = 8.2Hz, C<sub>3</sub>,C<sub>5</sub>-Ph"-H), 7.33-7.37 (5H , m, aromatic), 7.14 (1H, t, *J* = 7.8 Hz, C<sub>4</sub>-Ph"-H), 5.59 (2H, s, triazole-CH<sub>2</sub>), 4.14 (2H, s, S-CH<sub>2</sub>), 4.08 ( 2H, s, Ph-CH<sub>2</sub>), 2.57 (3H, s, COCH<sub>3</sub>), 2.06 (3H, s, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm) δ: 197.95, 163.90, 158.73, 141.37, 136.96, 136.02, 135.90, 135.05, 129.45, 129.12, 128.45, 128.39, 123.39, 52.80, 35.62, 27.23, 24.24, 10.59. ESI-MS: m/z514.4 (M+1), 536.2 (M+Na). C<sub>24</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>5</sub>O<sub>2</sub>S (513.08).

## 6-(2,6-dichlorobenzyl)-2-(((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5-m ethylpyrimidin-4(3H)-one (B5b2)

Recrystallized from methanol as a white crystal, yield 82.4%, mp: 224-226°C.<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ:12.68 (1H, s, NH), 7.32-7.35(5H, m, aromatic), 7.15-7.24 (3H, m, aromatic), 5.48 (2H, s, triazole-CH<sub>2</sub>), 4.17 (2H, s, S-CH<sub>2</sub>), 4.02 (2H, s, Ph-CH<sub>2</sub>), 2.06 (3H, s, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm) δ: 163.58, 161.15, 143.95, 136.01, 135.05, 132.61, 132.58, 130.63 (d, *J* = 9.0 Hz, C<sub>3</sub>,C<sub>5</sub>-Ph''), 129.42, 128.38, 123.05, 116.16, 115.94, 52.45, 35.63, 24.25, 10.58. ESI-MS: m/z 490.3 (M+1), 512.4 (M+Na). C<sub>22</sub>H<sub>18</sub>Cl<sub>2</sub>FN<sub>5</sub>OS (489.06).

## 2-(((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)thio)-6-(2,6-dichlorobenzyl)-5-methylpyri midin-4(3H)-one (B5b3)

Recrystallized from methanol as a light yellow crystal, yield 76.4%,mp: 240-242°C.<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ :12.59 (1H, s, NH), 7.35-7.40 (4H, m, aromatic),7.31 (2H, d, *J* = 8.0Hz, C<sub>3</sub>,C<sub>5</sub>-Ph'-H), 7.24 (2H, d, *J* = 6.8Hz, C<sub>2</sub>,C<sub>6</sub>-Ph'-H), 7.26-7.39 (6H, m, aromatic), 7.14 (1H, t, *J* = 7.9 Hz, C<sub>4</sub>-Ph''-H), 5.48 (2H, s, triazole-CH<sub>2</sub>), 4.17 (2H, s, S-CH<sub>2</sub>), 4.04 (2H, s, Ph-CH<sub>2</sub>), 2.06 (3H, s, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ : 170.78, 163.65, 144.26, 136.32, 136.03, 135.07, 129.42, 129.20, 128.64, 128.36, 123.11, 53.27, 35.64, 24.26, 10.59. ESI-MS: m/z 472.3 (M+1), 494.3 (M+Na). C<sub>22</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>5</sub>OS (471.07).

### 4-((4-(((4-(2,6-dichlorobenzyl)-5-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)thio)meth yl)-1H-1,2,3-triazol-1-yl)methyl)benzamide (B5b4)

Recrystallized from methanol as a white crystal, yield 78.7%,mp: 267-269°C.<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ :12.52 (1H, s, NH), 7.97 (1H, s, triazole-H),7.86 (2H, d, *J* = 8.1Hz, C<sub>3</sub>,C<sub>5</sub>-Ph'-H), 7.39 (1H, s), 7.34 (2H, d, *J* = 6.6Hz, C<sub>3</sub>,C<sub>5</sub>-Ph''-H), 7.28-7.34 (3H, m, aromatic), 7.13 (1H, t, *J* = 8.0 Hz, C<sub>4</sub>-Ph''-H), 5.54 (2H, s, triazole-CH<sub>2</sub>), 4.17 (2H, s, S-CH<sub>2</sub>), 4.02 (2H, s, Ph-CH<sub>2</sub>), 2.05 (3H, s, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ : 167.85, 144.02, 139.36, 136.01, 135.05, 134.54, 129.44, 128.39, 128.37, 128.09, 123.29, 52.83, 35.63, 24.22, 10.60. ESI-MS: m/z515.3 (M+1), 537.2 (M+Na). C<sub>23</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>6</sub>O<sub>2</sub>S (514.07).

### 6-(2,6-dichlorobenzyl)-2-(((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5 -methylpyrimidin-4(3H)-one (B5b5)

Recrystallized from methanol as a yellow crystal, yield 80.2%,mp: 184-186°C.<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ :12.62 (1H, s, NH), 7.33 (2H, d, *J* = 8.0Hz, C<sub>3</sub>,C<sub>5</sub>-Ph''-H), 7.28 (1H, s, triazole-H), 7.22 (2H, d, *J* = 8.6Hz, C<sub>2</sub>,C<sub>6</sub>-Ph'-H), 7.15 (1H, t, *J* = 7.8 Hz, C<sub>4</sub>-Ph''-H), 6.92 (2H, dd, *J* = 6.7, 1.8Hz, C<sub>3</sub>,C<sub>5</sub>-Ph'-H), 5.39 (2H, s, triazole-CH<sub>2</sub>), 4.17 (2H, s, S-CH<sub>2</sub>), 4.01 (2H, s, Ph-CH<sub>2</sub>), 3.74 (3H, s, OCH<sub>3</sub>), 2.06 (3H, s, CH<sub>3</sub>). <sup>13</sup>C NMR

(100 MHz, DMSO-d6, ppm) δ: 159.62, 143.81, 136.01, 135.05, 130.00, 129.45,
128.40, 128.22, 122.76, 114.58, 55.61, 52.80, 35.63, 24.23, 10.59. ESI-MS: m/z502.3
(M+1), 524.3 (M+Na) C<sub>23</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>5</sub>O<sub>2</sub>S (501.08).

### 4-((4-(((4-(2,6-dichlorobenzyl)-5-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)thio)meth yl)-1H-1,2,3-triazol-1-yl)methyl)benzonitrile (B5b6)

Recrystallized from methanol as a light yellow crystal, yield 82.7%, mp: 223-225°C. <sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) δ: 12.59 (1H, s, NH), 7.86 (2H, d, *J* = 8.8Hz, C<sub>3</sub>,C<sub>5</sub>-Ph"-H), 7.40-7.41 (3H, m, aromatic), 7.33 (2H, d, *J* = 8.0Hz, C<sub>2</sub>,C<sub>6</sub>-Ph'-H), 7.14 (1H, t, *J* = 7.9 Hz, C<sub>4</sub>-Ph"-H), 5.62 (2H, s, triazole-CH<sub>2</sub>), 4.17 (2H, s, S-CH<sub>2</sub>), 4.04(2H, s, Ph-CH<sub>2</sub>), 2.06 (3H, s, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm) δ: 163.70, 144.17, 141.80, 136.01, 135.05, 133.18, 129.41, 129.10, 128.37, 123.57, 118.98, 111.43, 52.63, 35.63, 24.26, 10.59. ESI-MS: m/z 497.4 (M+1), 519.2 (M+Na) C<sub>23</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>6</sub>OS (496.06).

## 4-((4-(((4-(2,6-dichlorobenzyl)-5-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)thio)meth yl)-1H-1,2,3-triazol-1-yl)methyl)benzenesulfonamide (B5b7)

Recrystallized from methanol as a light yellow crystal, yield 78.3%,mp: 243-245°C.<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ : 12.64 (1H, s, NH), 7.82 (2H, d, *J* = 8.2Hz, C<sub>3</sub>,C<sub>5</sub>-Ph'-H), 7.38-7.42 (5H, m, aromatic), 7.33 (2H, d, *J* = 8.0Hz, C<sub>2</sub>,C<sub>6</sub>-Ph'-H), 7.16 (1H, t, *J* = 8.0 Hz, C<sub>4</sub>-Ph''-H), 5.58 (2H, s, triazole-CH<sub>2</sub>), 4.18 (2H, s, S-CH<sub>2</sub>), 4.03 (2H, s, Ph-CH<sub>2</sub>), 2.06 (3H, s, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ : 163.25, 144.34, 144.09, 140.09, 136.03, 135.05, 129.43, 128.78, 128.39, 126.58, 123.37, 52.64, 35.64, 24.27, 10.60. ESI-MS: m/z551.3 (M+1), 573.1 (M+Na). C<sub>22</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>6</sub>O<sub>3</sub>S<sub>2</sub> (550.04).

## 2-(((1-(4-acetylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-6-(2,6-dichlorobenzyl)-5-io dopyrimidin-4(3H)-one (B5c1)

Recrystallized from methanol as a white crystal, yield 84.2%,mp: 213-215°C.<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ : 13.11 (1H, s, NH), 7.95 (2H, d, *J* = 8.2Hz, C<sub>3</sub>,C<sub>5</sub>-Ph''-H),

7.45 (1H, s, triazole-H), 7.36 (2H, d, J = 8.2 Hz,  $C_2, C_6$ -Ph'-H), 7.32 (2H, d, J = 8.0 Hz,  $C_3, C_4$ -Ph'-H), 7.16 (1H, t, J = 7.7 Hz,  $C_4$ -Ph''-H), 5.59 (2H, s, triazole-CH<sub>2</sub>), 4.29 (2H, s, S-CH<sub>2</sub>), 4.03 (2H, s, Ph-CH<sub>2</sub>), 2.57 (3H, s, CO-CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ : 197.95, 164.51, 143.62, 141.34, 136.97, 136.03, 135.93, 134.75, 129.73, 129.12, 128.48, 128.37, 123.56, 52.82, 42.71, 27.25, 24.66. ESI-MS: m/z 626.1 (M+1), 648.2 (M+Na).  $C_{23}H_{18}Cl_2IN_5O_2S$  (624.96).

## 6-(2,6-dichlorobenzyl)-2-(((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5-io dopyrimidin-4(3H)-one (B5c2)

Recrystallized from methanol as a white crystal, yield 82.3%,mp: 221-224°C.<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm) $\delta$ : 12.87 (1H, s, NH), 7.42 (1H, s, triazole-H), 7.31-7.36 (4H, m, aromatic), 7.16-7.24 (3H, m, aromatic), 5.48 (2H, s, triazole-CH<sub>2</sub>), 4.28 (2H, s, S-CH<sub>2</sub>), 3.96 (2H, s, Ph-CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ : 172.45, 164.15, 163.58, 143.85, 136.00, 134.96, 133.59, 130.66 (d, *J* = 9.0 Hz, C<sub>3</sub>,C<sub>5</sub>-Ph''), 130.13, 128.91, 128.32, 123.16, 116.16, 115.94, 52.47, 42.73, 24.70. ESI-MS: m/z 602.2 (M+1), 624.2 (M+Na). C<sub>21</sub>H<sub>15</sub>Cl<sub>2</sub>FIN<sub>5</sub>OS (600.94).

### 2-(((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)thio)-6-(2,6-dichlorobenzyl)-5-iodopyrimi din-4(3H)-one (B5c3)

Recrystallized from methanol as a white crystal, yield 86.2%,mp: 215-217°C.<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ : 13.12 (1H, s, NH), 7.33-7.36 (4H, m, aromatic), 7.28 (2H, d, *J* = 8.5Hz, C<sub>3</sub>,C<sub>5</sub>-Ph'-H), 7.26 (2H, d, *J* = 6.6Hz, C<sub>2</sub>,C<sub>6</sub>-Ph'-H), 7.13 (1H, t, *J* = 7.7 Hz, C<sub>4</sub>-Ph''-H), 5.49 (2H, s, triazole-CH<sub>2</sub>), 4.29 (2H, s, S-CH<sub>2</sub>), 4.02 (2H, s, Ph-CH<sub>2</sub>).<sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ : 143.47, 136.32, 136.04, 134.77, 129.70, 129.21, 128.63, 128.38, 128.36, 123.25, 53.30, 42.71, 24.69. ESI-MS: m/z584.0 (M+1), 606.1 (M+Na). C<sub>21</sub>H<sub>16</sub>Cl<sub>2</sub>IN<sub>5</sub>OS (582.95).

4-((4-(((4-(2,6-dichlorobenzyl)-5-iodo-6-oxo-1,6-dihydropyrimidin-2-yl)thio)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzamide (B5c4)

Recrystallized from methanol as a white crystal, yield 79.3%,mp: 248-250°C.<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ : 13.12 (1H, s, NH), 7.96 (1H, s, triazole-H),7.86 (2H, d, J = 8.2Hz, C<sub>3</sub>,C<sub>5</sub>-Ph'-H), 7.30-7.44 (6H, m, aromatic), 7.15 (1H, t, J = 7.8 Hz, C<sub>4</sub>-Ph''-H), 5.55 (2H, s, triazole-CH<sub>2</sub>), 4.29 (2H, s, S-CH<sub>2</sub>), 3.99 (2H, s, Ph-CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ : 167.86, 143.60, 139.33, 136.03, 134.79, 134.57, 129.70, 128.37, 128.12, 123.46, 52.86, 42.72, 24.66. ESI-MS: m/z627.1 (M+1), 649.2 (M+Na). C<sub>22</sub>H<sub>17</sub>Cl<sub>2</sub>IN<sub>6</sub>O<sub>2</sub>S (625.96).

### 6-(2,6-dichlorobenzyl)-5-iodo-2-(((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl) )thio)pyrimidin-4(3H)-one(B5c5)

Recrystallized from methanol as a light yellow crystal, yield 73.6%,mp: 206-209°C.<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ : 13.14 (1H, s, NH), 7.36 (1H, s, triazole-H), 7.46 (2H, d, *J* = 8.0Hz, C<sub>3</sub>,C<sub>5</sub>-Ph''-H), 7.24 (2H, d, *J* = 8.5Hz, C<sub>2</sub>,C<sub>6</sub>-Ph'-H), 7.18 (1H, t, *J* = 7.9 Hz, C<sub>4</sub>-Ph''-H), 6.93 (2H, d, *J* = 8.6Hz, C<sub>3</sub>,C<sub>5</sub>-Ph'-H), 5.40 (2H, s, triazole-CH<sub>2</sub>), 4.29 (2H, s, S-CH<sub>2</sub>), 3.97 (2H, s, Ph-CH<sub>2</sub>), 3.74 (3H, s, O-CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ : 164.40, 159.62, 143.35, 136.03, 134.76, 130.04, 129.74, 128.37, 128.21, 122.94, 114.57, 55.62, 52.83, 42.70, 24.65. ESI-MS: m/z614.1 (M+1), 636.1 (M+Na). C<sub>22</sub>H<sub>18</sub>Cl<sub>2</sub>IN<sub>5</sub>O<sub>2</sub>S (612.96).

4-((4-(((4-(2,6-dichlorobenzyl)-5-iodo-6-oxo-1,6-dihydropyrimidin-2-yl)thio)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzonitrile (B5c6)

Recrystallized from methanol as a white crystal, yield 76.6%,mp: 226-229°C.<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ : 13.16 (1H, s, NH), 7.87 (2H, d, *J* = 8.2Hz, C<sub>3</sub>,C<sub>5</sub>-Ph''-H), 7.48 (1H, s, triazole-H), 7.41 (2H, d, *J* = 8.2Hz, C<sub>3</sub>,C<sub>5</sub>-Ph'-H), 7.32 (2H, d, *J* = 8.0Hz, C<sub>2</sub>,C<sub>6</sub>-Ph'-H), 7.16 (1H, t, *J* = 7.6 Hz, C<sub>4</sub>-Ph''-H), 5.63 (2H, s, triazole-CH<sub>2</sub>), 4.30 (2H, s, S-CH<sub>2</sub>), 4.15 (2H, s, Ph-CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ : 164.46, 143.70, 141.76, 136.04, 134.74, 133.18, 129.69, 129.04, 128.34, 123.73, 118.96, 111.46,

52.66, 42.71, 24.69. ESI-MS: m/z609.1 (M+1), 631.2 (M+Na). C<sub>22</sub>H<sub>15</sub>Cl<sub>2</sub>IN<sub>6</sub>OS (607.94).

## 4-((4-(((4-(2,6-dichlorobenzyl)-5-iodo-6-oxo-1,6-dihydropyrimidin-2-yl)thio)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzenesulfonamide (B5c7)

Recrystallized from methanol as a white crystal, yield 74.3%,mp: 221-223°C.<sup>1</sup>H NMR (400 MHz, DMSO-d6, ppm)  $\delta$ : 13.14 (1H, s, NH), 7.82 (2H, d, *J* = 8.1Hz, C<sub>3</sub>,C<sub>5</sub>-Ph'-H), 7.46 (1H, s, triazole-H), 7.41 (2H, d, *J* = 8.1Hz, C<sub>3</sub>,C<sub>5</sub>-Ph''-H), 7.32-7.36 (4H, m, aromatic), 7.15 (1H, t, *J* = 8.0 Hz, C<sub>4</sub>-Ph''-H), 5.58 (2H, s, triazole-CH<sub>2</sub>), 4.29 (2H, s, S-CH<sub>2</sub>), 3.99 (2H, s, Ph-CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d6, ppm)  $\delta$ :163.24, 144.36, 140.04, 136.04, 134.77, 129.72, 128.82, 128.36, 126.57, 107.42, 52.67, 42.73, 24.67.ESI-MS: m/z663.1 (M+1), 685.1 (M+Na). C<sub>21</sub>H<sub>17</sub>Cl<sub>2</sub>IN<sub>6</sub>O<sub>3</sub>S<sub>2</sub> (661.92).

### 4.2. In vitro anti-HIV assay

Evaluation of the antiviral activity of the compounds against HIV-1 strain IIIB and HIV-2 strain (ROD) in MT-4 cells was performed using the MTT assay as previously described [15,16]. Stock solutions (10×final concentration) of test compounds were added in 25µL volumes to two series of triplicate wells so as to allow simultaneous evaluation of their effects on mock- and HIV-infected cells at the beginning of each experiment. Serial fivefold dilutions of test compounds were made directly in flat-bottomed 96 wells microtiter trays using a Biomek 3000 robot (Beckman instruments, Fuller-ton, CA). Untreated control HIV- and mock-infected cell samples were included for each sample.

HIV-1 (IIIB) or HIV-2 (ROD) [17] stock (50μL) at 100–300 CCID50 (cell culture infectious dose) or culture medium was added to either the infected or mock-infected wells of the microtiter tray. Mock-infected cells were used to evaluate the effect of test com-pound on uninfected cells in order to assess the cytotoxicity of the test compound. Exponentially growing MT-4 cells were cen-trifuged for 5 min at 1000 rpm and the supernatant was discarded. The MT-4 cells were resuspended at This article is protected by copyright. All rights reserved.

 $6 \times 10^5$  cells/mL, and 50-µL volumes were transferred to the microtiter tray wells. Five days after infection, the viability of mock- and HIV-infected cells was examined spectrophotometrically by the MTT assay.

The MTT assay is based on the reduction of yellow colored 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Acros Organics, Geel, Belgium) by mitochondrial dehydro-genase of metabolically active cells to a blue-purple formazan that can be measured spectrophotometrically. The absorbances were read in an eight-channel computer-controlled photometer (Multi-scan Ascent Reader, Labsystems, Helsinki, Finland), at two wave-lengths (540 and 690 nm). All data were calculated using the median OD (optical density) value of tree wells. The 50% cytotoxic concentration (CC<sub>50</sub>) was defined as the concentration of the test compound that reduced the absorbance (OD540) of the mock-in-fected control sample by 50%. The concentration achieving 50% protection from the cytopathic effect of the virus in infected cells was defined as the 50% effective concentration (EC<sub>50</sub>).

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### **Conflict of Interest**

The authors have declared no conflict of interest.

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### Table 1.

5-Hydrogen/methyl/iodo-6-(naphthalen-1-ylmethyl)-2-((1-(arylmethyl)-1H-1,2,3-triazol-4-yl)methylthio)pyrimidin-4(3H)-one.



Conned	R	A.,		EC <sub>50</sub> (μΜ) <sup>α</sup>		cc (ma)b		SI <sup>c</sup>	
Compa		Ar _	III <sub>B</sub>	RES056	ROD	(μw) <sup>*</sup>	III <sub>B</sub>	RES056	ROD
A5a1	н	4-F-Ph	>45.75	-	>45.75	45.75±18.35	<1	-	<1
A5a 2	н	Ph	>116.22	-	>116.22	116.22±14.5	<1	-	<1
						2			
A5a 3	н	4-OCH₃-Ph	>68.53	-	>68.53	68.53±13.47	<1	-	<1
A5a 4	н	4-CONH <sub>2</sub> -Ph	>105.33	-	>105.33	105.33±16.5	<1	-	<1
						0			
A5a 5	н	2-CN-Ph	>105.48	-	>105.48	105.48±18.3	<1	-	<1
						8			
A5a 6	Н	2-CH <sub>3</sub> -Ph	>90.35	-	>90.35	90.35±21.99	<1	-	<1
A5a 7	н	4-SO <sub>2</sub> NH <sub>2</sub> -Ph	>96.60	-	>96.60	96.60±7.57	<1	-	<1
A5b1	м	4-F-Ph	>30.60	-	>30.60	30.60±7.50	<1	-	<1
	e								
A5b2	М	Ph	>25.31	-	>25.31	25.31±2.34	<1	-	<1
	e								
A5b3	М	4-OCH <sub>3</sub> -Ph	>26.53	-	>26.53	26.53±1.35	<1	-	<1
	е								

	5
	5

	A5b4	М	4-CONH <sub>2</sub> -Ph	≥45.51	>70.20	>70.20	70.20±20.18	≤2	<1	<1
		e								
	A5b5	М	2-CN-Ph	>123.35	-	>123.35	123.35±18.1	<1	-	<1
		e					3			
	A5b6	М	2-CH₃-Ph	>24.01	-	>24.01	24.01±2.35	<1	-	<1
		e								
	A5b7	М	4-SO <sub>2</sub> NH <sub>2</sub> -Ph	32.92±4.58	>83.02	>83.02	83.02±16.80	3	<1	<1
		e								
	A5c1	I	4-F-Ph	>81.81	-	>81.81	81.81±7.23	<1	-	<1
1	A5c2	I	Ph	>86.75	-	>86.75	86.75±16.85	<1	-	<1
	A5c3	I	4-OCH₃-Ph	>85.15	-	>85.15	85.15±15.61	<1	-	<1
	A5c4	I	4-CONH <sub>2</sub> -Ph	>88.01	-	>88.01	88.01±6.64	<1	-	<1
	A5c5	I	2-CN-Ph	>75.93	-	>75.93	75.93±29.38	<1	-	<1
	A5c6	I	2-CH₃-Ph	>87.41	-	>87.41	87.41±9.07	<1	-	<1
	A5c7	I	4-SO <sub>2</sub> NH <sub>2</sub> -Ph	>86.78	-	>86.78	86.78±6.24	<1	-	<1
	NVP			0.312±0.056	≥7.59	-	>15.02	>48.08	>orX2	
	ЗТС			2.24±0.82	-	8.79±2.91	>87.24	>39	-	>10
	AZT			0.0071±0.002	0.0102±0.009	0.0066±0.001	>93.55	>13144	>9149	>142425
				9	2	4				
	DDI			23.20±7.60	-	44.90±19.44	>211.65	>9	-	>5
	EFV			0.0062±0.00	0.1561±0.014	-	>6.34	>1014	>41	-
					9					



<sup>a</sup>EC<sub>50</sub>: concentration of compound required to achieve 50% protection of MT-4 cell against HIV-1-induced cytotoxicity, as determined by the MTT method.

 ${}^{\rm b}{\rm CC}_{\rm 50}$ : concentration required to reduce the viability of mock-infected cells by 50%, as determined by the MTT method.

<sup>c</sup>SI: selectivity index (CC<sub>50</sub>/EC<sub>50</sub>).

**Table 2.** 5-Hydrogen/methyl/iodo-6-(2,6-dichlorobenzyl)-2-((1-(arylmethyl)-1H-1,2,3-triazol-4-yl)methylthio)pyrimidin-4(3H)-one.



Conned		<b>A</b>	EC₅₀ (μM)″			cc. (	SI <sup>c</sup>			
compu	R	Ar	III <sub>B</sub>	RES056	ROD	CC <sub>50</sub> (μινι)	III <sub>B</sub>	RES056	ROD	
B5a1	н	4-COCH₃-Ph	45.76±53.37	>148.72	>148.72	148.72±16.9	3	1	<1	
						5				
	н	4-F-Ph	107.48±78.93	>176.82	>176.82	176.82±12.9	2	1	<1	
B5a2						3				
B5a3	н	Ph	>272.71	>272.71	>272.71	>272.71	X1	X1	X1	
B5a4	н	4-CONH <sub>2</sub> -Ph	>132.03	-	>132.03	132.03±10.8	<1	-	<1	
						9				

B5a5	н	4-OCH₃-Ph	>143.37	>143.37	>143.37	143.37±5.57	<1	<1	<1
B5a6	н	4-CN-Ph	>41.12	>132.86	>132.86	132.86±19.6	≤3	<1	<1
						3			
B5a7	н	4-SO <sub>2</sub> NH <sub>2</sub> -Ph	>116.20	-	>116.20	116.20±10.6	<1	-	<1
						6			
B5b1	M e	4-COCH₃-Ph	3.86±0.60	>32.58	>32.58	32.58±3.52	8	<1	<1
B5b2	м	4-F-Ph	24 86+19 35	>82 85	>82 85	82 85+80 46	3	<1	<1
	e		2 1100213103	. 02.00		02.00-00110	5		-
B5b3	М	Ph	8.21±2.18	>79.55	>79.55	79.55±76.44	10	<1	<1
	e								
B5b4	М	4-CONH <sub>2</sub> -Ph	6.71±0.97	>143.26	>143.26	143.26±16.7	21	<1	<1
	e					8			
B5b5	М	4-OCH₃-Ph	4.56±0.97	>28.98	>28.98	28.98±3.18	6	<1	<1
	e								
B5b6	М	4-CN-Ph	5.77±0.52	>50.94	>50.94	50.94±27.74	9	<1	<1
	e								
B5b7	М	4-SO <sub>2</sub> NH <sub>2</sub> -Ph	3.22±0.16	>95.49	>95.49	95.49±28.47	30	<1	<1
	e								
B5c1	I	4-COCH₃-Ph	>95.73	>95.73	>95.73	95.73±8.59	<1	<1	<1
B5c2	I	4-F-Ph	>92.05	>92.05	>92.05	92.05±19.06	<1	<1	<1
B5c3	I	Ph	>119.84	>119.84	>119.84	103.96±5.70	<1	<1	<1
B5c4	I	4-CONH₂-Ph	>94.13	-	>94.13	94.13±6.62	<1	-	<1

B5c5	I	4-OCH₃-Ph	>75.91	-	>75.91	75.90±16.89	<1	-	<1
B5c6	I	4-CN-Ph	>88.82	>88.82	>88.82	88.82±13.31	<1	<1	<1
B5c7	I	4-SO <sub>2</sub> NH <sub>2</sub> -Ph	>97.91	-	>97.91	97.91±5.77	<1	-	<1
NVP			0.312±0.056	≥7.59		>15.02	>48.0	>orX2	
зтс			2.24±0.82		8.79±2.91	>87.24	>39		>10
AZT			0.0071±0.002	0.0102±0.009	0.0066±0.001	>93.55	>13144	>9149	>142425
			9	2	4				
DDI			23.20±7.60		44.90±19.44	>211.65	>9		>5
EFV			0.0062±0.001	0.1561±0.014		>6.34	>1014	>41	
			7	9					
DLV			0.6532±0.623	>43.81		>43.81	>67	X1	
ETV			0.0041±0.000	0.0250±0.003		>4.59	>1127	>184	
			2	0					

 $^{a}EC_{50}$ : concentration of compound required to achieve 50% protection of MT-4 cell against HIV-1-induced cytotoxicity, as determined by the MTT method.

 ${}^{\rm b}{\rm CC}_{50}$ : concentration required to reduce the viability of mock-infected cells by 50%, as determined by the MTT method.

<sup>c</sup>SI: selectivity index (CC<sub>50</sub>/EC<sub>50</sub>).









chain.



Scheme 1. Reagents and Conditions: (i) (a)  $MgCl_2$ ,  $Et_3N$ ,  $CH_3CN$ , rt, 2h; (b) CDI, rt, overnight then reflux, 2 h; (ii) thiourea, EtONa, EtOH, reflux, 6h; (iii)  $HC=CCH_2Br$ ,  $K_2CO_3$ , DMF; (iv) (substituted) $Ar^1$ - $CH_2N_3$ , VcNa, CuSO<sub>4</sub>.5H<sub>2</sub>O, H<sub>2</sub>O, tertiary butanol, 65°C; (v) HOAc, PbO<sub>2</sub>, I<sub>2</sub>.