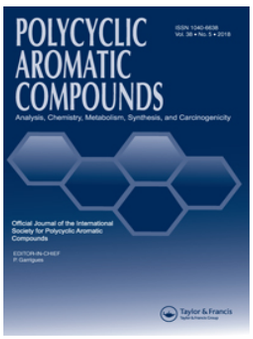

Polycyclic Aromatic Compounds

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# Novel Tricyclic 2-Alkoxy-8-methyl-6-(pyrrolidin-1-yl)-4*H*-[1,2,4]triazolo[5,1-*f*]purine Derivatives: Synthesis and Characterization

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# Novel Tricyclic 2-Alkoxy-8-methyl-6-(pyrrolidin-1-yl)-4*H*-[1,2,4]triazolo[5,1-*f*]purine Derivatives: Synthesis and Characterization

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**ABSTRACT**

A convenient approach for the synthesis of diversely functionalized [1,2,4]triazolo[5,1-*f*]purine heterocyclic framework have been accomplished. The products were obtained through the combination of 5-amino-3-(methylthio)-1*H*-1,2,4-triazole with 5-bromo-2,4-dichloro-6-methylpyrimidine followed by a $S_NAr$ alkoxylation of the novel tricyclic heterocyclic core with various aliphatic alcohols. All newly synthesized heterocycles were fully elucidated by both computational and spectral evaluations.

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[1,2,4]Triazolo[5,1-*f*]purine; 5-amino-3-(methylthio)-1*H*-1,2,4-triazole; 5-bromo-2,4-dichloro-6-methylpyrimidine; computational evaluations; heterocyclization

## Introduction

Imidazo[4,5-*d*]pyrimidine (Purine) as a privileged fused heterocyclic system was introduced by Hermann Emil Fischer in 1884.[1,2] As a pioneer in the synthesis of purine,[3] he demonstrated that adenine, xanthine, uric acid, guanine, and caffeine as natural products correspond to different derivatives of purine system.[4] In the last few years, purine scaffold has been contributed substantially to the development of biologically active compounds.[5] Vidarabine as an antiviral drug with purine-based structure has been extensively applied in clinics since 1976. Also, purine skeleton has been known as a key pharmacophore in the synthesis and function of nucleic acids and enzymes. Purine-containing skeletons are one of the most widely used heterocyclic core in the development of adenosine receptor modulators,[6] protein kinase inhibitors,[7,8] fructose bisphosphatase inhibitors,[9] and adenylation enzyme inhibitors.[10] Besides, Vidarabine **(A)** as antitumor, Acyclovir **(B)**, Penciclovir **(C)** as well as Ganciclovir **(D)** as antiviral, Azathioprine **(E)** as immunosuppressive and Theophylline **(F)** as bronchodilator (Figure 1) are the notable examples of bioactive purine-based heterocycles with versatile structures and activities.[11–16]

Consequently, in the light of such interesting bioactivities, several chemical procedures for the synthesis of purine derivatives have been developed.[17–21] Some synthetic routes include the synthesis of disubstituted adenines and trisubstituted xanthines through the heterocyclization of pyrimidine compounds[22] and the reactions such as couplings[23,24] or nucleophilic aromatic substitutions.[25]

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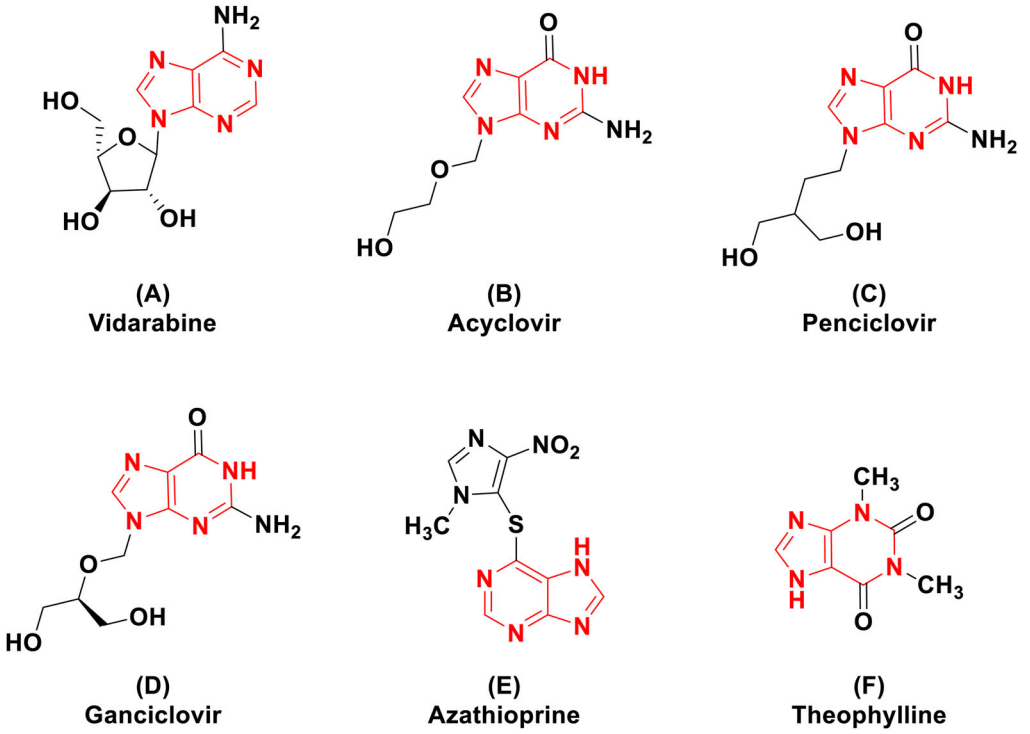


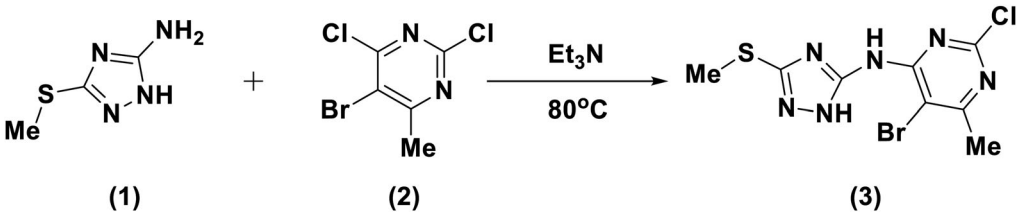

**Figure 1.** Examples of versatile pharmacologically active purines.

1,2,4-Triazoles are another important class of heterocyclic compounds with three nitrogen atoms in a five membered ring which have attributed a lot of interesting structural features and pharmacological activities[26] such as antimicrobial,[27] antimalarial,[28] antiproliferative,[29] neuroprotective,[30] antioxidant,[31] anti-HIV,[32] molluscicidal,[33] and anticonvulsant effects.[34] They have been synthesized from the starting materials such as aminoguanidine sulfate,[35] hydrazones,[36] chloralamides,[37] benzoyl thiosemicarbazide,[38] 1,3,4-oxadiazole,[39] amidrazones,[40] hydrazide,[27] amidines and imidates,[41] thioamide,[42] hydrazonoyl hydrochlorides and aldehydes,[43] aminoguanidine bicarbonate and oxalic acid,[44] maleimides and bisarylhydrazones,[45] 2-phenyl-1,3,4-oxadiazole,[46] 2-hydrazinopyridines and aldehydes[47] and from alkyl halides.[48]

Based on the importance and various applications of purines and triazoles in medicinal chemistry and in continuation of our desire in the synthesis of novel fused heterocyclic systems with potentially biological aspects,[49–54] we have developed a straightforward protocol for the synthesis of novel elegantly functionalized [1,2,4]triazolo[5,1-*f*]purine derivatives.

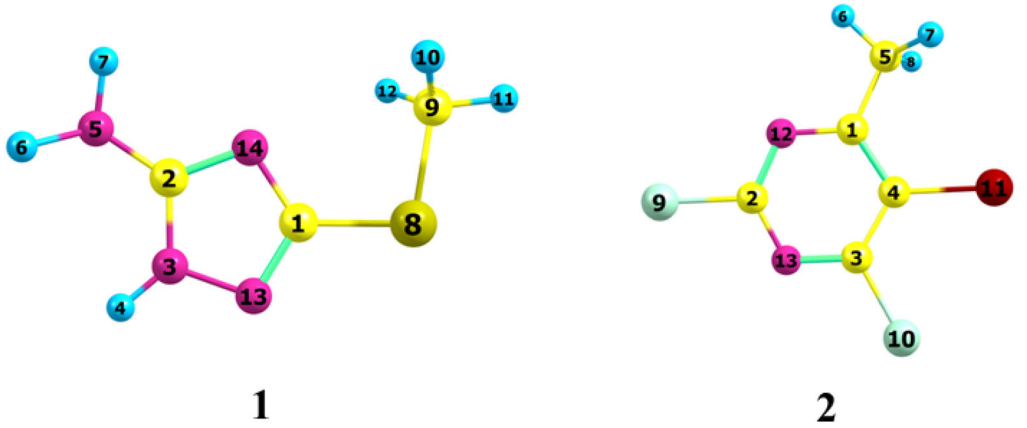
## Results and discussion

In the present study, potassium cyanocarbonimidodithioate was initially prepared from the reaction of cyanamide with carbon disulfide[55] which was subsequently underwent the methylation via treatment with iodomethane.[56] The obtained dimethyl cyanocarbonimidodithioate was subsequently heterocyclized into 3-(methylthio)-1*H*-1,2,4-triazol-5-amine **(1)** while treated with hydrazine monohydrate in refluxing EtOH. On the other hand, 5-bromo-2,4-dichloro-6-methylpyrimidine **(2)** was synthesized according to the previously reported method.[57] The treatment of compound **(1)** as a binucleophile with compound **(2)** in $Et_3N$ under heating condition afforded 5-bromo-2-chloro-6-methyl-*N*-(5-(methylthio)-4*H*-1,2,4-triazol-3-yl)pyrimidin-4-amine **(3)** (Scheme 1).




(1) (2) (3)

**Scheme 1.** Synthesis of 5-bromo-2-chloro-6-methyl-*N*-(5-(methylthio)-4*H*-1,2,4-triazol-3-yl)pyrimidin-4-amine.




**1** **2**

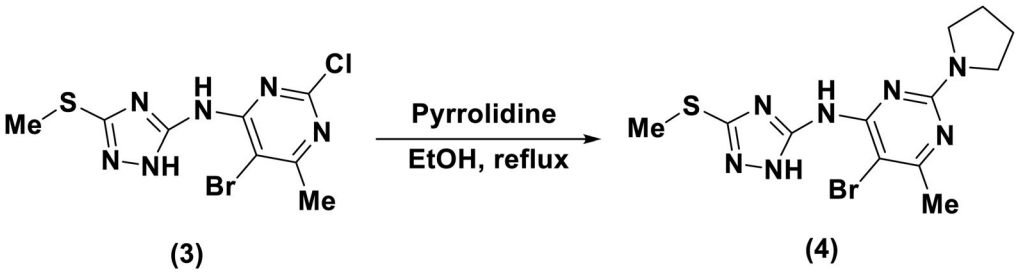
**Figure 2.** Optimized geometry of (**1**) and (**2**) precursors at M06-2X/def2SVP.

**Table 1.** NPA and condensed-Fukui indices of (**1**) and (**2**).

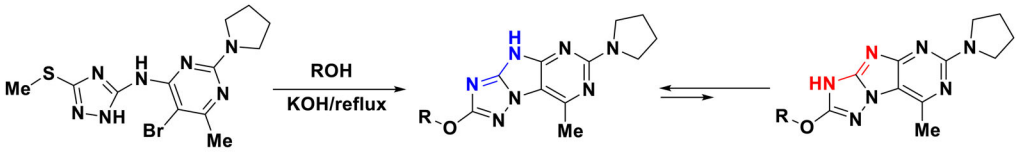
| | N9PA charges | | | Indices | | | |
|---|---|---|---|---|---|---|---|
| | Neutral | Anion | Cation | $f^-$ | $f^+$ | $f^0$ | Dual-descriptor |
| C2 | 0.4697 | 0.4786 | 0.5133 | 0.0437 | −0.0089 | 0.0174 | −0.0347 |
| C3 | 0.2524 | 0.1093 | 0.2745 | 0.0221 | 0.1431 | 0.0826 | 0.121 |
| N5 | −0.8581 | −0.905 | −0.7875 | 0.0706 | 0.0469 | 0.0587 | −0.0237 |
| N14 | −0.6401 | −0.6793 | −0.6045 | 0.0357 | 0.0392 | 0.0374 | 0.0035 |

The repulsive interaction between the lone pairs of nitrogen in pyrimidine and the $NH_2$ nucleophile for the 2-Cl substituent requires more severe condition in comparison with the 4-Cl one. Therefore, the selective 4-Cl substitution in pyrimidine by the $NH_2$ moiety is preferred. Nevertheless, computational evaluations were investigated as a further confirmation. To determine which sites are acting as nucleophile and electrophile on both reactants, condensed-Fukui indices were applied and calculated. Thus, geometrically optimized structures of (**1**) and (**2**) at M06-2X/def2SVP level[58] were considered for Fukui index computation with neutral, +1 and −1 net charged molecules to obtain the data needed for further considerations. The natural population analysis (NPA) charges were extracted to calculate condensed-Fukui indices via UCL-FUKUI v2.1.[59] All other calculations were performed with Gaussian 09 package.[60] Figure 2 depicts the optimized structure of (**1**) and (**2**) and Table 1 represents Fukui-indices in order to determine more susceptible Carbons/Nitrogens as electro/nucleophile sites, respectively.

According to the data derived from Table 1, C2 and C3 in compound (**2**) showed $f^+$ values of −0.0089 and 0.1431, respectively. These data confirmed that C3 is more electrophile than C2. In the other hand, more positive Dual-Descriptor amounts indicate more electrophilic moiety on the matter of interest site and negative values of such parameter reflect the nucleophilic sites. This




**Scheme 2.** Synthesis of 5-bromo-6-methyl-*N*-(5-(methylthio)-4*H*-1,2,4-triazol-3-yl)-2-(pyrrolidin-1-yl)pyrimidin-4-amine.




| entry | (5a) | (5b) | (5c) | (5d) | (5e) | (5f) | (5g) |
|---|---|---|---|---|---|---|---|
| RO | MeO | EtO | *n*-PrO | *iso*-PrO | *n*-BuO | *iso*-BuO | $EtNH(CH_2)_2O$ |

**Scheme 3.** Synthesis of 2-alkoxy-8-methyl-6-(pyrrolidin-1-yl)-4*H*-[1,2,4]triazolo[5,1-*f*]purine derivatives.

could be seen in N5 of compound **(2)** against N14 of it. Therefore, it could be deduced that suggested structure of compound **(3)** was approved and its regiochemistry was correctly guessed.

In continuation, when compound **(3)** stirred with pyrrolidine in boiling EtOH, the 2-Cl of pyrimidine heterocyclic core was substituted to yield 5-bromo-6-methyl-*N*-(5-(methylthio)-4*H*-1,2,4-triazol-3-yl)-2-(pyrrolidin-1-yl)pyrimidin-4-amine **(4)**. (Scheme 2)

Eventually, the treatment of compound **(4)** with some boiling alcohols in the presence of KOH generated various derivatives **(5a–e)** of 2-alkoxy-8-methyl-6-(pyrrolidin-1-yl)-4*H*-[1,2,4]triazolo[5,1-*f*]purine system with two possible tautomeric structure of **A** and **B**. (Scheme 3).

To the best of our knowledge, the conclusive evidence for the confirmation of the predicted tautomerism of final tricyclic products can be provided based on thermochemistry criteria. Hence, two possible tautomer of each derivative was optimized at M06-2X/def2SVP and showed in Figure 3. Frequency calculation revealed that the optimized molecules did not show an imaginary frequency and located in their true minima on the respective potential energy surface. The data derived from DFT calculations are corresponded to Gibbs free energy of **A** tautomers which are more stable than **B** structures in the range of 7.6–8.7 kcal $mol^{-1}$. An initiative searching for a transition state structure (TSS) showed $\Delta G^{\neq} \sim 73–74$ kcal $mol^{-1}$ among the pathway of **A** to **B** structure that is deduced to be accordingly high. Therefore, the data obtained from the computational study supports that it can be plausible to consider the structure **A** as more preferable thermodynamically tautomeric form in comparison with the structure **B**.

Therefore, it can be rationalized that the reaction has most likely proceeded through two successive $S_NAr$ mechanisms via intramolecular cyclocondensation and formation of a non-isolated adduct intermediate that immediately underwent an intermolecular aromatic nucleophilic substitution reaction on triazole moiety accompanied by the elimination of HBr and MeSH in each nucleophilic attack on compound **(4)** as depicted in Figure 4.

Moreover, the satisfactory elemental analyses and the spectral data of compounds **(5a–g)** are in agreement with the assigned structures. For example, the $^1H$ NMR spectrum of compound **(5d)** showed a singlet signal at 2.46 ppm due to the three protons of the methyl substituted on

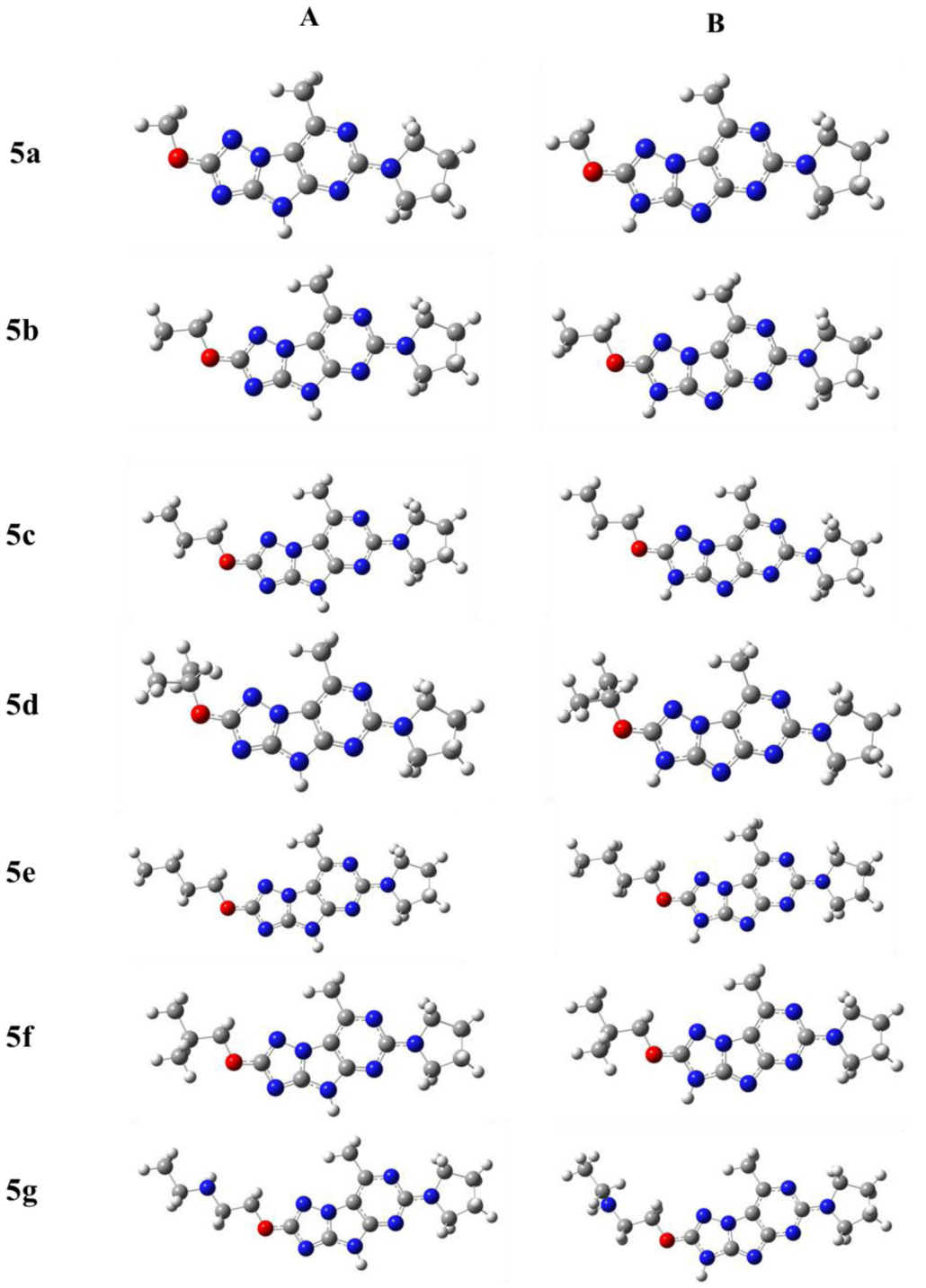



**Figure 3.** Geometrically optimized tautomerism structures of final products (**A** and **B**).

pyrimidine ring and a broad multiplet peak around $\delta$ 1.90–1.94 together with a triplet signal at 3.80 ppm belongs to the methylene groups of the pyrrolidine moiety. Also, the *iso*-propoxy signals were observed at $\delta$ 1.36 ppm (doublet, $^{3}J = 6.0$ Hz) and $\delta$ 5.10–5.22 ppm (septet, $^{3}J = 6.0$ Hz) due

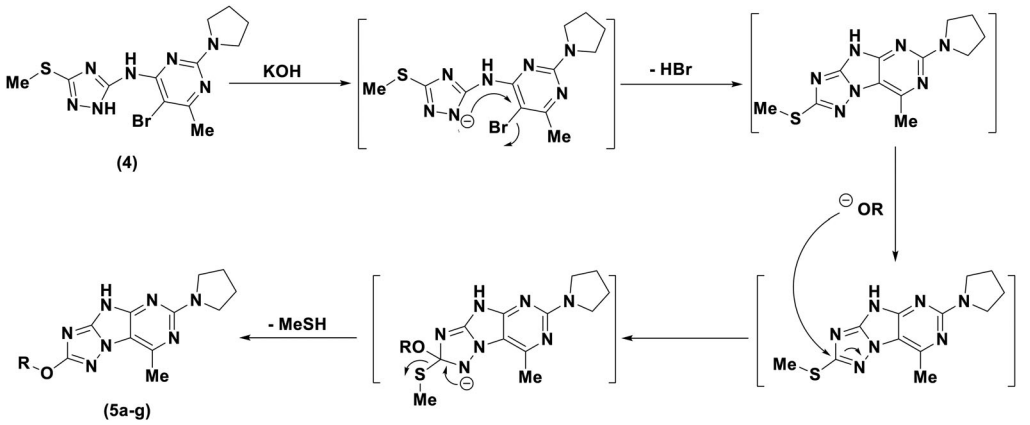



**Figure 4.** Plausible mechanism for synthesis of compounds **(5a–g)**.

to six protons of two equivalent $CH_3$ and the single proton of OCH moieties, respectively. It is noteworthy to mention that the NH signal did not detected in the $^1$H NMR spectrum. By assigning signal of OCH at $\delta$ 69.5 ppm as the most deshielded aliphatic carbon, the $^{13}$C NMR spectrum was divided into upfield with other four resolved aliphatic signals at $\delta = 22.0$, 25.7, 25.8, and 50.3 ppm and downfield with six distinct aromatic signals at $\delta = 94.2$, 95.9, 159.9, 161.8, 162.4, and 167.0 ppm. The mass spectrum of **(5d)** showed a molecular ion peak at *m/z* 310 consistent with the molecular formula of $C_{15}H_{20}N_6O$.

## Conclusion

In summary, we have accomplished the synthesis of diversely functionalized [1,2,4]triazolo[5,1-*f*]purines employing an efficient and simple procedure. This synthetic approach has been started from the reaction of 5-amino-3-(methylthio)-1*H*-1,2,4-triazole **(1)** with 5-bromo-2,4-dichloro-6-methylpyrimidine **(2)** in $Et_3N$ to give 5-bromo-2-chloro-6-methyl-*N*-(3-(methylthio)-1*H*-1,2,4-triazol-5-yl)pyrimidin-4-amine **(3)** which were subsequently underwent $S_NAr$ reaction with pyrrolidine in boiling EtOH to yield quantitatively the corresponding pyrrolidine-substituted compound **(4)**. Further reaction of the latter compound with different alcohols in the presence of KOH under reflux condition was resulted in cyclization and synthesis of various derivatives **(5a–g)** containing novel [1,2,4]triazolo[5,1-*f*]purine fused heterocyclic core.

## Experimental

Melting points were recorded on an Electro thermal type 9200 melting point apparatus. The IR spectra were obtained on Avatar 370 FT-IR Thermo Nicolet instrument and only noteworthy absorptions are listed. The $^1$H NMR (300 MHz) and the $^{13}$C NMR (75 MHz) spectra were recorded on a Bruker Avance-III 300 NMR Fourier transformer spectrometer. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. Elemental analyses were performed on a Thermo Finnigan Flash EA 1112 microanalyzer.

**Synthesis of 5-bromo-2-chloro-6-methyl-*N*-(5-(methylthio)-4*H*-1,2,4-triazol-3-yl)pyrimidin-4-amine (3):** To a mixture of compound **(1)** (6.5 mmol, 0.85 g) and compound **(2)** (6.5 mmol, 1.57 g), the excess amount of $Et_3N$ (2 mL) was added and the mixture was heated at 80 °C for 24 h. After the completion of the reaction, the resulting pasty precipitate was washed with acetone (2 × 10 mL) and filtered off. Then the resulting solid was washed with petroleum ether (2 × 10 mL) and water (2 × 20 mL) to remove the impurities.

Yellow powder, yield: 83%, mp: 180–182 °C, $^1$H NMR (DMSO-$d_6$): $\delta$ 2.52 (s, 3H, pyrimidine-$CH_3$), 2.53 (s, 3H, $SCH_3$), 10.58 (s, 1H, NH, $D_2O$-exchangable) ppm. $^{13}$C NMR (DMSO-$d_6$): $\delta$ 13.7, 26.6, 103.2, 151.9, 157.3, 158.4, 161.6, 172.4 ppm. IR (KBr disc): $\nu$ 3373 (NH), 3092, 1644, 1490, 1430, 1408, 1279, 991 (C–Cl), 744 (C–Br) cm$^{-1}$. MS (*m/z*) = 336 [$M^+$], 287 [$M^+$ – SMe], 255 [$M^+$ – Br], 208 [$M^+$ – SMe, Br]. *Anal.* Calcd. for $C_8H_8BrClN_6S$ (%): C, 28.63; H, 2.40; N, 25.04; S, 9.55. Found: C, 28.60; H, 2.38; N, 25.03; S, 9.51.

**Synthesis of 5-bromo-6-methyl-*N*-(5-(methylthio)-4*H*-1,2,4-triazol-3-yl)-2-(pyrrolidin-1-yl)pyrimidin-4-amine (4):** A mixture of compound **(3)** (3 mmol, 1.008 g) and excess amount of pyrrolidine (12 mmol, 1 mL) in EtOH (15 mL) was refluxed for 18 h. After the completion of the reaction, the solvent was removed by filtration. The resulting solid was then washed with water (2 × 20 mL), filtered off and recrystallized from ethanol.

Milky powder, yield: 78%, mp: 231–233 °C, $^1$H NMR ($CDCl_3$): $\delta$ 1.89–1.93 (m, 4H, $2CH_2$), 2.51 (s, 3H, pyrimidine-$CH_3$), 2.54 (s, 3H, $SCH_3$), 3.79 (t, 4H, $J$ = 7.5 Hz, $2NCH_2$), 6.57 (s, 1H, NH, $D_2O$-exchangable) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ 13.9, 25.7, 26.2, 50.8, 97.5, 152.6, 156.5, 158.7, 161.0, 166.7 ppm. IR (KBr disc): $\nu$ 3382, 2926, 1647, 1577, 1472, 1433, 1394, 1280, 1082, 765 (C–Br) cm$^{-1}$. MS (*m/z*) = 370 [$M^+$], 321 [$M^+$ – SMe], 252 [$M^+$ – pyrrolidine, SMe]. *Anal.* Calcd. for $C_{12}H_{16}BrN_7S$ (%): C, 38.93; H, 4.36; N, 26.48; S, 8.66. Found: C, 38.91; H, 4.33; N, 26.47; S, 8.62.

**Synthesis of 2-alkoxy-8-methyl-6-(pyrrolidin-1-yl)-4*H*-[1,2,4]triazolo[5,1-*f*]purine (5a-g); general procedure:** To a mixture of compound **4** (0.51 mmol, 0.188 g) and KOH (5 mmol, 0.28 g), the excess amount of the appropriate alcohol (5–7 mL) was added and the mixture was heated under reflux for 18–21 h. After the completion of the reaction, the mixture was cooled, poured into an ice/water bath and neutralized with aqueous 5% HCl solution. When a precipitate appeared, it was filtered, washed with water (2 × 10 mL), and dried at room temperature until constant weight. When a viscous mixture appeared, the solution was extracted with chloroform (3 × 10 mL). The organic layer was dried with anhydrous $NaSO_4$, filtered, and evaporated. The isolated solid was collected without further purification.

**2-Methoxy-8-methyl-6-(pyrrolidin-1-yl)-4*H*-[1,2,4]triazolo[5,1-*f*]purine (5a):** (The alcohol is $CH_3OH$). White powder, yield: 68%, mp: 47–49 °C, $^1$H NMR ($CDCl_3$): $\delta$ 1.90–1.95 (m, 4H, $2CH_2$), 2.44 (s, 3H, pyrimidine-$CH_3$), 3.57 (s, 3H, $OCH_3$), 3.88 (t, 4H, $J$ = 7.5 Hz, $2NCH_2$), 13.22 (s, 1H, NH, $D_2O$-exchangable) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ 19.9, 24.6, 49.8, 85.7, 128.0, 144.1, 153.2, 156.8, 157.0, 159.7 ppm. IR (KBr disc): $\nu$ 2966, 2877, 2819, 1648, 1597, 1478, 1401, 1339 cm$^{-1}$. MS (*m/z*) = 272 [$M^+$], 242 [$M^+$ – OMe], 203 [$M^+$ – pyrrolidine]. *Anal.* Calcd. for $C_{13}H_{16}N_6O$ (%): C, 57.34; H, 5.92; N, 30.86. Found: C, 57.33; H, 5.90; N, 30.83.

**2-Ethoxy-8-methyl-6-(pyrrolidin-1-yl)-4*H*-[1,2,4]triazolo[5,1-*f*]purine (5b):** (The alcohol is $C_2H_5OH$). White powder, yield: 73%, mp: 54–56 °C, $^1$H NMR ($CDCl_3$): $\delta$ 1.29 (t, 3H, $J$ = 6.0 Hz, $CH_3$), 1.80–1.85 (m, 4H, $2CH_2$), 2.37 (s, 3H, pyrimidine-$CH_3$), 3.71 (t, 4H, $J$ = 6.0 Hz, $2NCH_2$), 4.22 (q, 2H, $J$ = 6.0 Hz, $OCH_2$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ 14.6, 25.6, 25.7, 50.3, 62.8, 94.5, 96.0, 159.9, 160.1, 162.2, 166.8 ppm. IR (KBr disc): $\nu$ 2974, 2924, 2873, 1569, 1523, 13474, 1331, 1234, 1077, 777 cm$^{-1}$. MS (*m/z*) = 286 [$M^+$], 242 [$M^+$ – OEt], 217 [$M^+$ – pyrrolidine]. *Anal.* Calcd. for $C_{14}H_{18}N_6O$ (%): C, 58.73; H, 6.34; N, 29.35. Found: C, 58.70; H, 6.32; N, 29.34.

**8-Methyl-2-propoxy-6-(pyrrolidin-1-yl)-4*H*-[1,2,4]triazolo[5,1-*f*]purine (5c):** (The alcohol is *n*-$C_3H_7OH$). Yellow powder, yield: 89%, mp: 95–97 °C, $^1$H NMR ($CDCl_3$): $\delta$ 1.02 (t, 3H, $J$ = 7.5 Hz, $CH_3$), 1.74–1.86 (m, 2H, $CH_2$), 1.91–1.95 (m, 4H, $2CH_2$), 2.47 (s, 3H, pyrimidine-$CH_3$), 3.81 (t, 4H, $J$ = 6.0 Hz, $2NCH_2$), 4.21 (t, 2H, $J$ = 7.5 Hz, $OCH_2$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ 10.6, 22.3, 25.7, 25.8, 50.3, 68.7, 94.4, 96.0, 159.9, 162.4, 162.7, 166.9 ppm. IR (KBr disc): $\nu$ 2966, 2876, 1563, 1527, 1326 cm$^{-1}$. MS (*m/z*) = 300 [$M^+$], 258 [$M^+$– Pr], 242 [$M^+$ – OPr], 227 [$M^+$ – pyrrolidine, Me]. *Anal.* Calcd. for $C_{15}H_{20}N_6O$ (%): C, 59.98; H, 6.71; N, 27.98. Found: C, 59.96; H, 6.70; N, 27.96.

**2-Isopropoxy-8-methyl-6-(pyrrolidin-1-yl)-4*H*-[1,2,4]triazolo[5,1-*f*]purine (5d):** (The alcohol is *iso*-$C_3H_7OH$). Yellow powder, yield: 75%, mp: 42–44 °C, $^1$H NMR ($CDCl_3$): $\delta$ 1.36 (d, 6H, $J = 6.0$ Hz, $2CH_3$), 1.90–1.94 (m, 4H, $2CH_2$), 2.46 (s, 3H, pyrimidine-$CH_3$), 3.80 (t, 4H, $J = 6.0$ Hz, $2NCH_2$), 5.10–5.22 (m, 1H, OCH) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ 22.0, 25.7, 25.8, 50.3, 69.5, 94.2, 95.9, 159.9, 161.8, 162.4, 167.0 ppm. IR (KBr disc): $\nu$ 2972, 2920, 2871, 1562, 1387, 1316, 1233, 1115 $cm^{-1}$. MS (*m/z*) = 300 [$M^+$], 242 [$M^+$ – OPr], 227 [$M^+$ – pyrrolidine, Me], 202 [$M^+$ – pyrrolidine, 2Me]. *Anal.* Calcd. for $C_{15}H_{20}N_6O$ (%): C, 59.98; H, 6.71; N, 27.98. Found: C, 59.97; H, 6.69; N, 27.97.

**2-Butoxy-8-methyl-6-(pyrrolidin-1-yl)-4*H*-[1,2,4]triazolo[5,1-*f*]purine (5e):** (The alcohol is *n*-$C_4H_9OH$). Oily liquid, yield: 69%, $^1$H NMR ($CDCl_3$): $\delta$ 0.94 (t, 3H, $J = 6.0$ Hz, $CH_3$), 1.40–1.52 (m, 2H, $CH_2$), 1.69–1.78 (m, 2H, $CH_2$), 1.88–1.93 (m, 4H, $2CH_2$), 2.44 (s, 3H, pyrimidine-$CH_3$), 3.79 (t, 4H, $J = 7.5$ Hz, $2NCH_2$), 4.24 (t, 2H, $J = 7.5$ Hz, $OCH_2$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ 12.8, 18.2, 18.4, 24.7, 30.0, 49.2, 65.8, 93.4, 94.9, 158.8, 161.0, 161.3, 165.8 ppm. IR (KBr disc): $\nu$ 2958, 2872, 1565, 1457, 1403, 1331, 1078, 1022, 779 $cm^{-1}$. MS (*m/z*) = 314 [$M^+$], 300 [$M^+$ – Me], 258 [$M^+$ – Bu], 242 [$M^+$ – OBu], 230 [$M^+$ – pyrrolidine, Me], 158 [$M^+$ – pyrrolidine, Me, OBu]. *Anal.* Calcd. for $C_{16}H_{22}N_6O$ (%): C, 61.13; H, 7.05; N, 26.73. Found: C, 61.12; H, 7.04; N, 26.71.

**2-Isobutoxy-8-methyl-6-(pyrrolidin-1-yl)-4*H*-[1,2,4]triazolo[5,1-*f*]purine (5f):** (The alcohol is *iso*-$C_4H_9OH$). Oily liquid, yield: 73%, $^1$H NMR ($CDCl_3$): $\delta$ 0.99 (d, 6H, $J = 6.0$ Hz, $2CH_3$), 1.88–1.93 (m, 4H, $2CH_2$), 2.02–2.15 (m, 1H, CH), 2.44 (s, 3H, pyrimidine-$CH_3$), 3.79 (t, 4H, $J = 7.5$ Hz, $2NCH_2$), 4.01 (d, 2H, $J = 9.0$ Hz, $OCH_2$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ 18.3, 18.4, 24.7, 26.9, 46.2, 72.4, 93.3, 94.8, 158.8, 161.4, 165.1, 165.8 ppm. IR (KBr disc): $\nu$ 2958, 2873, 1597, 1564, 1456, 1318, 1328, 779 $cm^{-1}$. MS (*m/z*) = 314 [$M^+$], 258 [$M^+$ – Bu], 230 [$M^+$ – pyrrolidine, Me], 202 [$M^+$ – pyrrolidine, 3 Me]. *Anal.* Calcd. for $C_{16}H_{22}N_6O$ (%): C, 61.13; H, 7.05; N, 26.73. Found: C, 61.11; H, 7.03; N, 26.70.

***N*-Ethyl-2-((8-methyl-6-(pyrrolidin-1-yl)-4*H*-[1,2,4]triazolo[5,1-*f*]purin-2-yl)oxy)ethan-1-amine (5g):** (The alcohol is $C_2H_5NH(CH_2)_2OH$). Oily liquid, yield: 70%, $^1$H NMR ($CDCl_3$): $\delta$ 1.07 (t, 3H, $J = 6.0$ Hz, $CH_3$), 1.87–1.92 (m, 4H, $2CH_2$), 2.37 (s, 3H, pyrimidine-$CH_3$), 3.58 (t, 2H, $J = 6.0$ Hz, $NHCH_2CH_3$), 3.64 (t, 2H, $J = 6.0$ Hz, $OCH_2CH_2NH$), 3.74 (t, 4H, $J = 7.5$ Hz, $2NCH_2$), 3.83 (t, 2H, $J = 6.0$ Hz, $OCH_2$), 5.65 (s, 1H, NH, $D_2O$-exchangable) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ 13.1, 25.5, 25.7, 44.2, 46.2, 50.1, 64.5, 90.5, 92.1, 159.3, 161.0, 161.6, 164.5 ppm. IR (KBr disc): $\nu$ 3366 (NH), 2967, 2933, 2868 (CH, aliphatic) 1586, 1545, 1477, 1079, 1048, 775 $cm^{-1}$. MS (*m/z*) = 329 [$M^+$], 260 [$M^+$ – pyrrolidine, Me], 242 [$M^+$ – OEt-NEt], 217 [$M^+$ – pyrrolidine, EtNH]. *Anal.* Calcd. for $C_{16}H_{23}N_7O$ (%): C, 58.34; H, 7.04; N, 29.77. Found: C, 58.32; H, 7.03; N, 29.75.

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