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Synthesis and regioselective N- and O-alkylation of 3-alkyl-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-ones and 2-phenyl-9-propyl-9*H*-purin-6(1*H*)-one with evaluation of antiviral and antitumor activities

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ABSTRACT

3-Alkyl-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-ones were prepared by nitrosative cyclization of the appropriate 5,6-diamino-2-phenylpyrimidin-4(3*H*)-ones with nitrous acid and were subjected to regioselective alkylation with several alkylating agents in aprotic solvent at different temperature. Simultaneous 6-N- and 7-O-alkylation were observed and the regioselectivity varied remarkably with size and shape of the alkylating agents as well as with the reaction temperature. Similarly, N- and O-alkylation as well as selectivity was also observed in the case of 2-phenyl-9-propyl-9*H*-purin-6(1*H*)-one. Some of the synthesized compounds showed moderate antiviral and antitumor activities.

1. Introduction

The fused pyrimidine derivatives such as naturally occurring purine bases and their analogues have been focused of great interest over many years by reason of their diversified biological activities.[1–5] Particular interests are the structural modification of purine bases as well as introduction of different functional groups into these bases in the view of searching potential antineoplastic and antiviral agents. Introduction of different functional groups, e.g., amino, oxo, thioxo, alkylthio, alkyl/aryl groups, into purine bases at different positions has been assessed for potency and selectivity for the biological system.[2,6–11] 6-Chloro, thioxo, alkylthio, amino purine derivatives as well as 9-substituted purine derivatives have been reported for good antitumor and antiviral activities.[2,6,7,11] A few effective and clinically applicable antineoplastic and antiviral agents have been reported so far. Therefore, continuous efforts have been conducted for the synthesis of purines and their analogues for searching the effective biological agents. To be biologically active for any compound needs some active sites to interact with DNA or RNA. A minor modification of a biologically active compound can greatly alter its potentiality. Thus, more modifications of biologically active purine derivatives may lead to achieve the highly expected effective antiviral and antitumor drugs. Hence, our laboratory has designed the program for the synthesis of fused pyrimidines,[12–19] especially purine and modified purine derivatives, by introducing different substituents at different positions accompanied the alternation of natural sugar at the 3/9-position with alkyl/aryl groups in order to observe the change of antiviral and antitumor activities. Study of regioselective N- and O-alkylation of purine and modified purine derivatives is a part of the program since much attention has not been directed toward the selective O-alkylation for the synthesis of biologically active compounds in this area.

We reported[19] the synthesis of 1*H*-, 2*H*-, and 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones and their first regioselective 5-O-alkylation along with 4-N-alkylation. There are some reports[20–22] of preparation of 6-*O*-alkyl purine derivatives from 6-chloropurines and the conversion of 6-cyanopurines into 6-*O*-alkyl purine derivatives. Although there are many reports of alkylation of xanthine and hypoxanthine, all of them are involved in either N-alkylation[23–25] or S-alkylation.[26,27] The interest of most alkylation for xanthines, 8-azaxanthines, and 8-azahypoxanthines has been turned to the imidazole[23,24] and triazole rings.[25] In connection with the program of synthesis and regioselective alkylation of 8-azapurines, we report herein the synthesis of 3-alkyl-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-ones and 2-phenyl-9-propyl-9*H*-purin-6(1*H*)-one, and their regioselective N- and

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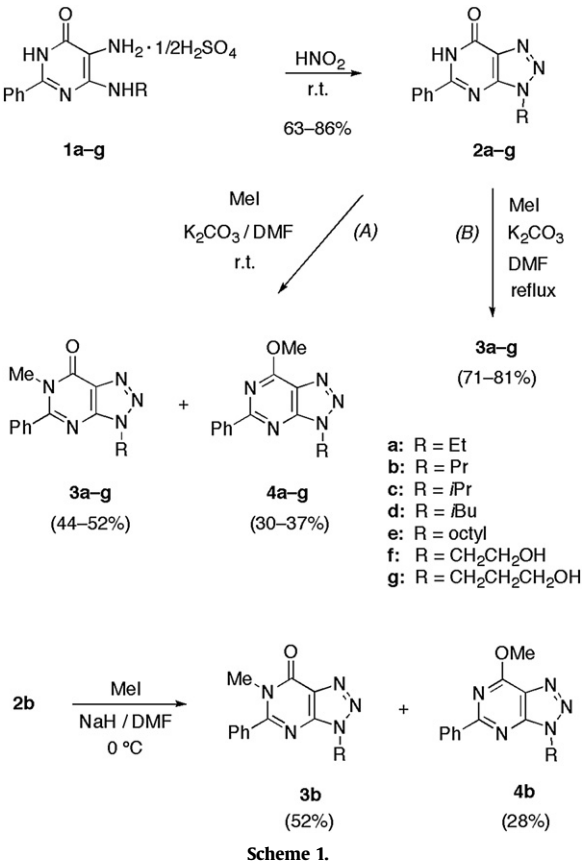
O-alkylation along with the evaluation of their antiviral and antitumor activities.

2. Results and discussion

2.1. Chemistry

The requisite key starting materials, 5,6-diamino-2-phenylpyrimidin-4(3*H*)-ones **1a**–**g**, were prepared from 6-chloro-2-phenylpyrimidin-4(3*H*)-one in simple three steps following the standard methods.[19,23,28] The nitrosative cyclization of these 5,6-diaminopyrimidine derivatives **1a**–**g** with nitrous acid at room temperature led to the formation of 3-alkyl-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-ones **2a**–**g** in 63–86% yields (Scheme 1). The methylation of **2a**–**g** with methyl iodide in the presence of anhydrous potassium carbonate in *N*,*N*-dimethylformamide at room temperature afforded the mixture of 6-*N*-methylated **3a**–**g** (44–52% yields) and 7-*O*-methylated derivatives **4a**–**g** (30–37% yields). The same methylation of **2a**–**g** with methyl iodide at boiling temperature gave the 6-*N*-methylated derivatives **3a**–**g** in 71–81% yields, exclusively. The methylation of **2b** with methyl iodide in the presence of sodium hydride in *N*,*N*-dimethylformamide at 0 °C gave **3b** and **4b** in 52% and 28% yields, respectively.



Scheme 1.

The acquit effect of temperature on methylation was examined by carrying out the reaction of **2b** with methyl iodide at different temperature from 0 to 153 °C as shown in Figure 1. It was observed that there was no effect of temperature between 0 and 100 °C on the ratio of yields, but at over 100–153 °C the 6-N-methylation was in preference to the 7-O-methylation. Thus, the 6-*N*-methylated derivative **3b** was prevailed exclusively at 153 °C. The priority for the formation of the *N*-methylated derivatives at higher

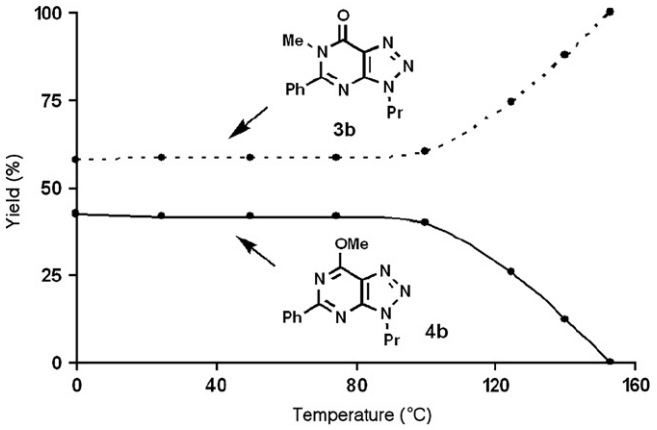
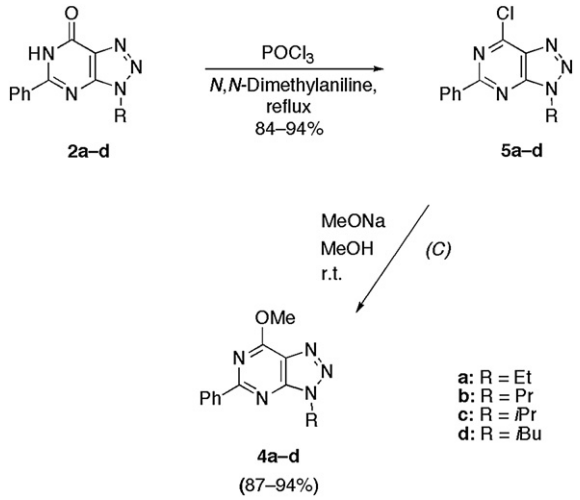


Figure 1. Relative yields of 6-*N*-methyl **3b** (dotted line) and 7-*O*-methyl **4b** (solid line) isomers yielded by the methylation of **2b** with MeI at different temperature.

temperature can be explained by the following fact. That is to say, an adequate energy is supplied at high temperature to conquer the steric interaction of 5-phenyl group with methyl iodide to give the comparatively more stable *N*-methylated products.[29]

The O-methylation was verified by another synthetic route. Namely, treatment of compounds **2a**–**d** with phosphoryl chloride in the presence of *N*,*N*-dimethylaniline gave the corresponding 7-chloro derivatives **5a**–**d** in quantitative yields, which on subsequent treatment with sodium methoxide in methanol at room temperature yielded the 7-methoxy derivatives **4a**–**d** in excellent yields (Scheme 2). The physical and spectral data of **4a**–**d** prepared by the second route were quite identical in all respects with the first fraction isolated by column chromatography from a mixture of products gained by methylation of **2a**–**d** with methyl iodide at room temperature. The IR, ^{1}H NMR, and UV spectra of the *O*- and *N*-methyl isomers provided satisfactory evidence for their discrimination and identification. Usually IR spectra of the 7-oxo derivatives **2a**–**g**, **3a**–**g** showed the characteristic absorption band in the region of 1690–1720 cm^{-1} for C=O group. In the case of the *O*-methylated derivatives, the absorption band based on the 7-C=O in the region of 1690–1720 cm^{-1} disappeared. Hence, this evidently revealed the disappearance of the 7-oxo group due to the formation of the 7-*O*-methylated derivatives **4a**–**g**. In addition, the ^{1}H NMR spectra displayed considerable confirmation exhibiting chemical shifts for 7-O-CH_3 protons (δ 4.37–4.40 for compounds **4a**–**g**) in more down field than that of 6-N-CH_3 protons (δ 3.53–3.55 for compounds **3a**–**g**) due to the inductive effect. The UV spectra of



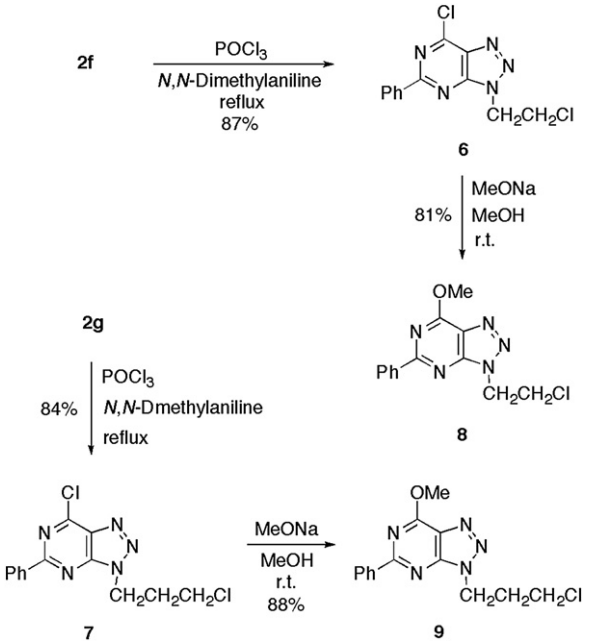
Scheme 2.

these regioisomers also provided the confirmation to assign the 7-O-methylation along with 6-N-methylation. The UV spectra of all *O*-methyl isomers in ethanol exhibited six maxima absorption bands (238, 245–246, 275–276, 284, 293–294, and 304 nm), while *N*-methyl isomers showed two maxima absorption bands (266–267 and 271–272 nm). It is also notable that the physical and spectral properties of the 7-*O*-methyl **4a**–**g** and 7-chloro derivatives **5a**–**d** are about quite analogous due to their structural resemblance. Thus, we distinguished and established the 7-O-methylation along with the 6-N-methylation by comparing several spectral data.

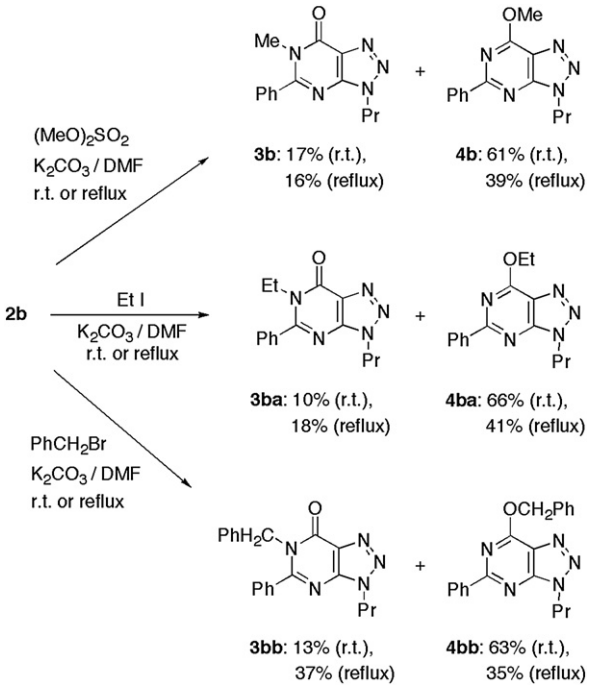
Chlorination of 3-(2-hydroxyethyl)- **2f** and 3-(3-hydroxy propyl)-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one **2g** was achieved in an analogous way to compounds **2a**–**d** (Scheme 3). Initially, it was expected that the chlorination might take place only at the 7-position, but actually, the alcoholic hydroxyl group of both compounds was also replaced by a chlorine to afford the corresponding 7-chloro-3-(2-chloroethyl)- **6** and 7-chloro-3-(3-chloropropyl)-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine **7** in 87% and 84% yields, respectively. The absence of the alcoholic absorption band in the IR spectra as well as the broad singlet signal attributable to the alcoholic OH proton in the ^{1}H NMR spectra of these two derivatives **6** and **7** showed the substitution of hydroxyl group to chlorine. When the dichlorinated derivatives **6** and **7** were treated with sodium methoxide in methanol at room temperature, the nucleophilic substitution took place only at the 7-position to give the corresponding 3-(2-chloroethyl)-7-methoxy- **8** and 3-(3-chloropropyl)-7-methoxy-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine **9** in 81% and 88% yields, respectively. ^{1}H NMR spectra of these two methoxy derivatives showed only one singlet signal (δ 4.38) attributable to the 7-*O*-methyl protons, which was consistent with the other 7-*O*-methyl derivatives (δ 4.37–4.40 for **4a**–**g**). Besides, the physical and spectral data of 3-(2-hydroxyethyl)-7-methoxy **4f** and 3-(3-hydroxypropyl)-7-methoxy-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine **4g** obtained by methylation of **2f** and **2g** were different from that of **8** and **9**, respectively. Hence, it is obvious that the replacement of chlorine by methoxy group took place selectively at the 7-position without the side chain of **6** and **7**.

To examine the effect of size and shape of the alkylating agents on the O- and N-alkylation, compound **2b** was chosen as the model compound. The alkylation of **2b** with dimethyl sulfate, ethyl iodide, or benzyl bromide in the presence of anhydrous potassium carbonate in *N*,*N*-dimethylformamide at room temperature afforded the 7-*O*-alkylated derivatives **4b**, **4ba**, and **4bb** as the major products (61–66% yields) along with the 6-*N*-alkylated derivatives **3b**, **3ba**, and **3bb** (10–17% yields) (Scheme 4). Even the methylation as well as ethylation of **2b** with dimethyl sulfate and ethyl iodide at boiling temperature led to the 7-*O*-methyl **4b** (39% yield) and 7-*O*-ethyl **4ba** (41% yield) derivatives as the major products accompanied with 6-*N*-methyl **3b** (16% yield) and 6-*N*-ethyl **3ba** (18% yield) derivatives, respectively. In the case of benzylation of **2b** at boiling temperature two regioisomers **3bb** and **4bb** were obtained almost in equal quantity. Hence, it is apparent that the 7-O-alkylation favored preference over the 6-N-alkylation for bulkier alkylating agents[19] due to the steric interaction of the alkylating agents with the phenyl group at the 5-position. That is, the energy produced at boiling temperature in *N*,*N*-dimethylformamide is not sufficient enough to overcome the steric interaction force for bulkier alkylating agents to give only the more stable 6-*N*-alkyl derivatives. For confirmation of the 7-O-alkylation, compound **4ba** was also prepared by treating **5b** with sodium ethoxide in ethanol at room temperature, which was identical in all respects with the 7-ethoxy derivative obtained by ethylation of **2b**. IR, ^{1}H NMR, and UV spectra as well as microanalyses for these 6-*N*-alkylated and 7-*O*-alkylated derivatives were also quite satisfactory to assign and differentiate the regioisomers as discussed for 6-*N*-methyl **3a**–**g** and 7-*O*-methyl **4a**–**g** regioisomers.

On the other hand, the similar regioselective N- and O-alkylation was also observed in the alkylation on purine ring. 2-Phenyl-9-propyl-9*H*-purin-6(1*H*)-one **10** was prepared by treating free 5,6-diaminopyrimidine derivative **1b** with 85% formic acid in order to observe the alkylation position on the pyrimidine ring of it (Scheme 5). The methylation of **10** with 1 equiv methyl iodide in the presence of anhydrous potassium carbonate in *N*,*N*-dimethylformamide at 0 °C gave the 1-*N*-methyl **11a** and 6-*O*-methyl isomer **11b** in 26% and 45% yields, respectively. The same methylation with excess methyl iodide at room temperature gave **11b** and 6,9-dihydro-1,7-dimethyl-6-oxo-2-phenyl-9-propyl-1*H*-purin-7-ium hydroxide **12** in 44% and 30% yields, respectively. Similar methylation of **10** with 1 equiv dimethyl sulfate at room

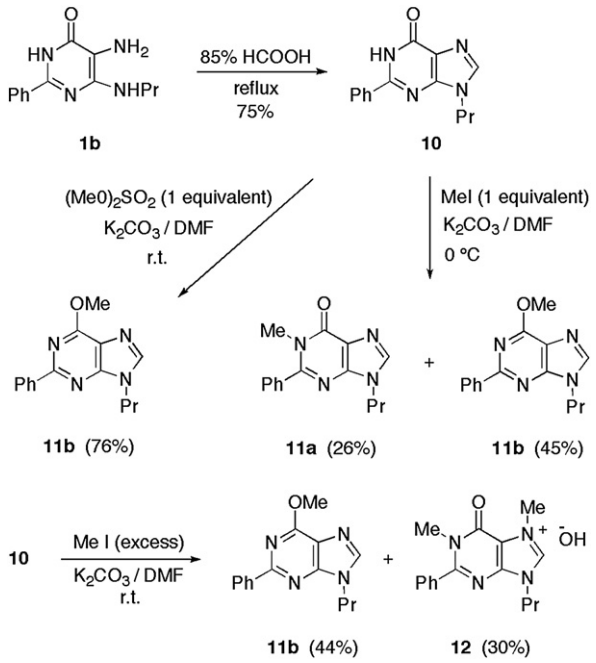


Scheme 3.



Scheme 4.

temperature gave only **11b** in 76% yield. Therefore, it is obvious that the O-methylation of 2-phenylhypoxanthine **10** takes place more preferentially over the N-methylation compared with that of 2-phenyl-8-axahypoxanthine **2**. Besides, the 1,9-disubstituted hypoxanthine **11a** forms the 1,7,9-trisubstituted quaternary salt **12** with excess alkylating agent. The quaternary salt was obtained as hydroxide salt. IR, ^{1}H NMR, and microanalysis data were quite satisfactory with the hydroxide salt **12**.



Scheme 5.

Table 1
Evaluation of antiviral and antitumor activities in vitro of compounds (**2a–g**, **3a–g**,**bb**, **4a–g**,**bb**, **5a–d**, **6**, and **8**)

Compd No.	Inhibitory concentration against Herpes Simplex Virus [ED_{50} (μg/mL)]		Inhibitory concentration against tumor cell lines [IC_{50} (μg/mL)]	
	HSV-1	HSV-2	CCRF-HSB-2	KB
2a	>20	>20	42.3	70.5
2b	>100	>100	51.0	57.8
2c	>100	>100	>100	67.5
2d	>20	>20	80.7	74.3
2e	>4	>4	17.5	11.0
2f	>100	>100	92.6	>100
2g	>100	>100	61.0	70.1
3a	>100	>100	>100	>100
3b	n.d.	n.d.	n.d.	n.d.
3c	>100	>100	82.3	>100
3d	>100	>100	97.6	>100
3e	>20	>20	25.9	29.0
3f	>100	>100	86.2	>100
3g	>100	>100	60.4	41.0
3bb	>20	>20	>100	>100
4a	>100	>100	>100	>100
4b	n.d.	n.d.	n.d.	n.d.
4c	>100	>100	>100	>100
4d	>20	>20	39.4	32.1
4e	n.d.	n.d.	n.d.	n.d.
4f	>100	>100	77.7	97.9
4g	>100	>100	>100	>100
4bb	>100	>100	>100	72.2
5a	>0.8	>0.8	32.6	43.4
5b	>20	>20	1.9	8.9
5c	>0.8	>0.8	8.4	36.4
5d	>20	>20	8.3	30.9
6	>20	>20	6.5	17.4
8	>20	>20	2.3	8.8
ACV[a]	0.16	0.16	n.d.	n.d.
Ara-C[b]	n.d.	n.d.	0.07	0.09

The n.d. means not done.
[a] ACV=acyclovir.
[b] Ara-C=arabinosylcytidine.

2.2. Biological activity

2.2.1. Antiviral activity

Compounds **2a–g**, **3a–g**,**bb**, **4a–g**,**bb**, **5a–d**, **6**, and **8** were evaluated for antiviral activity in vitro against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) according to the methods developed by Machida et al.[30,31] The results are summarized in Table 1. The potency of antiviral activity of each compound is expressed as a minimum inhibitory concentration (ED_{50}) required to reduce virus plaque formation by 50% under experimental conditions. Among the tested compounds, **5a** and **5c** were more potential (>0.8 μg/mL) against both viruses. Compound **2e** showed its activity at the concentration of >4 μg/mL. Some compounds, e.g., **2a**,**d**, **3e**,**bb**, **4d**, **5b**,**d**, **6**, and **8**, showed activity against both herpes viruses at the concentration of >20 μg/mL and some did not exhibit any activity up to 100 μg/mL. 7-Chloro derivatives are comparatively more active than 6-*N*-alkyl or 7-*O*-alkyl derivatives.

2.2.2. Antitumor activity

The modified[32] 3-(3,4-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay for cellular growth and survival application method developed by Mosmann[33] was used to determine the growth inhibitory effects (antitumor activity) of the synthesized compounds against CCRF-HSB-2 (human T-cell acute lymphoblastoid leukemia) and KB (human oral epidermoid carcinoma) cells in vitro. The results, i.e., 50% inhibitory concentration [IC_{50} (μg/mL)] of each compound against the both cells are summarized in Table 1. 7-Chloro-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidines (**5b–d**, **6**, and **8**) showed better activity against CCRF-HSB-2 cancer cells (1.9–8.4 μg/mL) than against KB cells (8.8–36.4 μg/mL). 3-Octyl-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one **2e** showed potential activity against CCRF-HSB-2 and KB cells at the concentration of 17.5 μg/mL and 11.0 μg/mL, respectively, while 6-*N*-methyl-3-octyl derivative **3e** exhibited about similar activity (25.9 μg/mL and 29.0 μg/mL) against both cells. Other compounds were too low toxic to exhibit potential activity. Thus, it is apparent that the presence of electronegative chlorine atom at the 7-position is significant for antitumor activity. Besides, among the alkyl groups at the 9-position, octyl group is responsible for increased activity due to its hydrophobic character. 6-*N*-Alkyl and 7-*O*-alkyl groups do not enhance antitumor activity.

3. Conclusion

Thus, this can be concluded that the NH proton on the pyrimidine ring of 5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-ones and 2-phenyl-9-propyl-9*H*-purin-6(1*H*)-one remains as lactam–lactim tautomers. Therefore, the N- and O-alkylation (electrophilic substitution) takes place simultaneously. The selectivity for the alkylation position onto 5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-ones is highly controllable by temperature as well as by the size and shape of the alkylating agents (electrophiles). A few of the synthesized compounds have moderate antiviral and antitumor activities. Therefore, this simple and facile methodology for simultaneous N- and O-alkylation of lactam–lactim tautomers might be used in future for the preparation of analogous compounds for searching potential biological agents.

4. Experimental

4.1. General

Mps were determined on a Yanagimoto micro-melting point hot stage apparatus and were uncorrected. IR spectra were obtained using a JASCO FT/IR-200 spectrophotometer in Nujol mulls. UV spectra were recorded with a Beckman DU-68 spectrophotometer in ethanol. IR and UV absorption values in italic refer to wave numbers and wave length, respectively, at which shoulders or inflexions occur in the absorption. ^{1}H NMR spectra were measured using a VXR 300 MHz spectrometer and chemical shift values were expressed in δ values (ppm) relative to TMS as an internal standard. Coupling constants are given in hertz and signals are quoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sext, sextet; sept, septed; br, broad; m, multiplet. Microanalyses were measured by a Yanako CHN Corder MT-5 apparatus. Reaction progress was monitored by analytical thin-layer chromatography (TLC) on pre-coated glass plates (silica gel 60 F_{254} Plate-Merck) and products were visualized by UV light. Column chromatography was accomplished on Daisogel IR-60 (63/210 μm, Daiso Co.).

4.2. General procedure for the synthesis of 6-alkylamino-5-amino-2-phenylpyrimidin-4(3*H*)-one hemisulfates (1a–g)

A mixture of an appropriate 6-alkylamino-5-nitroso-2-phenylpyrimidin-4(3*H*)-ones (8.0 mmol), acetic acid (5 mL), water (50 mL), and methanol (50 mL) was heated to ca. 60 °C and to it was added $Na_2S_2O_4$ (25–32 mmol) by portions with stirring. Then, the mixture was heated at 70 °C for 0.5–1.0 h. After the reaction was complete, the solution was concentrated to ca. 20 mL and to it was added water (25 mL). Upon keeping the mixture at room temperature (rt) for several hours, the solid deposited was collected by filtration to give the corresponding 5,6-diamino hemisulfate derivatives **1a**–**g** as pale yellow powdery crystals. For analysis a portion of these products were recrystallized from dilute H_2SO_4 except **1e**, which was recrystallized from a mixture of ethanol and dilute H_2SO_4.

*4.2.1. 5-Amino-6-ethylamino-2-phenylpyrimidin-4(3H)-one hemisulfate (**1a**)*

Yield 1.28 g (5.52 mmol, 69%); mp 217–218 °C (decomp.); R_f 0.26 (*n*-hexane/EtOAc, 1:3); IR (Nujol): 3345, 3070 (NH), 1635 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.21 (t, *J*=7.2 Hz, 3H, CH_3), 3.49 (br s, 2H, CH_2), 6.40 (br s, 1H, 6-NH), 7.43–7.52 (m, 3H, Ph-*m*,*p*H), 8.03–8.13 (m, 2H, Ph-*o*H). Anal. Calcd for $C_{12}H_{14}N_4O\cdot(1/2H_2SO_4+2/3H_2O)$: C, 49.47; H, 5.65; N, 19.23. Found: C, 49.53; H, 5.44; N, 19.23.

*4.2.2. 5-Amino-2-phenyl-6-propylaminopyrimidin-4(3H)-one hemisulfate (**1b**)*

Yield 1.58 g (6.48 mmol, 81%); mp 215–216 °C (decomp.); R_f 0.29 (*n*-hexane/EtOAc, 1:3); IR (Nujol): 3340, 3065 (NH), 1640 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.96 (t, *J*=7.5 Hz, 3H, CH_3), 1.57–1.66 (m, 2H, N-CH_2CH_2), 3.44 (br s, 2H, N-CH_2), 6.38 (br s, 1H, 6-NH), 7.41–7.53 (m, 3H, Ph-*m*,*p*H), 8.02–8.14 (m, 2H, Ph-*o*H). Anal. Calcd for $C_{13}H_{16}N_4O\cdot(1/2H_2SO_4+1/2H_2O)$: C, 51.64; H, 6.00; N, 18.53. Found: C, 51.67; H, 5.87; N, 18.38.

*4.2.3. 5-Amino-6-isopropylamino-2-phenylpyrimidin-4(3H)-one hemisulfate (**1c**)*

Yield 1.51 g (6.16 mmol, 77%); mp 208–210 °C (decomp.); R_f 0.29 (*n*-hexane/EtOAc, 1:3); IR (Nujol): 3270, 3060 (NH), 1655 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.23 (d, *J*=6.3 Hz, 6H, 2×CH_3), 4.24–4.41 (m, 1H, CH), 6.18 (br s, 1H, 6-NH), 7.49–7.64 (m, 3H, Ph-*m*,*p*H), 8.05–8.14 (m, 2H, Ph-*o*H). Anal. Calcd for $C_{13}H_{16}N_4O\cdot(1/2H_2SO_4+1/4H_2O)$: C, 52.42; H, 5.92; N, 18.81. Found: C, 52.60; H, 5.90; N, 18.44.

*4.2.4. 5-Amino-6-isobutylamino-2-phenylpyrimidin-4(3H)-one hemisulfate (**1d**)*

Yield 1.61 g (6.24 mmol, 78%); mp 205–206 °C (decomp.); R_f 0.31 (*n*-hexane/EtOAc, 1:3); IR (Nujol): 3280, 3070 (NH), 1630 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.94 (d, *J*=6.6 Hz, 6H, 2×CH_3), 1.83–1.96 (m, 1H, N-CH_2CH), 3.30 (s, 2H, N-CH_2), 6.31 (br s, 1H, 6-NH), 7.43–7.52 (m, 3H, Ph-*m*,*p*H), 8.12–8.21 (m, 2H, Ph-*o*H). Anal. Calcd for $C_{14}H_{18}N_4O\cdot1/2H_2SO_4$: C, 54.71; H, 6.23; N, 18.23. Found: C, 55.07; H, 6.18; N, 18.58.

*4.2.5. 5-Amino-6-octylamino-2-phenylpyrimidin-4(3H)-one hemisulfate (**1e**)*

Yield 1.91 g (6.08 mmol, 76%); mp 158–159 °C (decomp.); R_f 0.49 (*n*-hexane/EtOAc, 1:3); IR (Nujol): 3345, 3070 (NH), 1635 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.85 (s, 3H, CH_3), 1.25 (br s, 10H, $[CH_2]_5CH_3$), 1.50–1.66 (m, 2H, N-CH_2CH_2), 3.45 (br s, 2H, N-CH_2), 6.16 (br s, 1H, 6-NH), 7.40–7.52 (m, 3H, Ph-*m*,*p*H), 8.01–8.13 (m, 2H, Ph-*o*H). Anal. Calcd for $C_{18}H_{26}N_4O\cdot1/2H_2SO_4$: C, 59.48; H, 7.49; N, 15.41. Found: C, 59.87; H, 7.39; N, 15.45.

*4.2.6. 5-Amino-6-(2-hydroxyethylamino)-2-phenylpyrimidin-4(3H)-one hemisulfate (**1f**)*

Yield 1.64 g (6.64 mmol, 83%); mp 215–216 °C (decomp.); R_f 0.45 (EtOAc/EtOH, 4:1); IR (Nujol): 3320 (OH), 3200 (NH), 1640 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.44 (q, *J*=6.9 Hz, 2H, O-CH_2), 3.57 (br s, 2H, N-CH_2), 4.29 (br s, 1H, OH), 5.97 (br s, 1H, 6-NH), 7.38–7.45 (m, 3H, Ph-*m*,*p*H), 8.00–8.13 (m, 2H, Ph-*o*H). Anal. Calcd for $C_{12}H_{14}N_4O_2\cdot(1/2H_2SO_4+1/8H_2O)$: C, 48.44; H, 5.17; N, 18.83. Found: C, 48.37; H, 5.37; N, 18.59.

*4.2.7. 5-Amino-6-(3-hydroxypropylamino)-2-phenylpyrimidin-4(3H)-one hemisulfate (**1g**)*

Yield 1.56 g (6.0 mmol, 75%); mp 210–211 °C (decomp.); R_f 0.47 (EtOAc/EtOH, 4:1); IR (Nujol): 3310 (OH), 3200 (NH), 1640 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.73 (quin, *J*=6.6 Hz, 2H, N-CH_2CH_2), 3.44 (q, *J*=6.9 Hz, 2H, O-CH_2), 3.51 (t, *J*=5.7 Hz, 2H, N-CH_2), 4.18 (br s, 1H, OH), 6.27 (br s, 1H, 6-NH), 7.40–7.54 (m, 3H, Ph-*m*,*p*H), 8.01–8.13 (m, 2H, Ph-*o*H). Anal. Calcd for $C_{13}H_{16}N_4O_2\cdot1/2H_2SO_4$: C, 50.48; H, 5.54; N, 18.11. Found: C, 50.54; H, 5.62; N, 17.91.

4.3. General procedure for the synthesis of 3-alkyl-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-ones (2a–g)

A cooled solution of $NaNO_2$ (10.0 mmol) in water (5 mL) on ice was added to a solution of an appropriate **1a**–**g** (6.0 mmol) in 10% HCl (20 mL) at 0–5 °C with stirring over 20 min. Then, the reaction solution was brought to rt and stirred for 3–5 h. The solid deposited was collected by filtration, washed with water, and dried to afford the corresponding [1,2,3]triazolo derivatives **2a**–**g**.

*4.3.1. 3-Ethyl-5-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-one (**2a**)*

Pale yellow powdery crystals; yield 1.25 g (5.16 mmol, 86%); mp 257–258 °C (EtOAc); R_f 0.38 (*n*-hexane/EtOAc, 1:2); IR (Nujol): 3180 (NH), 1695 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.67 (t, *J*=7.2 Hz, 3H, CH_3), 4.66 (q, *J*=7.2 Hz, 2H, CH_2), 7.51–7.60 (m, 3H, Ph-*m*,*p*H), 8.21 (dd, $J_{o,p}$=2.1 Hz, $J_{o,m}$=7.8 Hz, 2H, Ph-*o*H), 12.36 (br s, 1H, NH); UV (EtOH): λ_{max} (log ε) *238* (4.44), *268* (4.35), 274 (4.37), 283 nm (4.36). Anal. Calcd for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.60; H, 4.56; N, 28.83.

*4.3.2. 5-Phenyl-3-propyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-one (**2b**)*

Pale yellow needles; yield 1.26 g (4.92 mmol, 82%); mp 206–207 °C (EtOAc); R_f 0.41 (*n*-hexane/EtOAc, 1:2); IR (Nujol): 3180 (NH), 1700 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.03 (t, *J*=7.5 Hz, 3H, CH_3), 2.10 (m, 2H, N-CH_2CH_2), 4.60 (t, *J*=7.2 Hz, 2H, N-CH_2), 7.61–7.63 (m,

3H, Ph-*m*,*p*H), 8.29 (dd, $J_{o,p}$=2.4 Hz, $J_{o,m}$=7.5 Hz, 2H, Ph-*o*H), 12.04 (s, 1H, NH); UV (EtOH): λ_{max} (log ε) *238* (4.43), 268 (4.34), 274 (4.36), 284 nm (4.34). Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.16; H, 5.13; N, 27.43. Found: C, 61.28; H, 5.28; N, 27.11.

*4.3.3. 3-Isopropyl-5-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-one (**2c**)*

Pale yellow powdery crystals; yield 1.20 g (4.68 mmol, 78%); mp 261–262 °C (EtOAc); R_f 0.42 (*n*-hexane/EtOAc, 1:2); IR (Nujol): 3180 (NH), 1690 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.75 (d, J=7.2 Hz, 6H, 2×CH_3), 5.20 (sept, J=7.2 Hz, 1H, CH), 7.52–7.61 (m, 3H, Ph-*m*,*p*H), 8.21 (dd, $J_{o,p}$=2.4 Hz, $J_{o,m}$=7.5 Hz, 2H, Ph-*o*H), 12.12 (s, 1H, NH); UV (EtOH): λ_{max} (log ε) *237* (4.4), *268* (4.31), 275 (4.34), 284 nm (4.34). Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.16; H, 5.13; N, 27.43. Found: C, 61.48; H, 5.19; N, 27.51.

*4.3.4. 3-Isobutyl-5-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-one (**2d**)*

Pale yellow prisms; yield 1.39 g (5.16 mmol, 86%); mp 203–204 °C (EtOAc); R_f 0.45 (*n*-hexane/EtOAc, 1:2); IR (Nujol): 3170 (NH), 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.02 (d, J=6.9 Hz, 6H, 2×CH_3), 2.40–2.53 (m, 1H, N-CH_2CH), 4.45 (d, J=7.2 Hz, 2H, N-CH_2), 7.58–7.65 (m, 3H, Ph-*m*,*p*H), 8.26 (dd, $J_{o,p}$=2.4 Hz, $J_{o,m}$=7.2 Hz, 2H, Ph-*o*H), 11.79 (s, 1H, NH); UV (EtOH): λ_{max} (log ε) *237* (4.47), *268* (4.38), 275 (4.40), 284 nm (4.39). Anal. Calcd for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.62; H, 5.66; N, 26.04.

*4.3.5. 3-Octyl-5-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-one (**2e**)*

Colorless powdery crystals; yield 1.51 g (4.62 mmol, 77%); mp 132–133 °C (*n*-hexane/EtOAc); R_f 0.53 (*n*-hexane/EtOAc, 1:2); IR (Nujol): 3190 (NH), 1690 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.86 (t, J=7.2 Hz, 3H, CH_3), 1.26 (br s, 6H, $CH_2[CH_2]_3CH_3$), 1.38 (br s, 4H, N-$CH_2CH_2[CH_2]_2$), 2.03–2.23 (m, 2H, N-CH_2CH_2), 4.63 (t, J=7.52 Hz, 2H, N-CH_2), 7.61–7.65 (m, 3H, Ph-*m*,*p*H), 8.25 (dd, $J_{o,p}$=2.1 Hz, $J_{o,m}$=7.5 Hz, 2H, Ph-*o*H), 11.55 (s, 1H, NH); UV (EtOH): λ_{max} (log ε) *238* (4.44), *268* (4.36), 273 (4.36), 284 nm (4.34). Anal. Calcd for $C_{18}H_{23}N_5O$: C, 66.44; H, 7.12; N, 21.52. Found: C, 66.52; H, 7.21; N, 21.42.

*4.3.6. 3-(2-Hydroxyethyl)-5-phenyl-3H-[1,2,3]triazolo[4,5-d]-pyrimidin-7(6H)-one (**2f**)*

Colorless powdery crystals; yield 1.16 g (4.50 mmol, 75%); mp 270–271 °C (EtOAc/EtOH); R_f 0.43 (EtOAc); IR (Nujol): 3360 (OH), 3185 (NH), 1715 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.94 (q, J=5.7 Hz, 2H, O-CH_2), 4.61 (t, J=5.7 Hz, 2H, N-CH_2), 4.98 (t, J=5.7 Hz, 1H, OH), 7.54–7.63 (m, 3H, Ph-*m*,*p*H), 8.15 (d, J=7.5 Hz, 2H, Ph-*o*H), 12.77 (s, 1H, NH); UV (EtOH): λ_{max} (log ε) *237* (4.46), *268* (4.37), 274 (4.39), 283 nm (4.38). Anal. Calcd for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.31; N, 27.22. Found: C, 56.09; H, 4.38; N, 27.42.

*4.3.7. 3-(3-Hydroxypropyl)-5-phenyl-3H-[1,2,3]triazolo[4,5-d]-pyrimidin-7(6H)-one (**2g**)*

Colorless prisms; yield 1.03 g (3.78 mmol, 63%); mp 193–194 °C (EtOAc); R_f 0.42 (EtOAc); IR (Nujol): 3375 (OH), 3180 (NH), 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.25 (quin, J=6.3 Hz, 2H, N-CH_2CH_2), 2.66 (br s, 1H, OH), 3.66 (t, J=6.0 Hz, 2H, O-CH_2), 4.76 (t, J=6.9 Hz, 2H, N-CH_2), 7.50–7.59 (m, 3H, Ph-*m*,*p*H), 8.18 (dd, $J_{o,p}$=1.5 Hz, $J_{o,m}$=7.8 Hz, 2H, Ph-*o*H), 12.41 (s, 1H, NH); UV (EtOH): λ_{max} (log ε) *237* (4.38), *268* (4.29), 273 (4.31), 284 nm (4.32). Anal. Calcd for $C_{13}H_{13}N_5O_2$: C, 57.56; H, 4.83; N, 25.82. Found: C, 57.63; H, 4.96; N, 25.55.

4.4. General procedure for the methylation of 2a–g with methyl iodide

4.4.1. At room temperature (A)

A mixture of an appropriate **2a**–**g** (2.5 mmol), anhydrous K_2CO_3 (5.0 mmol), and MeI (7.5 mmol) in dry DMF (25 mL) was stirred at rt for 5–6 h. Then, the solution was evaporated to dryness in vacuo and water (15 mL) was added to the residue. The solid deposited was collected by filtration and washed with water. The two regioisomers cropped were separated by column chromatography on silica gel using an appropriate mixture of *n*-hexane and EtOAc as eluting solvent to afford the corresponding 7-methoxy **4a**–**g** and 6-methyl derivatives **3a**–**g** as the first and second fractions, respectively.

*4.4.1.1. 3-Ethyl-6-methyl-5-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-one (**3a**).*

Colorless needles; yield 0.31 g (1.23 mmol, 49%); mp 221–222 °C (*n*-hexane/EtOAc); R_f 0.43 (*n*-hexane/EtOAc, 1:2); IR (Nujol): 1720 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.62 (t, J=7.2 Hz, 3H, CH_2CH_3), 3.53 (s, 3H, N-CH_3), 4.60 (q, J=7.2 Hz, 2H, CH_2), 7.53–7.59 (m, 5H, Ph-H); UV (EtOH): λ_{max} (log ε) 267 (4.29), *272* nm (4.28). Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.16; H, 5.13; N, 27.43. Found: C, 60.91; H, 4.98; N, 27.26.

*4.4.1.2. 6-Methyl-5-phenyl-3-propyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-one (**3b**).*

Pale yellow prisms; yield 0.34 g (1.28 mmol, 51%); mp 170–171 °C (*n*-hexane/EtOAc); R_f 0.49 (*n*-hexane/EtOAc, 1:2); IR (Nujol): 1715 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.99 (t, J=7.5 Hz, 3H, CH_2CH_3), 2.04 (sext, J=7.5 Hz, 2H, N-CH_2CH_2), 3.53 (s, 3H, N-CH_3), 4.50 (t, J=7.8 Hz, 2H, N-CH_2), 7.52–7.57 (m, 5H, Ph-H); UV (EtOH): λ_{max} (log ε) 267 (4.41), *272* nm (4.39). Anal. Calcd for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.13; H, 5.60; N, 26.02.

*4.4.1.3. 3-Isopropyl-6-methyl-5-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-one (**3c**).*

Colorless prisms; yield 0.30 g (1.10 mmol, 44%); mp 200–201 °C (*n*-hexane/EtOAc); R_f 0.51 (*n*-hexane/EtOAc, 1:2); IR (Nujol): 1720 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.69 (d, J=6.6 Hz, 6H, CH_3CHCH_3), 3.53 (s, 3H, N-CH_3), 5.11 (sept, J=6.6 Hz, 1H, CH), 7.53–7.59 (m, 5H, Ph-H); UV (EtOH): λ_{max} (log ε) 266 (4.33), *272* nm (4.32). Anal. Calcd for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.35; H, 5.62; N, 25.87.

*4.4.1.4. 3-Isobutyl-6-methyl-5-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-one (**3d**).*

Colorless needles; yield 0.35 g (1.23 mmol, 49%); mp 159–160 °C (*n*-hexane/EtOAc); R_f 0.52 (*n*-hexane/EtOAc, 1:2); IR (Nujol): 1720 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.97 (d, J=6.6 Hz, 6H, CH_3CHCH_3), 2.34–2.48 (m, 1H, N-CH_2CH), 3.54 (s, 3H, N-CH_3), 4.35 (d, J=7.2 Hz, 2H, N-CH_2), 7.52–7.59 (m, 5H, Ph-H); UV (EtOH): λ_{max} (log ε) 267 (4.38), *272* nm (4.37). Anal. Calcd for $C_{15}H_{17}N_5O$: C, 63.59; H, 6.05; N, 24.72. Found: C, 63.69; H, 6.09; N, 24.48.

*4.4.1.5. 6-Methyl-3-octyl-5-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-one (**3e**).*

Colorless powdery crystals; yield 0.38 g (1.13 mmol, 45%); mp 102–103 °C (*n*-octane/EtOAc); R_f 0.60 (*n*-hexane/EtOAc, 1:2); IR (Nujol): 1720 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.86 (t, J=6.9 Hz, 3H, CH_2CH_3), 1.24 (br s, 6H, $CH_2[CH_2]_3CH_3$), 1.34 (br s, 4H, N-$CH_2CH_2[CH_2]_2$), 1.94–2.04 (m, 2H, N-CH_2CH_2), 3.53 (s, 3H, N-CH_3), 4.52 (t, J=7.5 Hz, 2H, N-CH_2), 7.52–7.57 (m, 5H, Ph-H); UV (EtOH): λ_{max} (log ε) 266 (4.32), *271* nm (4.30). Anal. Calcd for $C_{19}H_{25}N_5O$: C, 67.23; H, 7.42; N, 20.63. Found: C, 67.57; H, 7.53; N, 20.43.

*4.4.1.6. 3-(2-Hydroxyethyl)-6-methyl-5-phenyl-3H-[1,2,3]triazolo-[4,5-d]pyrimidin-7(6H)-one (**3f**).*

Colorless powdery crystals; yield 0.35 g (1.30 mmol, 52%); mp 212–213 °C (EtOAc); R_f 0.50 (EtOAc); IR (Nujol): 3440 (OH), 1695 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.35 (t, J=6.6 Hz, 1H, OH), 3.54 (s, 3H, N-CH_3), 4.17 (q, J=6.0 Hz, 2H, O-CH_2), 4.72 (t, J=5.1 Hz, 2H, N-CH_2), 7.54–7.59 (m, 5H, Ph-H); UV (EtOH): λ_{max} (log ε) 267 (4.38), *271* nm (4.37). Anal. Calcd for $C_{13}H_{13}N_5O_2$: C, 57.56; H, 4.83; N, 25.82. Found: C, 57.85; H, 4.80; N, 26.20.

*4.4.1.7. 3-(3-Hydroxypropyl)-6-methyl-5-phenyl-3H-[1,2,3]triazolo-[4,5-d]pyrimidin-7(6H)-one (**3g**).*

Pale yellow powdery crystals; yield 0.34 g (1.20 mmol, 48%); mp 146–147 °C (*n*-hexane/EtOAc); R_f

0.49 (EtOAc); IR (Nujol): 3395 (OH), 1705 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.17 (quin, J=6.0 Hz, 2H, N-CH_2CH_2), 2.73 (br s, 1H, OH), 3.55 (s, 3H, N-CH_3), 3.61 (br s, 2H, O-CH_2), 4.73 (t, J=6.3 Hz, 2H, N-CH_2), 7.53–7.59 (m, 5H, Ph-H); UV (EtOH): λ_{max} (log ε) 267 (4.33), *271* nm (4.31). Anal. Calcd for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.30; N, 24.55. Found: C, 58.79; H, 5.29; N, 24.24.

*4.4.1.8. 3-Ethyl-7-methoxy-5-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**4a**).* Colorless needles; yield 0.23 g (0.90 mmol, 36%); mp 135–136 °C (*n*-octane/EtOAc); R_f 0.32 (*n*-hexane/EtOAc, 5:1); IR (Nujol): 1250, 1080 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.72 (t, J=7.2 Hz, 3H, CH_2CH_3), 4.37 (s, 3H, O-CH_3), 4.76 (q, J=7.2 Hz, 2H, N-CH_2), 7.47–7.51 (m, 3H, Ph-*m*,*p*H), 8.53 (dd, $J_{o,p}$=2.1 Hz, $J_{o,m}$=7.8 Hz, 2H, Ph-*o*H); UV (EtOH): λ_{max} (log ε) 238 (4.66), 245 (4.62), *276* (4.63), 284 (4.65), *294* (4.60), *304* nm (4.36). Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.16; H, 5.13; N, 27.43. Found: C, 61.12; H, 5.20; N, 27.21.

*4.4.1.9. 7-Methoxy-5-phenyl-3-propyl-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**4b**).* Colorless needles; yield 0.22 g (0.80 mmol, 32%); mp 119–120 °C (*n*-octane/EtOAc); R_f 0.35 (*n*-hexane/EtOAc, 5:1); IR (Nujol): 1245, 1080 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.02 (t, J=7.2 Hz, 3H, CH_2CH_3), 2.13 (sext, J=7.2 Hz, 2H, N-CH_2CH_2), 4.38 (s, 3H, O-CH_3), 4.68 (t, J=7.2 Hz, 2H, N-CH_2), 7.48–7.52 (m, 3H, Ph-*m*,*p*H), 8.55 (dd, $J_{o,p}$=2.4 Hz, $J_{o,m}$=7.5 Hz, 2H, Ph-*o*H); UV (EtOH): λ_{max} (log ε) 238 (4.61), 245 (4.58), *276* (4.57), 284 (4.58), *293* (4.54), *304* nm (4.31). Anal. Calcd for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.28; H, 5.62; N, 25.94.

*4.4.1.10. 3-Isopropyl-7-methoxy-5-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**4c**).* Colorless needles; yield 0.23 g (0.85 mmol, 34%); mp 139–140 °C (*n*-octane/EtOAc); R_f 0.37 (*n*-hexane/EtOAc, 5:1); IR (Nujol): 1245, 1065 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.80 (d, J=6.9 Hz, 6H, CH_3CHCH_3), 4.37 (s, 3H, O-CH_3), 5.32 (sept, J=6.9 Hz, 1H, CH), 7.50–7.52 (m, 3H, Ph-*m*,*p*H), 8.55 (dd, $J_{o,p}$=2.1 Hz, $J_{o,m}$=7.8 Hz, 2H, Ph-*o*H); UV (EtOH): λ_{max} (log ε) 238 (4.62), 245 (4.58), *276* (4.58), 284 (4.61), *293* (4.57), *304* nm (4.32). Anal. Calcd for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.13; H, 5.48; N, 25.96.

*4.4.1.11. 3-Isobutyl-7-methoxy-5-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**4d**).* Pale yellow plates; yield 0.26 g (0.93 mmol, 37%); mp 104–105 °C (*n*-octane/EtOAc); R_f 0.40 (*n*-hexane/EtOAc, 5:1); IR (Nujol): 1245, 1085 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.02 (d, J=6.6 Hz, 6H, CH_3CHCH_3), 2.47–2.59 (m, 1H, N-CH_2CH), 4.38 (s, 3H, O-CH_3), 4.52 (d, J=7.2 Hz, 2H, N-CH_2), 7.49–7.54 (m, 3H, Ph-*m*,*p*H), 8.56 (dd, $J_{o,p}$=2.1 Hz, $J_{o,m}$=7.5 Hz, 2H, Ph-*o*H); UV (EtOH): λ_{max} (log ε) 238 (4.60), 246 (4.57), *276* (4.58), 284 (4.60), *293* (4.56), *304* nm (4.32). Anal. Calcd for $C_{15}H_{17}N_5O$: C, 63.59; H, 6.05; N, 24.72. Found: C, 63.56; H, 6.08; N, 24.75.

*4.4.1.12. 7-Methoxy-3-octyl-5-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**4e**).* Pale yellow powdery crystals; yield 0.26 g (0.75 mmol, 30%); mp 58–59 °C (*n*-octane); R_f 0.47 (*n*-hexane/EtOAc, 5:1); IR (Nujol): 1245, 1080 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.86 (t, J=6.9 Hz, 3H, CH_2CH_3), 1.25 (br s, 6H, $CH_2[CH_2]_3CH_3$), 1.38 (br s, 4H, N-$CH_2CH_2[CH_2]_2$), 2.05–2.13 (m, 2H, N-CH_2CH_2), 4.38 (s, 3H, O-CH_3), 4.70 (t, J=7.2 Hz, 2H, N-CH_2), 7.49–7.52 (m, 3H, Ph-*m*,*p*H), 8.55 (dd, $J_{o,p}$=1.8 Hz, $J_{o,m}$=7.5 Hz, 2H, Ph-*o*H); UV (EtOH): λ_{max} (log ε) 238 (4.55), 246 (4.52), *275* (4.50), 284 (4.51), *293* (4.47), *304* nm (4.25). Anal. Calcd for $C_{19}H_{25}N_5O$: C, 67.23; H, 7.42; N, 20.63. Found: C, 66.98; H, 7.22; N, 20.85.

*4.4.1.13. 3-(2-Hydroxyethyl)-7-methoxy-5-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**4f**).* Colorless needles; yield 0.24 g (0.88 mmol, 35%); mp 163–164 °C (*n*-hexane/EtOAc); R_f 0.39 (*n*-hexane/EtOAc, 1:2); IR (Nujol): 3360 (OH), 1250, 1060 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.08 (t, J=6.6 Hz, 1H, OH), 4.28 (q, J=6.6 Hz, 2H, O-CH_2), 4.37 (s, 3H, O-CH_3), 4.90 (t, J=4.8 Hz, 2H, N-CH_2), 7.49–7.55 (m, 3H, Ph-*m*,*p*H), 8.49 (dd, $J_{o,p}$=2.1 Hz, $J_{o,m}$=7.5 Hz, 2H, Ph-*o*H); UV (EtOH): λ_{max} (log ε) 238 (4.70), 245 (4.67), *276* (4.67), 284 (4.69), *293* (4.65), *304* nm (4.41). Anal. Calcd for $C_{13}H_{13}N_5O_2$: C, 57.56; H, 4.83; N, 25.82. Found: C, 57.66; H, 4.75; N, 26.11.

*4.4.1.14. 3-(3-Hydroxypropyl)-7-methoxy-5-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**4g**).* Colorless needles; yield 0.21 g (0.75 mmol, 30%); mp 138–139 °C (*n*-octane/EtOAc); R_f 0.36 (*n*-hexane/EtOAc, 1:2); IR (Nujol): 3355 (OH), 1245, 1050 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.24 (quin, J=6.3 Hz, 2H, N-CH_2CH_2), 3.17 (br s, 1H, OH), 3.59 (t, J=5.7 Hz, 2H, O-CH_2), 4.40 (s, 3H, O-CH_3), 4.91 (t, J=6.3 Hz, 2H, N-CH_2), 7.48–7.53 (m, 3H, Ph-*m*,*p*H), 8.48 (dd, $J_{o,p}$=1.8 Hz, $J_{o,m}$=7.8 Hz, 2H, Ph-*o*H); UV (EtOH): λ_{max} (log ε) 238 (4.54), 246 (4.50), *276* (4.49), 284 (4.49), *294* (4.45), *304* nm (4.23). Anal. Calcd for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.30; N, 24.55. Found: C, 58.66; H, 5.29; N, 24.65.

4.4.2. At boiling temperature (B)

A mixture of an appropriate **2a**–**g** (1.8 mmol), anhydrous K_2CO_3 (3.6 mmol), and MeI (7.2 mmol) in dry DMF (20 mL) was refluxed for 1 h. Then, the solution was evaporated to dryness in vacuo and water (12 mL) was added to the residue. The solid deposited was filtered, washed with water, and recrystallized from an appropriate organic solvent to give the corresponding 6-*N*-methyl derivatives **3a**–**g** in 81%, 76%, 73%, 81%, 71%, 76%, and 74% yields, respectively.

4.5. Methylation of 2b with methyl iodide in the presence of NaH

A mixture of **2b** (0.4 g, 1.57 mmol), NaH (0.12 g, 5.0 mmol), and MeI (0.61 g, 4.3 mmol) in dry DMF (25 mL) was stirred at 0 °C for 7 h. After the usual work-up like above general method as described in Section 4.4.1, compounds **3b** and **4b** were obtained in 52% and 28% yields, respectively.

4.6. General procedure for the chlorination of 2a–d

To a cooled mixture of an appropriate **2a**–**d** (3.0 mmol) and phosphoryl chloride ($POCl_3$) (12 mL) was added *N*,*N*-dimethylaniline (0.7 mL) with stirring and the reaction mixture was refluxed gently for 3 h. Then, the excess $POCl_3$ was evaporated in vacuo and the residue was treated with cracked ice (20 g). Thus, the solid deposited was filtered, washed well with water, and dried to give the corresponding 7-chloro derivatives **5a**–**d**.

*4.6.1. 7-Chloro-3-ethyl-5-phenyl-3H-[1,2,3]triazolo[4,5-d]-pyrimidine (**5a**)*

Pale yellow powdery crystals; yield 0.65 g (2.52 mmol, 84%); mp 116–117 °C (*n*-hexane); R_f 0.41 (*n*-hexane/EtOAc, 5:1); IR (Nujol): 1590, 1560, 1460, 1400, 1155, 705 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.74 (t, J=7.2 Hz, 3H, CH_3), 4.85 (q, J=7.2 Hz, 2H, CH_2), 7.50–7.55 (m, 3H, Ph-*m*,*p*H), 8.56 (dd, $J_{o,p}$=2.4 Hz, $J_{o,m}$=8.1 Hz, 2H, Ph-*o*H); UV (EtOH): λ_{max} (log ε) 246 (4.68), 252 (4.66), 265 (4.42), 273 (4.41), *289* (4.44), 302 nm (4.48). Anal. Calcd for $C_{12}H_{10}ClN_5$: C, 55.50; H, 3.88; N, 26.97. Found: C, 55.71; H, 4.01; N, 26.79.

*4.6.2. 7-Chloro-5-phenyl-3-propyl-3H-[1,2,3]triazolo[4,5-d]-pyrimidine (**5b**)*

Pale yellow needles; yield 0.76 g (2.79 mmol, 93%); mp 98–99 °C (*n*-hexane); R_f 0.51 (*n*-hexane/EtOAc, 5:1); IR (Nujol): 1590, 1555, 1465, 1400, 1160, 710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.04 (t, J=7.5 Hz, 3H, CH_2CH_3), 2.16 (sext, J=7.5 Hz, 2H, N-CH_2CH_2), 4.73 (t, J=7.5 Hz, 2H, N-CH_2), 7.52–7.56 (m, 3H, Ph-*m*,*p*H), 8.56 (dd, $J_{o,p}$=1.8 Hz,

$J_{o,m}$=8.1 Hz, 2H, Ph-*o*H); UV (EtOH): λ_{max} (log ε) 247 (4.61), 253 (4.60), *265* (4.38), 272 (4.36), *290* (4.37), 302 nm (4.39). Anal. Calcd for $C_{13}H_{12}ClN_5$: C, 57.04; H, 4.42; N, 25.59. Found: C, 56.82; H, 4.39; N, 25.61.

*4.6.3. 7-Chloro-3-isopropyl-5-phenyl-3H-[1,2,3]triazolo[4,5-d]-pyrimidine (**5c**)*

Colorless needles; yield 0.71 g (2.61 mmol, 87%); mp 118–119 °C (*n*-hexane); R_f 0.52 (*n*-hexane/EtOAc, 5:1); IR (Nujol): 1590, 1560, 1460, 1380, 1160, 710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.83 (d, J=6.6 Hz, 6H, 2×CH_3), 5.36 (sept, J=6.6 Hz, 1H, CH), 7.48–7.53 (m, 3H, Ph-*m*,*p*H), 8.55 (dd, $J_{o,p}$=2.4 Hz, $J_{o,m}$=7.8 Hz, 2H, Ph-*o*H); UV (EtOH): λ_{max} (log ε) 247 (4.56), 252 (4.55), *265* (4.33), 272 (4.31), *290* (4.31), 301 nm (4.36). Anal. Calcd for $C_{13}H_{12}ClN_5$: C, 57.04; H, 4.42; N, 25.59. Found: C, 57.15; H, 4.45; N, 25.54.

*4.6.4. 7-Chloro-3-isobutyl-5-phenyl-3H-[1,2,3]triazolo[4,5-d]-pyrimidine (**5d**)*

Colorless needles; yield 0.81 g (2.82 mmol, 94%); mp 107–108 °C (*n*-octane); R_f 0.55 (*n*-hexane/EtOAc, 5:1); IR (Nujol): 1590, 1560, 1465, 1400, 1155, 710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.04 (d, J=6.6 Hz, 6H, 2×CH_3), 2.47–2.61 (m, 1H, N-CH_2CH), 4.58 (d, J=7.2 Hz, 2H, N-CH_2), 7.49–7.56 (m, 3H, Ph-*m*,*p*H), 8.56 (dd, $J_{o,p}$=2.1 Hz, $J_{o,m}$=7.5 Hz, 2H, Ph-*o*H); UV (EtOH): λ_{max} (log ε) 247 (4.62), 253 (4.61), *265* (4.42), 272 (4.40), *289* (4.39), 303 nm (4.42). Anal. Calcd for $C_{14}H_{14}ClN_5$: C, 58.44; H, 4.90; N, 24.34. Found: C, 58.29; H, 4.91; N, 24.09.

4.7. General procedure (C) for the synthesis of 4a–d from 5a–d

Sodium (0.05 g, 2.17 mmol) was dissolved in absolute methanol (30 mL) and to it was added an appropriate **5a**–**d** (1.0 mmol). The resulting solution was stirred at rt for 1–2 h. Then, the solution was evaporated in vacuo to dryness and water (10 mL) was added to the residue. Thus, the solid deposited was filtered, washed with water, and recrystallized from a mixture of *n*-octane and EtOAc to afford the corresponding products **4a**–**d** in 91%, 94%, 93%, and 87% yields, respectively.

4.8. 7-Chloro-3-(2-chloroethyl)-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (6)

Compound **6** was prepared from **2f** (0.50 g, 1.94 mmol) according to the general procedure for chlorination of **2a**–**d** as pale yellow needles; yield 0.50 g (87%); mp 129–130 °C (*n*-octane/EtOAc); R_f 0.22 (*n*-hexane/EtOAc, 5:1); IR (Nujol): 1590, 1555, 1460, 1160, 710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.17 (t, J=6.3 Hz, 2H, Cl-CH_2), 5.09 (t, J=6.3 Hz, 2H, N-CH_2), 7.51–7.58 (m, 3H, Ph-*m*,*p*H), 8.56 (dd, $J_{o,p}$=2.1 Hz, $J_{o,m}$=7.8 Hz, 2H, Ph-*o*H); UV (EtOH): λ_{max} (log ε) 246 (4.67), 252 (4.66), 265 (4.45), 273 (4.43), *290* (4.45), 302 nm (4.48). Anal. Calcd for $C_{12}H_9Cl_2N_5$: C, 49.00; H, 3.08; N, 23.81. Found: C, 48.90; H, 3.35; N, 23.57.

4.9. 7-Chloro-3-(3-chloropropyl)-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (7)

Compound **7** was prepared from **2g** (0.60 g, 2.21 mmol) in the similar way to **6** as colorless prisms; yield 0.57 g (84%); mp 120–121 °C (*n*-hexane); R_f 0.30 (*n*-hexane/EtOAc, 5:1); IR (Nujol): 1590, 1560, 1460, 1160, 710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.60 (quin, J=6.3 Hz, 2H, N-CH_2CH_2), 3.65 (t, J=6.3 Hz, 2H, Cl-CH_2), 4.96 (t, J=6.6 Hz, 2H, N-CH_2), 7.51–7.56 (m, 3H, Ph-*m*,*p*H), 8.57 (dd, $J_{o,p}$=2.4 Hz, $J_{o,m}$=7.8 Hz, 2H, Ph-*o*H); UV (EtOH): λ_{max} (log ε) 247 (4.53), 252 (4.53), *264* (4.37), *272* (4.38), *290* (4.31), 303 nm (4.33). Anal. Calcd for $C_{13}H_{11}Cl_2N_5$: C, 50.67; H, 3.60; N, 22.73. Found: C, 51.00; H, 3.74; N, 22.54.

4.10. 3-(2-Chloroethyl)-7-methoxy-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (8)

To a solution of sodium methoxide (from 0.03 g of Na, 1.30 mmol) in methanol (25 mL) was added **6** (0.15 g, 0.51 mmol) and the mixture was stirred at rt for 1 h. Then, the solvent was removed in vacuo and water (10 mL) was added to the residue. Thus, the solid deposited was collected by filtration, washed with water to give product **8** as pale yellow needles; yield 0.12 g (81%); mp 182–183 °C (*n*-octane/EtOAc); R_f 0.16 (*n*-hexane/EtOAc, 5:1); IR (Nujol): 1245, 1085 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.15 (t, J=6.3 Hz, 2H, Cl-CH_2), 4.38 (s, 3H, O-CH_3), 5.03 (t, J=6.3 Hz, 2H, N-CH_2), 7.49–7.53 (m, 3H, Ph-*m*,*p*H), 8.56 (dd, $J_{o,p}$=1.8 Hz, $J_{o,m}$=7.8 Hz, 2H, Ph-*o*H); UV (EtOH): λ_{max} (log ε) 237 (4.54), 244 (4.49), *276* (4.48), 284 (4.50), *292* (4.47), *304* nm (4.23). Anal. Calcd for $C_{13}H_{12}ClN_5O$: C, 53.89; H, 4.17; N, 24.17. Found: C, 53.84; H, 4.22; N, 24.10.

4.11. 3-(3-Chloropropyl)-7-methoxy-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (9)

Compound **9** was prepared from **7** (0.15 g, 0.49 mmol) in an analogous way to **8** as colorless needles; yield 0.13 g (88%); mp 115–116 °C (*n*-octane/EtOAc); R_f 0.18 (*n*-hexane/EtOAc, 5:1); IR (Nujol): 1250, 1085 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.58 (quin, J=6.3 Hz, 2H, N-CH_2CH_2), 3.64 (t, J=6.3 Hz, 2H, Cl-CH_2), 4.38 (s, 3H, O-CH_3), 4.90 (t, J=6.6 Hz, 2H, N-CH_2), 7.50–7.53 (m, 3H, Ph-*m*,*p*H), 8.56 (dd, $J_{o,p}$=1.8 Hz, $J_{o,m}$=8.1 Hz, 2H, Ph-*o*H); UV (EtOH): λ_{max} (log ε) 238 (4.63), 245 (4.59), *276* (4.59), 285 (4.62), *292* (4.60), *304* nm (4.35). Anal. Calcd for $C_{14}H_{14}ClN_5O$: C, 55.36; H, 4.65; N, 23.06. Found: C, 55.27; H, 4.63; N, 22.91.

4.12. Methylation of 2b with dimethyl sulfate

4.12.1. At room temperature

A mixture of **2b** (0.5 g, 1.96 mmol), anhydrous K_2CO_3 (0.54 g, 3.92 mmol), and dimethyl sulfate (0.37 g, 2.94 mmol) in dry DMF (25 mL) was stirred at rt for 8 h. After the usual work-up like the general method as described in Section 4.4.1, compounds **3b** and **4b** were obtained in 17% and 61% yields, respectively.

4.12.2. At boiling temperature

The above methylation of **2b** with dimethyl sulfate at boiling temperature for 3 h gave **3b** and **4b** in 16% and 39% yields, respectively.

4.13. Ethylation of 2b with ethyl iodide

4.13.1. At room temperature

A mixture of **2b** (0.62 g, 2.43 mmol), anhydrous K_2CO_3 (0.67 g, 4.86 mmol), and ethyl iodide (1.04 g, 7.3 mmoL) in dry DMF (25 mL) was stirred at rt for 8 h. Then, the solution was evaporated to dryness in vacuo and water (20 mL) was added to the residue. The solid deposited was collected by filtration and washed with water. The two regioisomers cropped were separated by column chromatography using *n*-hexane/EtOAc (6:1→1:1) as eluting solvent to afford the 7-*O*-ethyl **4ba** and 6-*N*-ethyl derivatives **3ba** as the first and second fractions, respectively.

*4.13.1.1. 6-Ethyl-5-phenyl-3-propyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-one (**3ba**).* Pale yellow needles; yield 0.07 g (10%); mp 145–146 °C (*n*-hexane/EtOAc); R_f 0.48 (*n*-hexane/EtOAc, 1:2); IR (Nujol): 1710 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.98 (t, J=7.5 Hz, 3H, 3-$CH_2CH_2CH_3$), 1.22 (t, J=7.2 Hz, 3H, 6-CH_2CH_3), 2.03 (sext, J=7.5 Hz, 2H, 3-CH_2CH_2), 4.08 (q, J=7.2 Hz, 2H, 6-CH_2), 4.49 (t, J=7.2 Hz, 2H, 3-CH_2), 7.48–7.59 (m, 5H, Ph-H); UV (EtOH): λ_{max} (log ε) 265 (4.33),

272 nm (4.30). Anal. Calcd for $C_{15}H_{17}N_5O$: C, 63.59; H, 6.05; N, 24.72. Found: C, 63.89; H, 6.17; N, 24.58.

*4.13.1.2. 7-Ethoxy-5-phenyl-3-propyl-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**4ba**).* Colorless needles; yield 0.45 g (66%); mp 73–74 °C (*n*-octane/EtOAc); R_f 0.40 (*n*-hexane/EtOAc, 5:1); IR (Nujol): 1245, 1085 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.01 (t, J=7.2 Hz, 3H, 3-N-$CH_2CH_2CH_3$), 1.61 (t, J=7.2 Hz, 3H, O-CH_2CH_3), 2.13 (sext, J=7.2 Hz, 2H, N-CH_2CH_2), 4.67 (t, J=7.2 Hz, 2H, N-CH_2), 4.87 (q, J=7.2 Hz, 2H, O-CH_2), 7.48–7.54 (m, 3H, Ph-*m*,*p*H), 8.54 (dd, $J_{o,p}$=2.1 Hz, $J_{o,m}$=7.5 Hz, 2H, Ph-*o*H); UV (EtOH): λ_{max} (log ε) 239 (4.48), 246 (4.45), *277* (4.44), 285 (4.45), *292* (4.42), *304* nm (4.15). Anal. Calcd for $C_{15}H_{17}N_5O$: C, 63.59; H, 6.05; N, 24.72. Found: C, 63.49; H, 6.10; N, 24.67.

4.13.2. At boiling temperature

The above ethylation of **2b** with little more excess ethyl iodide (ca. 5 equiv) at boiling temperature for 4 h gave **3ba** and **4ba** in 18% and 41% yields, respectively.

4.14. Preparation of 4ba from 5b

To a solution of sodium ethoxide (from 0.02 g of Na, 0.87 mmol) in absolute ethanol (20 mL) was added **5b** (0.11 g, 0.40 mmol) and the solution was stirred at rt for 1 h. The solvent was removed in vacuo and water (10 mL) was added to the residue. Thus, the solid deposited was collected by filtration, washed with water to give **4ba** (0.09 g, 79%), which was identical in all respects with authentic sample prepared by another method.

4.15. Benzylation of 2b with benzyl bromide

4.15.1. At room temperature

A mixture of **2b** (0.55 g, 2.16 mmol), anhydrous K_2CO_3 (0.60 g, 4.32 mmol), and benzyl bromide (0.55 g, 3.24 mmol) in dry DMF (25 mL) was stirred at rt for 8 h. Then, the solution was evaporated to dryness in vacuo and water (20 mL) was added to the residue. The solid deposited was collected by filtration and washed with water. The two regioisomers cropped were separated by column chromatography using *n*-hexane/EtOAc (6:1→1:1) as eluting solvent to afford the 7-*O*-benzyl **4bb** and 6-*N*-benzyl derivatives **3bb** as the first and second fractions, respectively.

*4.15.1.1. 6-Benzyl-5-phenyl-3-propyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-one (**3bb**).* Colorless needles; yield 0.10 g (13%); mp 156–157 °C (*n*-hexane/EtOAc); R_f 0.55 (*n*-hexane/EtOAc, 1:2); IR (Nujol): 1715 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.99 (t, J=7.5 Hz, 3H, CH_3), 2.04 (sext, J=7.5 Hz, 2H, N-CH_2CH_2), 4.50 (t, J=7.5 Hz, 2H, N-CH_2), 5.30 (s, 2H, CH_2Ph), 6.84–6.88 (m, 2H, Ph-H), 7.17–7.27 (m, 5H, Ph-H), 7.42 (t, J=7.8 Hz, 2H, Ph-H), 7.49–7.55 (m, 1H, Ph-H); UV (EtOH): λ_{max} (log ε) 265 (4.36), *272* nm (4.33). Anal. Calcd for $C_{20}H_{19}N_5O$: C, 69.55; H, 5.54; N, 20.28. Found: C, 69.73; H, 5.65; N, 20.06.

*4.15.1.2. 7-Benzyloxy-5-phenyl-3-propyl-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**4bb**).* Colorless needles; yield 0.47 g (63%); mp 105–106 °C (*n*-octane/EtOAc); R_f 0.40 (*n*-hexane/EtOAc, 5:1); IR (Nujol): 1250 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.02 (t, J=7.5 Hz, 3H, CH_3), 2.12 (sext, J=7.2 Hz, 2H, N-CH_2CH_2), 4.67 (t, J=7.2 Hz, 2H, N-CH_2), 5.86 (s, 2H, CH_2Ph), 7.34–7.43 (m, 3H, Ph-H), 7.50–7.53 (m, 3H, Ph-H), 7.61 (d, J=7.2 Hz, 2H, Ph-H), 7.55 (dd, J=2.1 Hz, J=7.5 Hz, 2H, Ph-H); UV (EtOH): λ_{max} (log ε) 240 (4.60), 247 (4.57), *276* (4.51), 284 (4.53), *293* (4.49), *304* nm (4.26). Anal. Calcd for $C_{20}H_{19}N_5O$: C, 69.55; H, 5.54; N, 20.28. Found: C, 69.59; H, 5.63; N, 20.12.

4.15.2. At boiling temperature

The above benzylation of **2b** with benzyl bromide at boiling temperature for 1 h gave **3bb** and **4bb** in 37% and 35% yields, respectively.

4.16. Preparation of 2-phenyl-9-propyl-9*H*-purin-6(1*H*)-one (10)

A solution of free 5,6-diaminopyrimidine derivative **1b** (1.0 g, 4.09 mmol) in 85% aqueous formic acid (15 mL) was heated under reflux for overnight. Then, the solution was concentrated to ca. 2 mL and to it was added water (15 mL). Thus, the solid deposited was collected by filtration and washed with water to afford **10** as pale yellow powdery crystals; yield 0.78 g (75%); mp 265–267 °C (EtOAc/EtOH); R_f 0.47 (EtOAc/EtOH, 4:1); IR (Nujol): 3175 (NH), 1690 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.0 (t, J=7.5 Hz, 3H, CH_3), 1.98 (sext, J=7.4 Hz, 2H, N-CH_2CH_2), 4.21 (t, J=7.4 Hz, 2H, N-CH_2), 7.52–7.62 (m, 3H, Ph-*m*,*p*H), 7.81 (s, 1H, N=CH), 8.22–8.25 (m, 2H, Ph-*o*H), 11.90 (s, 1H, NH); UV (EtOH): λ_{max} (log ε) *261* (3.99), 302 nm (4.14). Anal. Calcd for $C_{14}H_{14}N_4O\cdot 1/8H_2O$: C, 65.55; H, 5.60; N, 21.84. Found: C, 65.49; H, 5.64; N, 21.89.

4.17. Methylation of 10

4.17.1. With 1 equiv MeI at 0 °C

A mixture of **10** (0.4 g, 1.57 mmol), anhydrous K_2CO_3 (0.4 g, 2.89 mmol), and MeI (0.23 g, 1.62 mmol) in dry DMF (20 mL) was stirred at 0 °C for 1.5 days. Then, the solution was evaporated to dryness in vacuo and water (10 mL) was added to the residue. The products were extracted with CH_2Cl_2 and the extract was dried over anhydrous $MgSO_4$. Solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel column using *n*-hexane/EtOAc (2:1→1:10) as eluting solvent to give **11b** and **11a** as the first and second fractions, respectively.

*4.17.1.1. 1-Methyl-2-phenyl-9-propyl-9H-purin-6(1H)-one (**11a**).* Colorless needles; yield 0.11 g (26%); mp 169–170 °C (*n*-hexane/EtOAc); R_f 0.53 (EtOAc/EtOH, 4:1); IR (Nujol): 1685 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.96 (t, J=7.5 Hz, 3H, CH_2CH_3), 1.90 (sext, J=7.4 Hz, 2H, N-CH_2CH_2), 3.53 (s, 3H, N-CH_3), 4.12 (t, J=7.4 Hz, 2H, N-CH_2), 7.53 (s, 5H, Ph-H), 7.77 (s, 1H, N=CH); UV (EtOH): λ_{max} (log ε) 254 (4.02), 282 nm (4.01). Anal. Calcd for $C_{15}H_{16}N_4O$: C, 67.15; H, 6.01; N, 20.88. Found: C, 67.29; H, 6.11 N, 20.77.

*4.17.1.2. 6-Methoxy-2-phenyl-9-propyl-9H-purine (**11b**).* Pale yellow powdery crystals; yield 0.19 g (45%); mp 115 °C (*n*-hexane/EtOAc); R_f 0.22 (*n*-hexane/EtOAc, 1:1); IR (Nujol): 1240, 1080 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.0 (t, J=7.5 Hz, 3H, CH_2CH_3), 2.01 (sext, J=7.4 Hz, 2H, N-CH_2CH_2), 4.26 (t, J=7.4 Hz, 2H, N-CH_2), 4.29 (s, 3H, O-CH_3), 7.43–7.52 (m, 3H, Ph-*m*,*p*H), 7.89 (s, 1H, N=CH), 8.53 (dd, $J_{o,p}$=2.1 Hz, $J_{o,m}$=7.8 Hz, 2H, Ph-*o*H); UV (EtOH): λ_{max} (log ε) 231 (4.30), 237 (4.28), 282 (4.37), *290* (4.34), *305* nm (3.97). Anal. Calcd for $C_{15}H_{16}N_4O$: C, 67.15; H, 6.01; N, 20.88. Found: C, 66.93; H, 6.12; N, 20.80.

4.17.2. With 1 equiv Me_2SO_4 at room temperature

A mixture of **10** (0.3 g, 1.18 mmol), anhydrous K_2CO_3 (0.3 g, 2.17 mmol), and Me_2SO_4 (2.3 g, 1.62 mmol) in dry DMF (20 mL) was stirred at rt for 1 day. Then, the solution was evaporated to dryness in vacuo and water (10 mL) was added to the residue. The products were extracted with CH_2Cl_2 and the extract was dried over anhydrous $MgSO_4$. Solvent was removed in vacuo and the residue was recrystallized from *n*-hexane to give **11b** (0.24 g, 76%).

4.17.3. With excess MeI at room temperature

A mixture of **10** (0.4 g, 1.57 mmol), anhydrous K_2CO_3 (0.45 g, 3.26 mmol), and MeI (0.60 g, 4.23 mmol) in DMF (20 mL) was stirred at rt for 15 h. Then, another portion of MeI (0.50 g, 3.52 mmol) was added to the reaction mixture and the mixture was stirred at rt for additional 15 h. The usual work-up like method as described in Section 4.17.1 gave **12** and **11b** as the first and second fractions in 30% and 44% yields, respectively.

*4.17.3.1. 6,9-Dihydro-1,7-dimethyl-6-oxo-2-phenyl-9-propyl-1H-purin-7-ium hydroxide (**12**).* Colorless prisms; mp 147 °C (*n*-hexane); R_f 0.48 (*n*-hexane/EtOAc, 1:1); IR (Nujol): 3350 (OH), 1680 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.99 (t, J=7.5 Hz, 3H, CH_2CH_3), 1.68 (sext, J=7.4 Hz, 2H, N-CH_2CH_2), 3.08 (s, 3H, 1-N-CH_3), 3.54–3.61 (m, 2H, N-CH_2), 4.04 (s, 3H, 7-N-CH_3), 4.95 (br s, 1H, OH), 7.43–7.48 (m, 3H, Ph-*m*,*p*H), 8.0 (s, 1H, N=CH), 8.43 (dd, $J_{o,p}$=2.1 Hz, $J_{o,m}$=7.5 Hz, 2H, Ph-*o*H); UV (EtOH): λ_{max} (log ε) *240* (4.67), 246 (4.69), 262 (4.40), 299 nm (4.02). Anal. Calcd for $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.59; H, 6.65; N, 18.61.

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