Heteroatom Chemistry
Volume 17, Number 4, 2006

An Expedient Synthesis of Novel, Fused Pyrimido[4,5-*d*]pyrimidine and Pyrimido[5,4-*e*] [1,2,4]triazolo[4,3-*c*]pyrimidine Analogues from 4-Amino-2,6-dichloropyrimidine

Pratibha Sharma, Ashok Kumar, and Nilesh Rane

School of Chemical Sciences, Devi Ahilya University, Takshila Campus, Khandwa Road, Indore 452 017, MP, India

Received 24 May 2005; revised 19 September 2005

ABSTRACT: *A number of potent pyrimido[4,5-d]pyrimidine have efficiently been synthesized by the condensation of 4-amino-2,6-dichloropyrimidine with various substituted benzaldehyde followed by cyclization with ammonium thiocyanate. Also, these newly synthesized derivatives were utilized for the construction of novel pyrimido[5,4-e][1,2,4]triazolo[4,3-c]pyrimidine analogues via oxidative cyclization involving 1,5-hydrogen abstraction. Structure of all the newly constructed derivatives was corroborated by the elemental and spectral data.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:245–253, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20177

INTRODUCTION

The pyrimidine and heterocyclic annulated pyrimidine system undoubtedly belong to the most ubiquitous heterocycles in the nature. They have attracted considerable attention of both synthetic and medicinal chemists by virtue of their interesting biological activities [1] and immense synthetic potential for the construction of many pharmacologically important novel heterocycles [2].

Particularly, pyrimido[4,5-*d*]pyrimidine fused system represents attractive targets owing to diverse pharmacological applications of these molecules that include modulator of antitumor drug activity [3], antioxidant (as inhibitor of lipid peroxidation) [4], antiviral (as inhibitor of herpes simplex virus reactivation) [5], hepatoprotective [6], potent inhibitory action on epidermal growth factor receptor [7], and 5-phosphoribosyl-1-pyrophosphate synthetase [8].

The development of pyrimidopyrimidines as potential hosts in the enantioselective recognition of oxo anions in polytopic abiotic receptors [9] and anchor modules for oxo anionic functions of molecular guests species complexed by polytopic artificial receptors is also well documented [10] and gave an impetus for the chemistry of such system.

Similarly, a number of compounds with triazolo-fused pyrimidine ring system exhibiting adenosine receptor antagonist activity are described as possible template for adenosine receptor subtype [11], further providing continuous demand to explore efficient synthetic routes to gain rapid access to these functionalized molecules.

In this context, as well as to pursue our interest in developing versatile synthesis of pyrimidopyrimidine heteroaromatic ring system [12,13]

Correspondence to: Pratibha Sharma; e-mail: drpratibhasharma@yahoo.com.

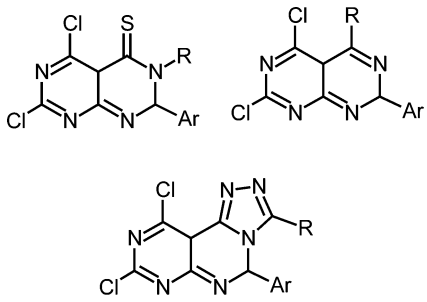


FIGURE 1 Structure of synthesized pyrimido[4,5-*d*]pyrimidine and triazolo-fused pyrimidine derivative.

and other heterocycles [14–16], we herein report a facile new synthesis of structurally diverse pyrimido[4,5-*d*]pyrimidine and pyrimido[5,4-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine derivatives which can be envisioned as new lead compounds, using 4-amino-2,6-dichloropyrimidine as a starting material.

RESULTS AND DISCUSSION

The most promising methods for the generation of pyrimidopyrimidine nucleus are multistep synthesis starting from 1,3-disubstituted-5-cyanouracils [17] or from polymer-bound 2-(alkylsufanyl)-4-aminopyrimidine-5-carbonitrile [18]. However, these approaches involve relatively longer synthetic pathways, lower yields, or the use of stoichiometric amounts of expensive resin as a polymer support. Our synthetic plan commences from readily available 4-amino-2,6-dichloropyrimidine, which offers large number of annulated heterocycles (Fig. 1) in efficient yields.

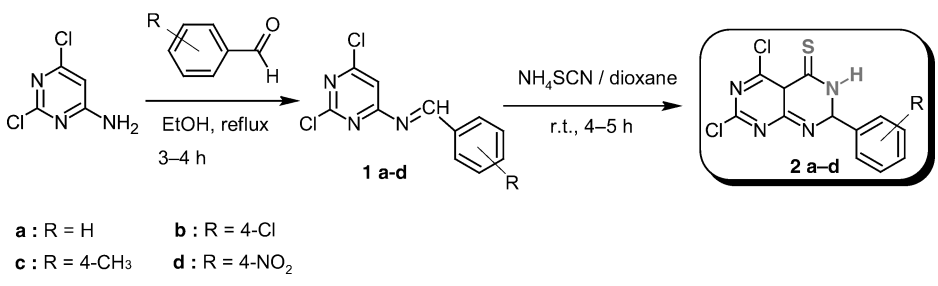
The requisite starting material, i.e., 2,6-dichloro-4-arylmethylideneamino-pyrimidine **1** was prepared in excellent yields by Schiff-base [19] type condensation of 4-amino-2,6-dichloropyrimidine with appropriately substituted benzaldehyde in refluxing ethanol. These 6-aminoarylidine-substituted pyrimidines on subsequent condensation with ammonium thiocyanate in dioxane generates the desired products, i.e., 5,7-dichloro-2-aryl-2,-4a-dihydropyrimido[4,5-*d*]pyrimidine-4(3*H*)-thione **2a–d** in 87–95% yields (Scheme 1).

TABLE 1 Characteristics for Newly Synthesized Pyrimido-[4,5-*d*]pyrimidines and Pyrimido[5,4-*e*][1,2,4]triazolo[4,3-*c*]-pyrimidines **2–6**

Product	*MP (°C)*	*Reaction Time*	*Yields[a] (%)*	*m/z (M^+)*
1a	150–152	3 h	94	252
1b	159–160	4 h	87	286
1c	142–143	3 h	95	266
1d	121–123	3 h	88	297
2a	156–158	5 h	91	311
2b	210–211	5 h	76	345
2c	145–147	4 h	85	325
2d	132–134	4 h	90	356
3a	128–130	1 h	70	325
3b	141–142	30 min	77	359
3c	167–168	30 min	65	339
3d	197–199	1 h	74	339
3e	178–180	1 h	83	373
3f	199–200	30 min	68	353
4a	219–221	10 min	79	309
4b	147–148	15 min	82	343
4c	170–172	10 min	75	323
4d	132–135	45 min	77	354
5a	201–202	4 h	74	397
5b	194–195	5 h	80	431
5c	161–163	5 h	85	411
5d	149–151	4 h	79	442
6a	243–245	6 h	70	395
6b	219–220	5 h	68	429
6c	189–190	4 h	66	409
6d	225–226	5 h	74	440

[a]Yields refer to isolated pure products.

The structure of the products was assigned on the basis of spectroscopic and elemental data (Table 1). The IR spectrum of **2a** exhibited NH stretching absorption band at 3260 cm^{-1}, whereas C=S and C–Cl absorption bands were visible at 1070 and 580 cm^{-1}, respectively. In the ^1H NMR spectrum, the NH proton appeared as a singlet at



SCHEME 1

$\delta = 10.28$, while the ^{13}C NMR spectrum showed the signal for C=S at $\delta = 199.0$.

Consequently, to construct pyrimido[4,5-*d*]-pyrimidine skeleton, the pyrimidine nucleus, fused to the 4-amino-2,6-dichloropyrimidine ring was generated by cyclocondensation between C—C—N—C fragment, derived from **1** with N—C fragment provided by ammonium thiocyanate.

In order to extend the synthetic utility of newly generated compounds, we have also constructed several N-3 and C-4 substituted pyrimido[4,5-*d*]pyrimidines and triazolo-fused pyrimidines using **2** as a starting material.

In this regard, the required key compound 5,7-dichloro-4-hydrazino-2-aryl-2,4a-dihydropyrimido-[4,5-*d*]pyrimidine **4a–c** used in the course of reaction was efficiently synthesized by the reaction of **2** with excess hydrazine hydrate (80%) under reflux condition for 10 min. The subsequent treatment of 4-hydrazino derivative **4a–d** thus obtained, with benzaldehyde (1.5 equiv.) in glacial AcOH at room temperature afforded the corresponding 4-aldehyde hydrazones **5a–d** in 74–85% yields, as indicated in Table 1. The ^1H NMR spectrum of **4a** displayed the two broad singlets at $\delta = 9.11$ and 6.22 corresponding to —NH and NH_2 group, respectively of hydrazino functionality. Moreover, disappearance of the signal for C=S group at $\delta = 199.0$, in the ^{13}C NMR spectrum, augment the proposed structure. The presence of diagnostic signal for the azomethine proton at $\delta = 8.45$ in the ^1H NMR spectra further confirms the transformation of **4** to **5**.

Likewise, oxidative heterocyclization of hydrazones **5a–d** by treatment with lead tetraacetate (1.5 equiv.) in 1,4-dioxane exclusively produces the 8,10-dichloro-5-aryl-3-phenyl-5,10a-dihydro-pyrimido[4,5-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine **6a–d** (Scheme 2) in good to moderate yields, which was favored by intramolecular interaction between the N-3 and the carbon of —N=CH—Ar fragment. The assignment of the structure of the triazolo[4,3-*c*]-pyrimidine derivatives **6a–d** thus obtained was based on spectroscopic data and microanalyses (Table 1). In ^1H NMR spectrum of final product, the absence of azomethine proton supports the successful transformation of **5** to triazolo analogues via oxidative intramolecular cyclization occurring at azomethine functionality.

We assume that oxidative cyclization, the key step in the sequence, involves the 1,5-internal hydrogen abstraction by the free radical, which is generated by the attack of lead tetraacetate on **5** followed by intramolecular addition of nitrogen anion to the carbonium of azomethine functionality in order to facilitate the triazolopyrimidine system (Fig. 2).

The N-3 substituted derivatives, i.e., 5,7-dichloro-3-alkyl-2-aryl-2,4a-dihydro-3*H*-pyrimido[4,-5-*d*]pyrimidine-4-thione, were synthesized by electrophilic replacement of N-3 proton by various alkyl halides in pyridine under reflux conditions. Also, the formation of **3a** is confirmed by the absence of signal for NH proton of pyrimidine ring and presence of N-3 methyl protons at $\delta = 3.12$ in the ^1H NMR spectra.

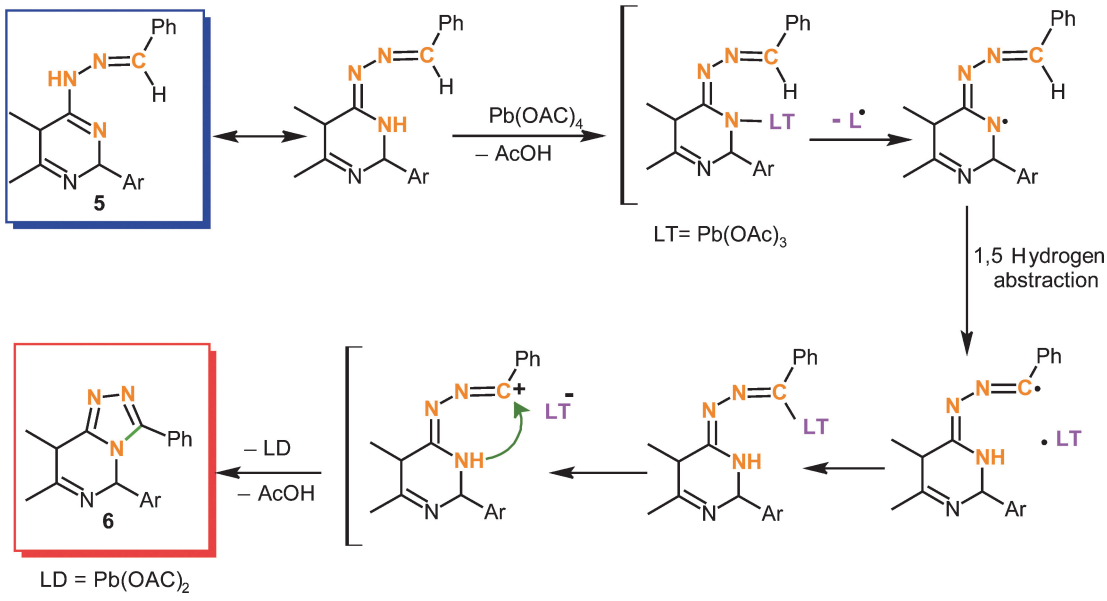
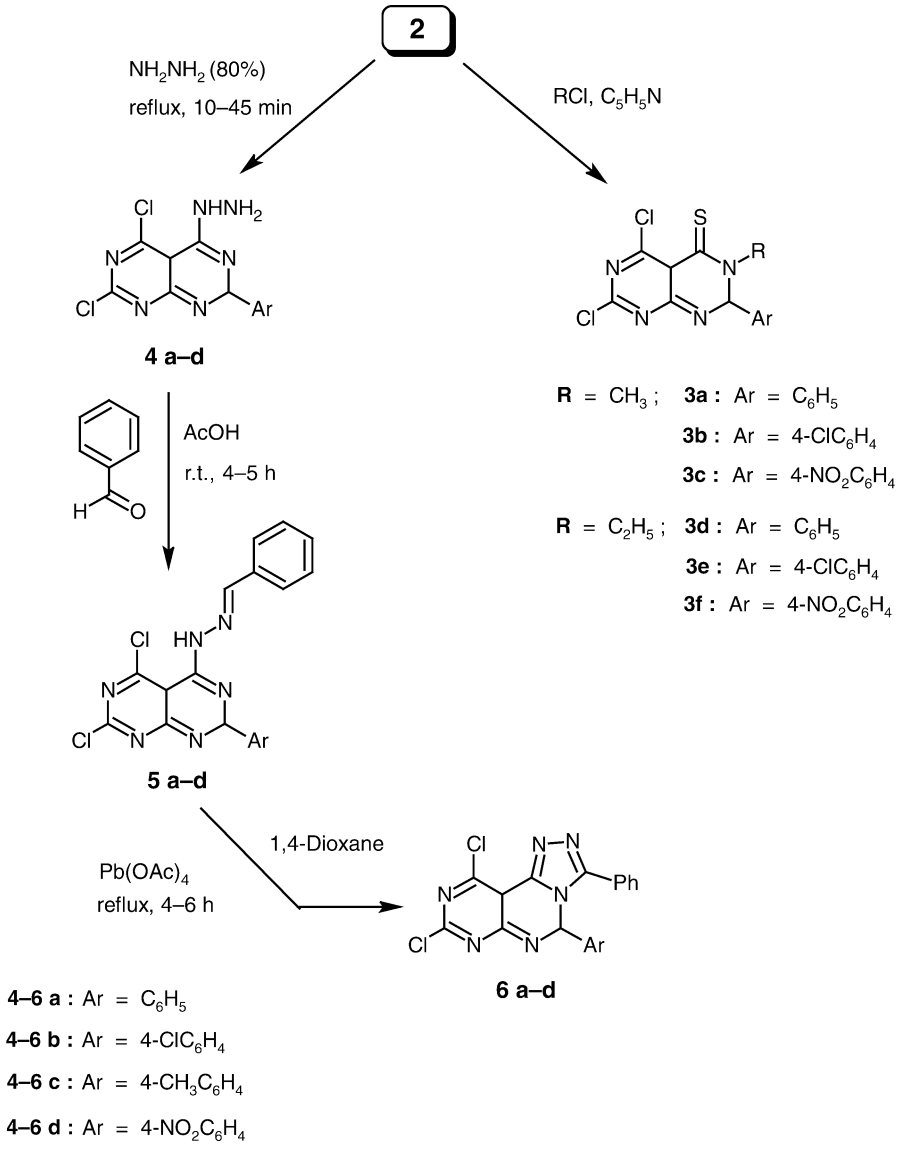


FIGURE 2 Mechanistic details for the transformation of **5** to **6**.



SCHEME 2

In conclusion, we have successfully constructed a number of highly functionalized N-3, C-4 substituted pyrimido[4,5-*d*]pyrimidines, and C-3, C-5 aryl substituted pyrimido[5,4-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines of potential biological significance in an excellent yields by a new and efficient synthesis using 4-amino-2,6-dichloropyrimidine. The adopted protocol is effective and involves simple experimental procedures and product identification.

Furthermore, the results delineated above have illustrated that the title compound **2** can be a useful building block for the generation of array of fused nitrogen heterocycles. The extensive biological screening of these newly synthesized compounds is the subject of further optimization.

EXPERIMENTAL

All the chemicals used were of AR grade purity from E. Merck. Solvents used for the experiments were distilled or dried prior to use. IR spectra were recorded on a Shimadzu 460 FTIR-spectrometer in KBr disks. Frequencies are reported in cm^{-1}. The NMR spectra were recorded on a Jeol NMR 200 MHz (^1H) and Bruker DRX 400 MHz (^{13}C) spectrometers in $CDCl_3$. The chemical shifts are quoted in ppm value on the δ scale, using TMS as an internal reference and coupling constants (J) in Hz. Mass spectra were taken with a Jeol D-300 spectrometer. Melting points were determined on an electrothermal apparatus by open capillary method and are uncorrected.

Reaction monitoring and purity of all the synthesized compounds were ascertained by TLC resolution studies on silica gel G (E. Merck) using ethyl acetate–xylene (3:7, v/v) as eluent and HPLC analysis, performed on Shimadzu LC10AS using L7 phenyl packing column, a 254 nm UV Shimadzu ASVP detector and acetonitrile/methanol/water (60:30:10) as eluent with a flow rate of 1 mL/min.

2,6-Dichloro-4-arylmethylideneamino-pyrimidine **1**

A mixture of 4-amino-2,6-dichloropyrimidine (3.28 g, 20 mmol) and corresponding arylaldehyde (20 mmol) was heated in EtOH (50 mL) under reflux to the completion of reaction (monitored via TLC). The solvent was removed in vacuo and the residue was recrystallized from MeOH to give products **1a–d**.

2,6-Dichloro-4-benzylideneamino-pyrimidine **1a**

ν_{max}(KBr)/cm^{-1}: 3010 (CH, sp^2), 1650 (C=C/C=N), 1600, 1525, 1435 (C⋯C, ring str.), 640 (C—Cl). δ_H ($CDCl_3$): 8.64 (s, 1H, N=CH), 7.8 (s, 1H, CH), 7.4 (s, 5H, Ph). δ_C ($CDCl_3$): 187.7 (C-2), 163.7 (N=CH), 162.2 (C-4), 160.6 (C-6), 132.4, 130.3, 129.1, 128.6 (Ph), 114.4 (C-5). Anal. Calcd for $C_{11}H_7Cl_2N_3$ (252.10): C, 52.41; H, 2.80; N, 16.67. Found C, 52.35; H, 2.86; N, 16.60.

2,6-Dichloro-4-(4-cholrobenzylidineamino)-pyrimidine **1b**

ν_{max}(KBr)/cm^{-1}: 3000 (CH, sp^2), 1640 (C=C/C=N), 1590, 1540, 1412 (C⋯C, ring str.), 645 (C—Cl). δ_H ($CDCl_3$): 8.45 (s, 1H, N=CH), 7.7 (s, 1H, CH), 7.4 (d, 2H, $J = 8.0$ Hz, ArH), 7.3 (d, 2H, $J = 8.0$ Hz, ArH). δ_C ($CDCl_3$): 190.4 (C-2), 166.7 (N=CH), 163.2 (C-4), 160.1 (C-6), 136.8, 131.4, 129.3, 129.0 (Ar), 112.0 (C-5). Anal. Calcd for $C_{11}H_6Cl_3N_3$ (286.54): C, 46.11; H, 2.11; N, 14.66. Found C, 46.05; H, 2.20; N, 14.75.

2,6-Dichloro-4-(4-methylbenzylidineamino)-pyrimidine **1c**

ν_{max}(KBr)/cm^{-1}: 3010 (CH, sp^2), 2935 (CH, sp^3), 1630 (C=C/C=N), 1574, 1540, 1440 (C⋯C, ring str.), 640 (C—Cl). δ_H ($CDCl_3$): 8.51 (s, 1H, N=CH), 7.6 (s, 1H, CH), 7.5 (d, 2H, $J = 8.0$ Hz, ArH), 7.3 (d, 2H, $J = 8.0$ Hz, ArH), 2.46 (s, 3H, CH_3). δ_C ($CDCl_3$): 188.2 (C-2), 164.3 (N=CH), 162.9 (C-4), 159.7 (C-6), 140.4, 135.6, 128.7, 126.4 (Ar), 118.1 (C-5), 20.4 (Ar—CH_3). Anal. Calcd for $C_{12}H_9Cl_3N_3$ (266.13): C, 54.16; H, 3.41; N, 15.79. Found C, 54.22; H, 3.34; N, 15.69.

2,6-Dichloro-4-(4-nitrobenzylidineamino)-pyrimidine **1d**

ν_{max}(KBr)/cm^{-1}: 3020 (CH, sp^2), 1660 (C=C/C=N), 1570, 1512, 1485 (C⋯C, ring str.), 1385 (NO_2), 665 (C—Cl). δ_H ($CDCl_3$): 8.60 (s, 1H, N=CH), 7.8 (s, 1H, CH), 7.5 (d, 2H, $J = 8.0$ Hz, ArH), 7.4 (d, 2H, $J = 8.0$ Hz, ArH). δ_C ($CDCl_3$): 184.8 (C-2), 168.4 (N=CH), 165.1 (C-4), 161.2 (C-6), 132.2, 130.5, 129.0, 128.5 (Ar), 111.0 (C-5). Anal. Calcd for $C_{11}H_6Cl_2N_4O_2$ (297.10): C, 44.47; H, 2.04; N, 18.86. Found C, 44.51; H, 2.12; N, 18.77.

5,7-Dichloro-2-aryl-2,4a-dihydropyrimido[4,5-d]pyrimidine-4(3H)-thione **2**

To a solution of 2,6-dichloro-4-arylmethylidine-amino-pyrimidine **1** (20 mmol) in dioxane (30 mL), ammonium thiocyanate (2.736 g, 36 mmol) was added and dissolved by slow warming with continuous stirring. The reaction mixture was stirred for 30 min at room temperature and subsequently allowed to reflux for required time (Table 1). The solvent was distilled off under reduced pressure and solid thus obtained was washed repeatedly with water, dried in vacuo and recrystallized form EtOH.

5,7-Dichloro-2-phenyl-2,4a-dihydropyrimido[4,5-d]pyrimidine-4(3H)-thione **2a**

ν_{max}(KBr)/cm^{-1}: 3260 (NH), 1646 (C=C/C=N), 1546, 1510, 1480 (C⋯C, ring str.), 1070 (C=S), 1017, 947 (CH, in-plane bending), 845, 771 (CH, out-of-plane bending), 580 (C—Cl). δ_H ($CDCl_3$): 10.28 (br s, 1H, NH), 7.1 (s, 5H, Ph), 4.11 (s, 1H, H-2), 3.24 (s, 1H, H-4a). δ_C ($CDCl_3$): 199.0 (C-4), 164.0 (C-5), 163.0 (C-7), 161.0 (C-8a), 142.4, 128.3, 127.1, 126.5 (Ph), 70.5 (C-2), 52.7 (C-4a). Anal. Calcd for $C_{12}H_8Cl_2N_4S$ (311.19): C, 46.32; H, 2.59; N, 18.00. Found C, 46.25; H, 2.62; N, 17.95.

5,7-Dichloro-2-(4-chlorophenyl)-2,4a-dihydro-pyrimido[4,5-d]pyrimidine-4(3H)-thione **2b**

ν_{max}(KBr)/cm^{-1}: 3250 (NH), 1650 (C=C/C=N), 1610, 1585, 1489 (C⋯C, ring str.), 1072 (C=S), 1030, 936 (CH, in-plane bending), 852, 768 (CH, out-of-plane bending), 684 (C—Cl). δ_H ($CDCl_3$): 10.51 (br s, 1H, NH), 7.0 (d, 2H, $J = 8.0$ Hz, ArH), 7.4 (d, 2H, $J = 8.0$ Hz, ArH), 4.24 (s, 1H, H-2), 3.18 (s, 1H, H-4a). δ_C ($CDCl_3$): 198.6 (C-4), 165.0 (C-5), 164.0 (C-7), 160.0 (C-8a), 140.5, 131.8, 128.9, 128.5 (Ar), 72.4 (C-2), 52.8 (C-4a). Anal. Calcd for $C_{12}H_7Cl_3N_4S$ (345.65): C, 41.70; H, 2.04; N, 16.21. Found C, 41.62; H, 2.10; N, 16.26.

5,7-Dichloro-2-(4-methylphenyl)-2,4a-dihydropyrimido [4,5-d]pyrimidine-4(3H)-thione **2c**

ν_{max}(KBr)/cm^{-1}: 3260 (NH), 2869 (CH, sp^3), 1655 (C=C/C=N), 1590, 1512, 1460 (C···C, ring str.), 1084 (C=S), 1034, 921 (CH, in-plane bending), 841, 745 (CH, out-of-plane bending), 645 (C—Cl). δ_H ($CDCl_3$): 9.85 (br s, 1H, NH), 7.20 (d, 2H, $J = 8.0$ Hz, ArH), 7.36 (d, 2H, $J = 8.0$ Hz, ArH), 4.43 (s, 1H, H-2), 3.65 (s, 1H, H-4a), 2.34 (s, 3H, CH_3). δ_C ($CDCl_3$): 199.4 (C-4), 162.0 (C-5), 161.0 (C-7), 160.0 (C-8a), 139.7, 135.4, 129.1, 127.2 (Ar), 70.9 (C-2), 51.2 (C-4a), 23.6 (Ar—CH_3). Anal. Calcd for $C_{13}H_{10}Cl_2N_4S$ (325.22): C, 48.01; H, 3.10; N, 17.23. Found C, 48.09; H, 3.16; N, 17.16.

5,7-Dichloro-2-(4-nitrophenyl)-2,4a-dihydropyrimido[4,5-d]pyrimidine-4(3H)-thione **2d**

ν_{max}(KBr)/cm^{-1}: 3310 (NH), 1636 (C=C/C=N), 1619, 1547, 1475 (C···C, ring str.), 1361 (NO_2), 1050 (C=S), 1012, 920 (CH, in-plane bending), 864, 741 (CH, out-of-plane bending), 680 (C—Cl). δ_H ($CDCl_3$): 10.11 (br s, 1H, NH), 7.17 (d, 2H, $J = 8.0$ Hz, ArH), 7.25 (d, 2H, $J = 8.0$ Hz, ArH), 4.10 (s, 1H, H-2), 3.56 (s, 1H, H-4a). δ_C ($CDCl_3$): 196.0 (C-4), 161.0 (C-5), 160.0 (C-7), 155.0 (C-8a), 148.5, 146.4, 128.0, 123.4 (Ar), 71.9 (C-2), 50.5 (C-4a). Anal. Calcd for $C_{12}H_7Cl_2N_5O_2S$ (356.17): C, 40.46; H, 1.98; N, 19.66. Found C, 40.54; H, 2.06; N, 19.60.

5,7-Dichloro-3-alkyl-2-aryl-2,4a-dihydropyrimido[4,5-d]pyrimidine-4(3H)-thione **3**

To a solution of 5,7-dichloro-2-aryl-2,4a-dihydropyrimido[4,5-*d*]pyrimidine-4(3*H*)-thione **2** (5 mmol) in minimum quantity of pyridine (20 mL) at 0°C, alkyl chloride (10 mmol) was added dropwise with constant stirring. The reaction mixture was further stirred for 0.5–1.5 h and poured into ice-cold acidified water. The solid was collected by filtration, washed repeatedly with water and recrystallized from EtOH.

5,7-Dichloro-3-methyl-2-phenyl-2,4a-dihydropyrimido[4,5-d]pyrimidine-4(3H)-thione **3a**

ν_{max}(KBr)/cm^{-1}: 2980 (CH, sp^3), 1620 (C=C/C=N), 1589, 1500, 1474 (C···C, ring str.), 1087 (C=S), 956 (CH, in-plane bending), 862, 740 (CH, out-of-plane bending), 675 (C—Cl). δ_H ($CDCl_3$): 7.3 (s, 5H, Ph), 4.78 (s, 1H, H-2), 3.69 (s, 1H, H-4a), 3.12 (s, 3H, N—CH_3). δ_C ($CDCl_3$): 197.1 (C-4), 164.0 (C-5), 163.0 (C-7), 160.0 (C-8a), 137.2, 128.3, 128.0, 126.8 (Ph), 70.1 (C-2), 50.2 (C-4a), 32.6 (N—CH_3). Anal. Calcd for $C_{13}H_{10}Cl_2N_4S$ (325.22): C, 48.01; H, 3.10; N, 17.23. Found C, 48.10; H, 3.19; N, 17.20.

5,7-Dichloro-3-methyl-2-(4-chlorophenyl)-2,4a-dihydropyrimido[4,5-d]pyrimidine-4(3H)-thione **3b**

ν_{max}(KBr)/cm^{-1}: 2970 (CH, sp^3), 1630 (C=C/C=N), 1590, 1524, 1404 (C···C, ring str.), 1060 (C=S), 950 (CH, in-plane bending), 854, 761 (CH, out-of-plane bending), 680 (C—Cl). δ_H ($CDCl_3$): 7.10–7.54 (m, 4H, ArH), 4.72 (s, 1H, H-2), 3.21 (s, 1H, H-4a), 3.10 (s, 3H, N—CH_3). δ_C ($CDCl_3$): 196.0 (C-4), 162.0 (C-5), 160.0 (C-7), 158.0 (C-8a), 140.2, 135.1, 129.6, 126.4 (Ar), 70.6 (C-2), 52.7 (C-4a), 35.4 (N—CH_3). Anal. Calcd for $C_{13}H_9Cl_3N_4S$ (359.66): C, 43.41; H, 2.52; N, 15.58. Found C, 43.48; H, 2.44; N, 15.50.

5,7-Dichloro-3-methyl-2-(4-nitrophenyl)-2,4a-dihydropyrimido[4,5-d]pyrimidine-4(3H)-thione **3c**

ν_{max}(KBr)/cm^{-1}: 2880 (CH, sp^3), 1641 (C=C/C=N), 1540, 1467, 1420 (C···C, ring str.), 1340 (NO_2), 1065 (C=S), 974 (CH, in-plane bending), 862, 755 (CH, out-of-plane bending), 670 (C—Cl). δ_H ($CDCl_3$): 6.98–7.36 (m, 4H, ArH), 4.52 (s, 1H, H-2), 3.42 (s, 1H, H-4a), 3.24 (s, 3H, N—CH_3). δ_C ($CDCl_3$): 198.1 (C-4), 165.0 (C-5), 161.0 (C-7), 159.0 (C-8a), 131.2, 130.0, 126.4, 124.5 (Ar), 71.2 (C-2), 51.1 (C-4a), 32.8 (N—CH_3). Anal. Calcd for $C_{14}H_{12}Cl_2N_4S$ (339.24): C, 49.57; H, 3.57; N, 16.52. Found C, 49.51; H, 3.63; N, 16.41.

5,7-Dichloro-3-ethyl-2-phenyl-2,4a-dihydropyrimido[4,5-d]pyrimidine-4(3H)-thione **3d**

ν_{max}(KBr)/cm^{-1}: 2970 (CH, sp^3), 1630 (C=C/C=N), 1590, 1524, 1435 (CH_2/C···C, ring str.), 1052 (C=S), 997 (CH, in-plane bending), 821, 758 (CH, out-of-plane bending), 640 (C—Cl). δ_H ($CDCl_3$): 7.12–7.51 (m, 5H, Ph), 4.89 (s, 1H, H-2), 4.12 (q, 2H, $J = 6.0$ Hz, CH_2), 3.26 (s, 1H, H-4a), 1.17 (t, 3H, $J = 8.0$ Hz, CH_3). δ_C ($CDCl_3$): 210.0 (C-4), 169.0 (C-5), 166.0 (C-7), 160.0 (C-8a), 141.3, 139.4, 127.1, 125.0 (Ph), 74.2 (C-2), 50.9 (C-4a), 40.3 (CH_2), 13.5 (CH_3). Anal. Calcd for $C_{14}H_{12}Cl_2N_4S$ (339.24): C, 49.57; H, 3.57; N, 16.52. Found C, 49.63; H, 3.50; N, 16.40.

5,7-Dichloro-3-ethyl-2-(4-chlorophenyl)-2,4a-dihydropyrimido[4,5-d]pyrimidine-4(3H)-thione **3e**

ν_{max}(KBr)/cm^{-1}: 2984 (CH, sp^3), 1640 (C=C/C=N), 1584, 1512, 1465 (CH_2/C···C, ring str.), 1050 (C=S),

945 (CH, in-plane bending), 828, 764 (CH, out-of-plane bending), 645 (C—Cl). δ_H ($CDCl_3$): 7.14–7.49 (m, 4H, ArH), 4.84 (s, 1H, H-2), 4.15 (q, 2H, $J = 6.0$ Hz, CH_2), 3.32 (s, 1H, H-4a), 1.10 (t, 3H, $J = 8.0$ Hz, CH_3). δ_C ($CDCl_3$): 197.9 (C-4), 168.0 (C-5), 163.0 (C-7), 158.0 (C-8a), 142.7, 140.2, 128.1, 125.2 (Ar), 74.0 (C-2), 50.7 (C-4a), 43.5 (CH_2), 15.9 (CH_3). Anal. Calcd for $C_{14}H_{11}Cl_3N_4S$ (373.69): C, 45.00; H, 2.97; N, 14.99. Found C, 45.09; H, 2.90; N, 14.93.

5,7-Dichloro-3-ethyl-2-(4-nitrophenyl)-2,4a-dihydropyrimido[4,5-d]pyrimidine-4(3H)-thione **3f**

ν_{max}(KBr)/cm^{-1}: 2880 (CH, sp^3), 1620 (C=C/C=N), 1570, 1517, 1440 (CH_2/C···C, ring str.), 1340 (NO_2), 1045 (C=S), 936 (CH, in-plane bending), 835, 758 (CH, out-of-plane bending), 640 (C—Cl). δ_H ($CDCl_3$): 7.15–7.56 (m, 4H, ArH), 4.78 (s, 1H, H-2), 4.21 (q, 2H, $J = 6.0$ Hz, CH_2), 3.31 (s, 1H, H-4a), 1.22 (s, 3H, $J = 8.0$ Hz, CH_3). δ_C ($CDCl_3$): 199.1 (C-4), 167.0 (C-5), 162.0 (C-7), 158.0 (C-8a), 139.1, 128.4, 127.2, 126.3 (Ar), 75.0 (C-2), 53.4 (C-4a), 41.5 (CH_2), 13.2 (CH_3). Anal. Calcd for $C_{15}H_{14}Cl_2N_4S$ (353.27): C, 51.00; H, 3.99; N, 15.86. Found C, 49.94; H, 4.11; N, 15.75.

5,7-Dichloro-4-hydrazino-2-aryl-2,4a-dihydropyrimido[4,5-d]pyrimidine **4**

A mixture of 5,7-dichloro-2-aryl-2,4a-dihydropyrimido[4,5-*d*]pyrimidine-4(3*H*)-thione **2** (20 mmol) and 80% hydrazine hydrate (10 mL) was heated under reflux for 10 min. After cooling, the precipitated crystals were collected from filtration under vacuum, washed with water, dried, and recrystallized from EtOH to yield corresponding hydrazino derivatives **4a–d**.

5,7-Dichloro-4-hydrazino-2-phenyl-2,4a-dihydropyrimido[4,5-d]pyrimidine **4a**

ν_{max}(KBr)/cm^{-1}: 3425 (NH_2, sym.), 3340 (NH_2, asym.), 3210 (NH), 1617 (C=C/C=N), 1558, 1514, 1475 (C···C, ring str.), 1012, 920 (CH, in-plane bending), 864, 741 (CH, out-of-plane bending), 680 (C—Cl). δ_H ($CDCl_3$): 9.11 (br s, 1H, NH), 7.11–7.48 (m, 5H, Ph), 6.22 (s, 2H, NH_2), 4.62 (s, 1H, H-2), 3.19 (s, 1H, H-4a). δ_C ($CDCl_3$): 166.0 (C-7), 164.0 (C-4), 163.0 (C-5), 160.0 (C-8a), 137.7, 129.2, 128.4, 125.5 (Ph), 71.1 (C-2), 30.3 (C-4a). Anal. Calcd for $C_{12}H_{10}Cl_2N_6$ (309.15): C, 46.62; H, 3.26; N, 27.18. Found C, 46.52; H, 3.20; N, 27.27.

5,7-Dichloro-4-hydrazino-2-(4-chlorophenyl)-2,4a-dihydropyrimido[4,5-d]pyrimidine **4b**

ν_{max}(KBr)/cm^{-1}: 3475 (NH_2, sym.), 3362 (NH_2, asym.), 3217 (NH), 1623 (C=C/C=N), 1561, 1510, 1412 (C···C, ring str.), 1017, 939 (CH, in-plane bending), 854, 762 (CH, out-of-plane bending), 662 (C—Cl). δ_H ($CDCl_3$): 9.24 (br s, 1H, NH), 7.18–7.33 (m, 4H, ArH), 6.27 (s, 2H, NH_2), 4.69 (s, 1H, H-2), 3.11 (s, 1H, H-4a). δ_C ($CDCl_3$): 164.0 (C-7), 163.0 (C-4), 160.0 (C-5), 159.0 (C-8a), 139.8, 130.8, 130.6, 128.7 (Ar), 73.4 (C-2), 32.1 (C-4a). Anal. Calcd for $C_{12}H_9Cl_3N_6$ (343.60): C, 41.95; H, 2.64; N, 24.46. Found C, 42.11; H, 2.57; N, 24.53.

5,7-Dichloro-4-hydrazino-2-(4-methylphenyl)-2,4a-dihydropyrimido[4,5-d]pyrimidine **4c**

ν_{max}(KBr)/cm^{-1}: 3450 (NH_2, sym.), 3374 (NH_2, asym.), 3221 (NH), 2865 (CH, sp^3), 1612 (C=C/C=N), 1586, 1534, 1410 (C···C, ring str.), 1021, 926 (CH, in-plane bending), 832, 750 (CH, out-of-plane bending), 674 (C—Cl). δ_H ($CDCl_3$): 9.15 (br s, 1H, NH), 7.10–7.42 (m, 4H, ArH), 6.75 (s, 2H, NH_2), 4.59 (s, 1H, H-2), 3.24 (s, 1H, H-4a), 2.48 (s, 3H, $J = 8.0$ Hz, CH_3). δ_C ($CDCl_3$): 167.0 (C-7), 163.0 (C-4), 161.0 (C-5), 160.0 (C-8a), 134.7, 132.1, 129.8, 127.5 (Ar), 72.4 (C-2), 30.4 (C-4a), 20.2 (Ar—CH_3). Anal. Calcd for $C_{13}H_{12}Cl_2N_6$ (323.18): C, 48.31; H, 3.74; N, 26.00. Found C, 48.39; H, 3.63; N, 26.07.

5,7-Dichloro-4-hydrazino-2-(4-nitrophenyl)-2,4a-dihydropyrimido[4,5-d]pyrimidine **4d**

ν_{max}(KBr)/cm^{-1}: 3446 (NH_2, sym.), 3381 (NH_2, asym.), 3246 (NH), 1619 (C=C/C=N), 1576, 1507, 1431 (C···C, ring str.), 1365 (NO_2), 1020, 940 (CH, in-plane bending), 848, 747 (CH, out-of-plane bending), 691 (C—Cl). δ_H ($CDCl_3$): 9.28 (br s, 1H, NH), 7.11–7.39 (m, 4H, ArH), 6.12 (s, 2H, NH_2), 4.55 (s, 1H, H-2), 3.43 (s, 1H, H-4a). δ_C ($CDCl_3$): 167.0 (C-7), 165.0 (C-4), 162.0 (C-5), 160.0 (C-8a), 145.4, 142.6, 130.1, 123.4 (Ar), 71.2 (C-2), 31.8 (C-4a). Anal. Calcd for $C_{12}H_9Cl_2N_7O_2$ (354.15): C, 40.70; H, 2.56; N, 27.69. Found C, 40.67; H, 2.49; N, 27.78.

5,7-Dichloro-4-benzylidenehydrazino-2-aryl-2,4a-dihydropyrimido[4,5-d]pyrimidine **5**

A mixture of 5,7-dichloro-4-hydrazino-2-aryl-2,4a-dihydropyrimido[4,5-*d*]pyrimidine **4** (20 mmol) and benzaldehyde (3.18 mL, 30 mmol) in glacial AcOH (30 mL), stirred at room temperature for 4–5 h. After completion of the reaction, the precipitated solid was collected by suction filtration, washed with EtOH

and recrystallized from DMF to give the corresponding hydrazones **5a–d**.

5,7-Dichloro-4-benzylidenehydrazino-2-phenyl-2,4a-dihydropyrimido[4,5-d]pyrimidine **5a**

ν_{max}(KBr)/cm^{-1}: 3420 (NH), 3010 (CH, sp^2), 1623 (C═C/C═N), 1582, 1523, 1452 (C⋯C, ring str.), 691 (C—Cl). δ_H ($CDCl_3$): 10.45 (br s, 1H, NH), 8.45 (s, 1H, N═CH), 7.10–7.62 (m, 10H, 2 × Ph), 4.82 (s, 1H, H-2), 3.10 (s, 1H, H-4a). δ_C ($CDCl_3$): 170.0 (C-7), 168.0 (C-4), 164.0 (C-5), 160.0 (C-8a), 154.7 (N═CH), 137.2, 131.5, 130.8, 129.2, 129.0, 128.6, 128.4, 125.5 (2 × Ph), 71.5 (C-2), 30.8 (C-4a). Anal. Calcd for $C_{19}H_{14}Cl_2N_6$ (397.26): C, 57.44; H, 3.55; N, 21.16. Found C, 57.50; H, 3.45; N, 21.23.

5,7-Dichloro-4-benzylidenehydrazino-2-(4-chlorophenyl)-2,4a-dihydropyrimido[4,5-d]-pyrimidine **5b**

ν_{max}(KBr)/cm^{-1}: 3410 (NH), 3025 (CH, sp^2), 1618 (C═C/C═N), 1589, 1534, 1465 (C⋯C, ring str.), 684 (C—Cl). δ_H ($CDCl_3$): 10.32 (br s, 1H, NH), 8.23 (s, 1H, N═CH), 7.11–7.58 (m, 9H, Ph/Ar), 5.21 (s, 1H, H-2), 3.28 (s, 1H, H-4a). δ_C ($CDCl_3$): 172.0 (C-7), 168.0 (C-4), 165.0 (C-5), 161.0 (C-8a), 152.1 (N═CH), 140.2, 136.7, 132.8, 130.6, 128.8, 128.1, 125.4, 121.3 (Ph/Ar), 70.7 (C-2), 30.2 (C-4a). Anal. Calcd for $C_{19}H_{13}Cl_3N_6$ (431.71): C, 52.86; H, 3.04; N, 19.47. Found C, 52.79; H, 3.12; N, 19.40.

5,7-Dichloro-4-benzylidenehydrazino-2-(4-methylphenyl)-2,4a-dihydropyrimido[4,5-d]pyrimidine **5c**

ν_{max}(KBr)/cm^{-1}: 3425 (NH), 3040 (CH, sp^2), 2864 (CH, sp^3), 1640 (C═C/C═N), 1581, 1500, 1460 (C⋯C, ring str.), 680 (C—Cl). δ_H ($CDCl_3$): 10.62 (br s, 1H, NH), 8.26 (s, 1H, N═CH), 7.14–7.63 (m, 9H, Ph/Ar), 5.17 (s, 1H, H-2), 3.49 (s, 1H, H-4a), 2.45 (s, 3H, CH_3). δ_C ($CDCl_3$): 169.0 (C-7), 164.0 (C-4), 162.0 (C-5), 160.0 (C-8a), 154.0 (N═CH), 138.8, 137.5, 129.1, 129.0, 127.6, 127.2, 124.1, 124.0 (Ph/Ar), 72.4 (C-2), 32.6 (C-4a), 20.2 (Ar—CH_3). Anal. Calcd for $C_{20}H_{16}Cl_2N_6$ (411.29): C, 58.41; H, 3.92; N, 20.43. Found C, 58.35; H, 4.01; N, 20.37.

5,7-Dichloro-4-benzylidenehydrazino-2-(4-nitrophenyl)-2,4a-dihydropyrimido[4,5-d]pyrimidine **5d**

ν_{max}(KBr)/cm^{-1}: 3484 (NH), 3050 (CH, sp^2), 1621 (C═C/C═N), 1591, 1514, 1434 (C⋯C, ring str.), 681 (C—Cl). δ_H ($CDCl_3$): 10.24 (br s, 1H, NH), 8.39 (s, 1H, N═CH), 7.19–7.61 (m, 9H, Ph/Ar), 4.89 (s, 1H, H-2), 3.22 (s, 1H, H-4a). δ_C ($CDCl_3$): 170.0 (C-7), 166.0 (C-4), 162.0 (C-5), 160.0 (C-8a), 152.7 (N═CH), 145.8, 140.2, 131.8, 130.0, 129.4, 128.6, 126.1, 125.8 (Ph/Ar), 71.5 (C-2), 30.4 (C-4a). Anal. Calcd for $C_{19}H_{13}Cl_2N_7O_2$ (442.26): C, 51.60; H, 2.96; N, 22.17. Found C, 51.55; H, 3.03; N, 22.12.

8,10-Dichloro-3-phenyl-5-aryl-5,10a-dihydro-pyrimido-[5,4-e][1,2,4]triazolo[4,3-c]pyrimidine **6**

A mixture of 5,7-dichloro-4-benzylidenehydrazino-2-aryl-2,4a-dihydropyrimido[4,5-*d*]pyrimidine **5** (20 mmol) with lead tetraacetate (30 mmol) in 1,4-dioxane was heated under reflux and stirring for 4–6 h (to the disappearance of starting material). After the completion of reaction, the residue was removed by filtration and the filtrate was concentrated under reduced pressure to leave solid, which was washed with EtOH and recrystallized from DMF to give the corresponding triazolopyrimidines.

8,10-Dichloro-3,5-diphenyl-5,10a-dihydro-pyrimido[5,4-e][1,2,4]triazolo[4,3-c]pyrimidine **6a**

ν_{max}(KBr)/cm^{-1}: 1632 (C═C/C═N), 1584, 1535, 1400 (C⋯C, ring str.), 1015 (CH, in-plane bending), 852 (out-of-plane bending), 662 (C—Cl). δ_H ($CDCl_3$): 6.98—7.56 (m, 10H, 2 × Ph), 4.62 (s, 1H, H-5), 3.11 (s, 1H, H-10a). δ_C ($CDCl_3$): 165.0 (C-8), 163.0 (C-10), 162.0 (C-10b), 160.0 (C-6a), 151.0 (C-3), 137.6, 136.5, 129.2, 129.0, 128.5, 128.4, 127.0, 125.4 (2 × Ph), 71.4 (C-5), 33.1 (C-10a). Anal. Calcd for $C_{19}H_{12}Cl_2N_6$ (395.24): C, 57.74; H, 3.06; N, 21.26. Found C, 57.68; H, 3.00; N, 21.38.

8,10-Dichloro-3-phenyl-5-(4-chlorophenyl)-5,10-a-dihydropyrimido[5,4-e][1,2,4]triazolo[4,3-c]pyrimidine **6b**

ν_{max}(KBr)/cm^{-1}: 1622 (C═C/C═N), 1600, 1567, 1423 (C⋯C, ring str.), 1021 (CH, in-plane bending), 850 (out-of-plane bending), 665 (C—Cl). δ_H ($CDCl_3$): 7.18–7.62 (m, 9H, Ph/Ar), 4.98 (s, 1H, H-5), 3.26 (s, 1H, H-10a). δ_C ($CDCl_3$): 169.0 (C-8), 167.0 (C-10), 164.0 (C-10b), 161.0 (C-6a), 154.2 (C-3), 138.9, 134.2, 128.6, 128.5, 126.0, 125.2, 124.0, 122.1 (Ph/Ar), 74.2 (C-5), 32.0 (C-10a). Anal. Calcd for $C_{19}H_{11}Cl_3N_6$ (429.69): C, 53.11; H, 2.58; N, 19.56. Found C, 53.23; H, 2.51; N, 19.61.

8,10-Dichloro-3-phenyl-5-(4-methylphenyl)-5, 10a-dihydropyrimido[5,4-e][1,2,4]triazolo[4,3-c]pyrimidine **6c**

ν_{max}(KBr)/cm^{-1}: 2960 (CH, sp^3), 1643 (C═C/C═N), 1589, 1475, 1412 (C⋯C, ring str.), 1024 (CH, in-plane bending), 845 (out-of-plane bending), 665 (C─Cl). δ_H ($CDCl_3$): 7.05–7.60 (m, 9H, Ph/Ar), 4.75 (s, 1H, H-5), 3.35 (s, 1H, H-10a), 2.47 (s, 3H, CH_3). δ_C ($CDCl_3$): 166.0 (C-8), 163.0 (C-10), 162.0 (C-10b), 161.0 (C-6a), 152.0 (C-3), 134.7, 130.2, 128.7, 128.5, 126.6, 125.4, 124.9, 124.2 (Ph/Ar), 71.2 (C-5), 30.4 (C-10a), 24.3 (Ar─CH_3). Anal. Calcd for $C_{20}H_{14}Cl_2N_6$ (409.27): C, 58.69; H, 3.45; N, 20.53. Found C, 58.79; H, 3.36; N, 20.60.

8,10-Dichloro-3-phenyl-5-(4-nitrophenyl)-5,10a-dihydropyrimido[5,4-e][1,2,4]triazolo[4,3-c]-pyrimidine **6d**

ν_{max}(KBr)/cm^{-1}: 1622 (C═C/C═N), 1575, 1460, 1410 (C⋯C, ring str.), 1019 (CH, in-plane bending), 832 (out-of-plane bending), 670 (C─Cl). δ_H ($CDCl_3$): 7.00–7.52 (m, 9H, Ph/Ar), 4.84 (s, 1H, H-5), 3.26 (s, 1H, H-10a). δ_C ($CDCl_3$): 167.0 (C-8), 165.0 (C-10), 163.0 (C-10b), 162.0 (C-6a), 154.7 (C-3), 142.6, 139.2, 130.1, 129.7, 128.4, 128.0, 126.5, 125.9 (Ph/Ar), 75.4 (C-5), 32.6 (C-10a). Anal. Calcd for $C_{19}H_{11}Cl_2N_7O_2$ (440.24): C, 51.84; H, 2.52; N, 22.27. Found C, 51.79; H, 2.61; N, 22.35.

ACKNOWLEDGMENTS

We are thankful to Director, Indian Institute of Technology, Chennai and Central Drug Research Institute, Lucknow for providing the spectroanalytical facilities.

REFERENCES

[1] Lunt, E. In Comprehensive Organic Chemistry; Barton, D.; Ollis, W. D. (Eds.); Pergamon: Oxford, 1979; Vol. 4.
[2] Brown, J. D. In Comprehensive Heterocyclic Chemistry; Katritzky, A. R.; Rees, C. W. (Eds.); Pergamon: Oxford, 1984; Vol. 3.
[3] Curtin, N. J.; Barlow, H. C.; Bowman, K. J.; Calvert, A. H.; Richard Davison, R.; Golding, B. T.; Huang, B.; Loughlin, P. J.; Newell, D. R.; Smith, P. G.; Griffin, R. J. J Med Chem 2004, 47, 4905.
[4] De la Cruz, J. P.; Carrasco, T.; Ortega, G.; Sanchez, De la Cuesta, F. Lipid 1992, 27, 192.
[5] Sanghvi, Y. S.; Larson, S. B.; Matsumoto, S. S.; Nord, L. D.; Smee, D. F.; Willis, R. C.; Avery, T. H.; Robins, R. K.; Revankar, G. R. J Med Chem 1989, 32, 629.
[6] Ram, V. J.; Goel, A.; Sarkhel, S.; Maulik, P. R. Bioorg Med Chem 2002, 10, 1275.
[7] Rewcastle, G. W.; Bridges, A. J.; Fry, D. W.; Rubin, J. R.; Denny, W. A. J Med Chem 1997, 40, 1820.
[8] Fry, D. W.; Becker, M. A.; Switzer, R. L. Mol Pharmacol 1995, 47, 810.
[9] Kurzmeier, H.; Schmidtehen, F. P. J Org Chem 1990, 55, 3749.
[10] Kosasayama, A.; Ishikawa, F. Chem Pharm Bull 1979, 72, 1596.
[11] Baraldi, P. G.; Cacciari, B.; Borea, P. A.; Varani, K.; Pastorin, G.; Da Ros, T.; Tabrizi, M. A.; Fruttarolo, F.; Spalluto, G. Curr Pharm Des 2002, 8, 2299.
[12] Sharma, P.; Kumar, A.; Rane, N.; Gurram, V. K. Tetrahedron 2005, 61, 4237.
[13] Sharma, P.; Rane, N.; Gurram, V. K. Bioorg Med Chem Lett 2004, 14, 4185.
[14] Sharma, P.; Kumar, A.; Sharma, S.; Rane, N. Bioorg Med Chem Lett 2005, 15, 937.
[15] Sharma, P.; Sharma, S.; Rane, N. Bioorg Med Chem 2004, 12, 3135.
[16] Sharma, P.; Kumar, A.; Mandloi, A. Synth Comm 2003, 33, 373.
[17] (a) Hirota, K.; Kitade, Y.; Sajiki, M.; Maki, Y. Synthesis 1984, 589. (b) Hirota, K.; Kitade, Y.; Sajiki, H.; Maki, Y. J Chem Soc, Perkin Trans 1, 1990, 1, 123.
[18] Srivastava, S. W.; Haq, W.; Chauhan, P. M. S. Bioorg Med Chem Lett 1999, 9, 965.
[19] Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. Vogel's Text Book of Practical Organic Chemistry, 5th ed.; Addison Wesley, Longman: England, 1989.