The "International Journal of Pharma and Bio Sciences" (IJPBS) is an international journal in English published quarterly. The aim of IJPBS is to publish peer reviewed research and review articles rapidly without delay in the developing field of pharmaceutical and biological sciences.

Indexed in Chemical Abstract Services (USA), Index copernicus, Ulrichs Directory of Periodicals, Google scholar, CABI, DOAJ, PZOAR, EBSCO, Open J gate, Proquest, SCOPUS, EMBASE, etc.

Indexed in Elsevier Bibliographic Database (Scopus and EMBASE)
SCImago Journal Rank 0.288
Impact factor 2.958*
Elsevier Bibliographic databases
(Scopus & Embase)

**SNIP value** – 0.77
**SJR** - 0.288
**IPP** - 0.479

SNIP – Source normalised impact per paper
SJR – SCImago Journal rank
IPP – Impact per publication

Source – [www.journalmetrics.com](http://www.journalmetrics.com)
(Powered by Scopus (ELSEVIER))

---

International Journal of Pharma and Bio Sciences

<table>
<thead>
<tr>
<th>Indicator</th>
<th>2006-2013</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SJR</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Cites per doc</td>
<td></td>
<td>0.51</td>
</tr>
<tr>
<td>Total cites</td>
<td></td>
<td>852</td>
</tr>
</tbody>
</table>

www.scimagojr.com

And indexed/catalogued in many more university databases

*Instruction to Authors visit [www.ijpbs.net](http://www.ijpbs.net)
For any Queries, visit “contact” of www.ijpbs.net*
STUDIES ON 5-CYANOURACILS: EXPEDIENT SYNTHETIC PROTOCOL FOR SYNTHESIS OF NOVEL PYRIDO[2,3-d]PYRIMIDINE AND PYRIMIDO [4,5-d]PYRIMIDINE ANALOGS WITH POTENTIAL PHARMACOLOGICAL ACTIVITY

YOGESH Y. PEDGAONKAR, ARUNDHATI C. LELE, NUTAN H. PALSULE DESAI AND MARIAM S. DEGANI*

Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Nathalal Parikh Marg, Matunga, Mumbai-400019, India.

ABSTRACT

Novel, diverse pyrido [2,3-d] pyrimidine and pyrimido [4,5-d] pyrimidine analogs were synthesized by the reaction of 1,3-substituted-5-cyano uracil derivatives with appropriate nucleophile under mild conditions. Utilising 5-cyano uracil with various substitutions as a substrate leads to rapid synthesis of annulated uracils with diverse biological properties.

KEYWORDS: Cyanouracils, pyrido[2,3-d]pyrimidine, pyrimido[4,5-d]pyrimidine, multicomponent.

MARIAM S. DEGANI
Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Nathalal Parikh Marg, Matunga, Mumbai-400019, India.
INTRODUCTION

Uracils and their annulated derivatives like pyrido[2,3-d]pyrimidines and pyrimido[4,5-d]pyrimidines, represent important classes of heterocyclic compounds with biological significance, as they have similarity with pteridine system. Various derivatives of these scaffolds display a wider range of pharmacological properties; e.g., Inhibitory actions against 5-phosphoribosyl-1-pyrophosphate synthetase, dihydrofolate reductases, and the tyrosine kinase domain of the epidermal growth factor receptor have been fully demonstrated. More recently, compounds such as RS-25344 and CP-77059 bearing the pyridopyrimidine moiety exhibited excellent PDE-4 inhibitory activity, based on these findings Nam et al developed new pyridopyrimidine derivatives exhibiting promising activity for PDE-4 inhibition. Bulicz et al. demonstrated that selectivity of adenosine receptor antagonists could be increased with polar substitution on pyridopyrimidine ring. Thus, considerable attention has been focused on the development of new methodologies to synthesize these annulated systems. Several reported synthetic methods delineate that 6-amino-1, 3-disubstituted uracils have been extensively explored for the synthesis of pyrido [2,3-d] pyrimidines and pyrimido [4,5-d] pyrimidines. Different synthetic approaches based on 6-aminouracils include; (a) a multicomponent reaction of 6-amino uracils with orthoformate, or aldehyde along with appropriate substrate, (b) conversion of 6-amino uracils to 6-amino-5-formyl uracils followed by reaction with malononitrile, (c) reaction of 6-amino-5-imino uracils derived from 6-amino uracils with malononitrile and amides. In addition, several other substrates such as 2-amino nicotinonitrile derivatives, isoxazolo[3,4-d]-pyrimidine and 5-nitrosopyrrolo pyrimidine, were employed for synthesis of the pyrido[2,3-d]pyrimidines and pyrimido[4,5-d]pyrimidines. Reported procedures for the synthesis of aforesaid annulated derivatives lack diversity, take longer reaction time and require drastic reaction conditions. Thus, new routes for the diversity oriented synthesis of these derivatives or 5-cyanouracils which could act as precursors have attracted considerable attention in the search for an efficient synthesis of these heterocycles. In continuation of our studies on synthesis of substituted 5-cyano uracils and their application in synthesis of fused uracils of biological importance, we describe here a simple synthetic procedure for novel pyrido[2,3-d]pyrimidines and pyrimido[4,5-d]pyrimidines from 5-cyanouracils.

MATERIALS AND METHODS

All chemicals used for synthesis were procured from Sigma Aldrich and S. D. Fine chemicals and were used directly. Melting points were determined in open capillaries on ThermomixCompbell electronics, having oil-heating system and are uncorrected. The monitoring of reaction for completion and the purity of the compounds were routinely checked by thin-layer chromatography (TLC) and was accomplished on 0.2 mm pre-coated plates of silica gel 60 F-254 (Merck, Darmstadt-Germany). FTIR spectra were obtained on a Perkin-Elmer Infrared spectrometer with KBr discs and 1H NMR spectra were recorded in CDCl₃ or DMSO-d₆ on a JEOL 60 MHz and 300 MHz spectrometer with tetramethylsilane as internal standard. Mass spectral data were obtained with micromass - Q – TOF (YA105) spectrometer. 5-cyanouracils with various substitutions synthesized in-house using developed multicomponent system, when reacted with two different nucleophiles such as ethylcyanoacetate and malononitrile resulted in pyrido[2,3-d]pyrimidines and that with thiourea resulted in pyrimido[4,5-d]pyrimidines in good yields. Reaction of 5-cyano uracils, 1, with equimolar quantities of ethyl cyanoacetate and malononitrile resulted in pyrido[2,3-d]pyrimidines and that with thiourea resulted in pyrimido[4,5-d]pyrimidines in good yields. Reaction of 5-cyano uracils, 1, with equimolar quantities of ethyl cyanoacetate or malononitrile in refluxing ethanol, in presence of sodium ethoxide gave 7-amino-pyrido [2,3-d]pyrimidine-6-carboxylate and 7-amino-pyrido[2,3-d]pyrimidine-6-carbonitrile respectively (Scheme 1).
Typical synthetic procedure for synthesis of 7-amino-pyrido[2,3-d] pyrimidine-6-carboxylate: A mixture of 5-cyanouracil 1 (0.5 g, 1.65 mmol) and ethyl cyanoacetate (0.21 g, 1.65 mmol) was added to ethanolic sodium ethoxide (prepared by dissolving 100 mg of metallic sodium in 15 ml of ethanol) and refluxed for 30 minutes affording precipitates which, after recrystallization from chloroform:methanol, (90:10) afforded 7-amino-pyrido[2,3-d]pyrimidine-6-carboxylate. Typical synthetic procedure for synthesis of 7-amino-pyrido[2,3-d] pyrimidine-6-carbonitrile: A mixture of 5-cyanouracil 1 (0.5 g, 1.65 mmol) and malononitrile (0.91 ml, 1.65 mmol) was added in freshly prepared ethanolic sodium ethoxide (100 mg of metallic sodium in 15 ml of ethanol) and refluxed for 20 minutes. After cooling the mixture to room temperature, crystals precipitated out were collected by filtration and recrystallized from a mixture of N,N-dimethylformamide:ethanol (20:80) to give yellow colored crystals of 7-amino-pyrido[2,3-d]pyrimidine-6-carbonitrile. Typical synthetic procedure for synthesis of 7-amino-pyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione: A mixture of 5-cyano-uracil 1 (0.5 g, 1.65 mmol) and thiourea (0.38 g, 4.95 mmol) were added to ethanolic sodium ethoxide (110 mg of metallic sodium in 15 ml ethanol) and refluxed for 30 minutes. The solvent was removed under reduced pressure and the residue was triturated with a small amount of water. The resulting precipitate was collected by filtration, washed with water, and dried to give the 7-amino-pyrimido[4,5-d]pyrimidine-2,4(1H,3H)-Dione.

RESULTS AND DISCUSSION

Various 5-cyanouracil derivatives were reacted with ethyl cyanoacetate, malononitrile or thiourea, the results are as summarized in Table 1. All reactions were carried out at 0.5 g scale of uracil 1 in refluxing ethanol in the presence of sodium ethoxide for 30 minutes. The nature of substituent on the phenyl ring attached to N1 nitrogen of uracil ring has no significant effect on yields of the product (Entry 1-6, Table 1). In general, reaction carried out with ethyl cyanoacetate results in better yields. Isolation of the product required evaporation of solvent and then precipitation of product with aqueous methanol followed by filtration and washing. However, in case of malononitrile as nucleophile, slightly lower yields were obtained, although with ease of isolation of the product. The IR spectrum of...
the isolated compounds exhibited sharp bands at 3336 cm\(^{-1}\) (NH), 2223 cm\(^{-1}\) (CN in case of 3a, 3b, 3c), 1715 cm\(^{-1}\) (C=O ester, in case of 2a, 2b, 2c), and \(^1\)H NMR shows presence of aromatic proton of pyridine ring between \(\delta\) 8.45- 9.01 ppm, depending on the nature of the derivative. Similarly, reaction of 5-cyano uracils 1, with excess of thiourea, in refluxing ethanol in presence of sodium ethoxide gave 7-amino-pyrimido-[4,5-d]pyrimidine-2,4(1H,3H)-diones. The nature of substituent present on the phenyl ring of \(N_1\) nitrogen of uracil ring has no significant effect on yields of the product (Entry 7-9, Table 1). The IR spectrum of isolated compounds exhibited sharp bands at 3336 cm\(^{-1}\) (NH), and absence of nitrile group whereas, \(^1\)H NMR shows presence of aromatic proton of pyrimidine ring at \(\delta\) 8.5 ppm.

### Table 1

**Synthesis of pyrido[2,3-d]pyrimidines and pyrimido[4,5-d]pyrimidines.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>5-cyano Uracil</th>
<th>Nucleophile</th>
<th>Product</th>
<th>Yield (%)</th>
<th>M.P. ºC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1a</td>
<td>Ethyl cyanoacetate</td>
<td>2a</td>
<td>92</td>
<td>240-241</td>
</tr>
<tr>
<td>2.</td>
<td>1b</td>
<td>Ethyl cyanoacetate</td>
<td>2b</td>
<td>90</td>
<td>262-264</td>
</tr>
<tr>
<td>3.</td>
<td>1c</td>
<td>Ethyl cyanoacetate</td>
<td>2c</td>
<td>94</td>
<td>213-214</td>
</tr>
<tr>
<td>4.</td>
<td>1a</td>
<td>Malononitrile</td>
<td>3a</td>
<td>89</td>
<td>&gt;280</td>
</tr>
<tr>
<td>5.</td>
<td>1b</td>
<td>Malononitrile</td>
<td>3b</td>
<td>86</td>
<td>&gt;280</td>
</tr>
<tr>
<td>6.</td>
<td>1c</td>
<td>Malononitrile</td>
<td>3c</td>
<td>88</td>
<td>&gt;280</td>
</tr>
<tr>
<td>7.</td>
<td>1a</td>
<td>Thiourea</td>
<td>4a</td>
<td>67</td>
<td>265-267</td>
</tr>
<tr>
<td>8.</td>
<td>1b</td>
<td>Thiourea</td>
<td>4b</td>
<td>65</td>
<td>&gt;280</td>
</tr>
<tr>
<td>9.</td>
<td>1c</td>
<td>Thiourea</td>
<td>4c</td>
<td>58</td>
<td>&gt;280</td>
</tr>
</tbody>
</table>

**SUPPORTING INFORMATION**

**Synthesis of 7-amino-3-benzyl-2,4-dioxo-1-phenyl-1,2,3,4-tetrahydropyrido[2,3-d] pyrimidine-6-carboxylate (Compound 2a)**

A mixture of 5-cyano-3-benzyl-1-phenyluracil (0.5 g, 1.65 mmol) and ethyl cyanoacetate (0.21 g, 1.65 mmol) was added to ethanolic sodium ethoxide (prepared by dissolving 100 mg of metallic sodium in 15 ml of ethanol) and refluxed for 30 minutes affording precipitate which, after recrystallization from chloroform:methanol (90:10), afforded buff colored ethyl 7-amino-3-benzyl-2,4-dioxo-1-phenyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate, M.P. 240-241 ºC; \(^1\)H NMR (400 MHz, \(\delta\) ppm, CDCl\(_3\)) 8.89 (1 H, s), 8.19 (1 H, s), 7.79 – 7.21 (10 H, m), 5.49 (1 H, s), 5.22 (2 H, s), 4.40 – 4.25 (2 H, q) 1.45 – 1.25 (3 H, t); \(^13\)C NMR (75 MHz, \(\delta\) ppm, CDCl\(_3\)) 166.1, 161.3, 160.6, 154.0, 151.3, 143.1, 136.8, 136.4, 133.0, 132.9, 132.1, 131.7, 130.0, 129.7 128.7, 128.0, 126.8, 126.7, 125.8, 104.2, 101.1, 61.6, 45.2, 14.5; IR (KBr \(\nu_{\max}\) cm\(^{-1}\)) 3492, 3351, 3061, 2957, 1715, 1691, 1669, 1612, 1555, 1472, 1275.
Figure

$^1$H NMR spectrum of 7-amino-3-benzyl-2,4-dioxo-1-phenyl-1,2,3,4-tetrahydropyrido [2,3-d]pyrimidine-6-carboxylate (Compound 2a)

Figure

$^{13}$C NMR spectrum of 7-amino-3-benzyl-2,4-dioxo-1-phenyl-1,2,3,4-tetrahydropyrido [2,3-d]pyrimidine-6-carboxylate (Compound 2a)
Figure

IR spectrum of 7-amino-3-benzyl-2,4-dioxo-1-phenyl-1,2,3,4-tetrahydro pyrido[2,3-d]pyrimidine-6-carboxylate (Compound 2a)

Synthesis of 7-amino-3-benzyl-1-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydro pyrido [2,3-d] pyrimidine -6-carboxylate (Compound 2b)

Reaction of 5-cyano-3-benzyl-1-(4-methoxy-phenyl)uracil (0.5g, 1.5mmol) with ethyl cyanoacetate (0.21 g, 1.65 mmol) in refluxing ethanolic sodium ethoxide (prepared by dissolving 100 mg of metallic sodium in 15 ml of ethanol) for 30 minutes affording precipitate which, after recrystallization from chloroform-methanol (90:10), afforded buff colored ethyl 7-amino-3-benzyl-1-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d] pyrimidine -6-carboxylate, M.P. 262-264 ºC; ¹H NMR (400 MHz, δ ppm, DMSO-d₆) 8.65 (1 H, s), 7.80 – 7.92 (2 H, d), 7.49 – 7.24 ( 9 H, m), 5.08 ( 2 H, s), 4.30 – 4.28 ( 2 H, q), 3.83 (3 H, s), 1.30 – 1.34 ( 3 H, t); IR (KBr Vₘₐₓ cm⁻¹) 3492, 3351, 3061, 2957, 1715, 1691, 1669, 1612, 1555, 1472, 1275.
Figure

$^1$H NMR spectrum of 7-amino-3-benzyl-1-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d] pyrimidine-6-carboxylate (Compound 2b)

Figure

IR spectrum of 7-amino-3-benzyl-1-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d] pyrimidine-6-carboxylate (Compound 2b)
Synthesis of 7-amino-3-benzyl-2,4-dioxo-1-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydropyrido [2,3-d]pyrimidine-6-carboxylate (Compound 2c)

A mixture of 5-cyano-3-benzyl-1-(3-(trifluoromethyl)phenyl) uracil (0.5g, 1.5mmol) and ethyl cyanoacetate (0.21 g, 1.65 mmol) was added to ethanolic sodium ethoxide (prepared by dissolving 100 mg of metallic sodium in 15 ml of ethanol) and refluxed for 30 minutes affording precipitate which, after recrystallization from chloroform-methanol (90:10) afforded buff colored ethyl 7-amino-3-benzyl-1-(3-(trifluoromethyl)phenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d] pyrimidine -6-carboxylate, M.P. 213-214 ºC; $^1$H NMR (400 MHz, δ ppm, DMSO-d$_6$) 8.65 (1 H, s), 7.80 – 7.92 (2 H, d), 7.49 – 7.24 ( 9 H, m), 5.08 ( 2 H, s), 4.30 – 4.28 ( 2 H, q) 1.30 – 1.34 ( 3 H, t); IR (KBr $\nu$ max cm$^{-1}$) 3365, 2963, 1696, 1676, 1619, 1560, 1453, 1332, 1284.

Figure

$^1$H NMR spectrum of 7-amino-3-benzyl-2,4-dioxo-1-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydropyrido [2,3-d]pyrimidine-6-carboxylate (Compound 2c)
IR spectrum of 7-amino-3-benzyl-2,4-dioxo-1-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydropyrido [2,3-d]pyrimidine-6-carboxylate (Compound 2c)

Synthesis of 7-amino-3-benzyl-2,4-dioxo-1-phenyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (Compound 3a)

A mixture of 5-cyano-3-benzyl-1-phenyluracil (0.5 g, 1.65 mmol) and malononitrile (0.91 ml, 1.65 mmol) was added in freshly prepared ethanolic sodium ethoxide (100 mg of metallic sodium in 15 ml of ethanol) and refluxed for 20 minutes. After cooling the mixture to room temperature, crystals precipitated out were collected by filtration and recrystallized from a mixture of N,N-dimethyl formamide:ethanol (20:80) to give yellow colored crystals of 7-amino-3-benzyl-2,4-dioxo-1-phenyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile. M.P. >280 ºC; ¹H NMR (400 MHz, δ ppm, DMSO-d₆) 8.45 (1 H, s), 7.70 (2 H, s), 7.55 – 7.23 (10 H, m), 5.07 (2 H, s); IR (KBr V_max cm⁻¹) 3445, 3336, 3059, 2967, 2223, 1710, 1664, 1603, 1560, 1493, 1285.
Figure

$^1$H NMR spectrum of 7-amino-3-benzyl-2,4-dioxo-1-phenyl-1,2,3,4-tetrahydro pyrido [2,3-d]pyrimidine-6-carbonitrile (Compound 3a)

Figure

IR spectrum of 7-amino-3-benzyl-2,4-dioxo-1-phenyl-1,2,3,4-tetrahydro pyrido [2,3-d]pyrimidine-6-carbonitrile (Compound 3a)
Synthesis of 7-amino-3-benzyl-1-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydro pyrido [2,3-d] pyrimidine-6-carbonitrile (Compound 3b)

A mixture of 5-cyano-3-benzyl-1-(4-methoxy-phenyl)uracil (0.5g, 1.5mmol) and malononitrile (0.91 ml, 1.65 mmol) was added to freshly prepared ethanolic sodium ethoxide (100 mg of metallic sodium in 15 ml of ethanol) and refluxed for 20 minutes. After cooling the mixture to room temperature, crystals precipitated out were collected by filtration and recrystallized from a mixture of N,N-dimethyl formamide:ethanol (20:80) to give yellow colored crystals of 7-amino-3-benzyl-1-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d] pyrimidine-6-carbonitrile. M.P. >280°C; ¹H NMR (400 MHz, δ ppm, CDCl₃ + DMSO-d₆) 8. 85 (1 H, s), 7.53 – 7.18 (9 H, m), 5.82 (2 H, s), 5.14 (2 H, s), 3.79 (3 H, s); IR (KBr V_max cm⁻¹) 3445, 3336, 3059, 2967, 2223, 1710, 1664, 1636, 1603, 1560, 1493, 1285.

Figure

¹H NMR spectrum of 7-amino-3-benzyl-1-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d] pyrimidine-6-carbonitrile (Compound 3b)
Synthesis of 7-amino-3-benzyl-2,4-dioxo-1-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine-6-carbonitrile (Compound 3c)
A mixture of 5-cyano-3-benzyl-1-(3-trifluoromethyl phenyl)uracil (0.5g, 1.35 mmol) and malononitrile (0.91 ml, 1.65 mmol) was added to freshly prepared ethanolic sodium ethoxide (100 mg of metallic sodium in 15 ml of ethanol) and refluxed for 20 minutes. After cooling the mixture to room temperature, crystals precipitated out were collected by filtration and recrystallized from a mixture of N,N-dimethylformamide:ethanol (20:80) to give yellow colored crystals of 7-amino-3-benzyl-2,4-dioxo-1-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine-6-carbonitrile. M.P. >280°C; $^1$H NMR (400 MHz, δ ppm, CDCl$_3$) 8.51 (1 H, s), 7.54 – 7.2 (9 H, m), 5.51 (2 H, s), 5.21 (2 H, s); IR (KBr $V_{max}$ cm$^{-1}$) 3332, 3208, 2928, 2834, 1716, 1654, 1602, 1598, 1441, 1326.

Figure
$IR$ spectrum of 7-amino-3-benzyl-1-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile(Compound 3b)

$^1$H NMR spectrum of 7-amino-3-benzyl-2,4-dioxo-1-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine-6-carbonitrile (Compound 3c)
IR spectrum of 7-amino-3-benzyl-2,4-dioxo-1-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine-6-carbonitrile (Compound 3c)

Figure

Synthesis of 7-amino-3-benzyl-1-phenylpyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione (Compound 4a)

A mixture of 5-cyano-3-benzyl-1-phenyluracil (0.5 g, 1.65 mmol) and thiourea (0.38 g, 4.95 mmol) were added to ethanolic sodium ethoxide (110 mg metallic sodium in 15 ml ethanol) and refluxed for 30 minutes. The solvent was removed under reduced pressure and the residue was triturated with a small amount of water. The resulting precipitate was collected by filtration, washed with water, and dried to give the 7-amino-3-benzyl-1-phenylpyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione. M.P. 265-267 ºC; $^1$H NMR (300 MHz, δ ppm, DMSO-d$_6$) 9.01 (1 H, s), 7.63 – 7.23 (10 H, m), 5.43 ( 2 H, s), 5.20 (2 H, s); $^{13}$C NMR (75 MHz, δ ppm, DMSO-d$_6$) 165.1, 160.6, 160.2, 158.2, 151.8, 136.7, 135.3, 129.2, 129.1, 128.7, 128.5, 128.3, 127.5, 98.9, 44.3; IR (KBr $V_{\text{max}}$ cm$^{-1}$) 3467, 3279, 3176, 1721, 1679, 1633, 1599, 1557, 1432, 1325.
Figure

$^1$H NMR spectrum of 7-amino-3-benzyl-1-phenylpyrimido [4,5-d]pyrimidine-2,4(1H,3H)-dione (Compound 4a)

Figure

$^{13}$C NMR spectrum of 7-amino-3-benzyl-1-phenylpyrimido [4,5-d]pyrimidine-2,4(1H,3H)-dione (Compound 4a)
Synthesis of 7-amino-3-benzyl-1-(4-methoxyphenyl)pyrimido[4,5-d]pyrimidine-2,4 (1H,3H)-dione (Compound 4b)

A mixture of the 5-cyano-3-benzyl-1-(4-methoxy-phenyl) uracil (0.5g, 1.5mmol) and thiourea (0.38 g, 4.95 mmol) were added to ethanolic sodium ethoxide (110 mg metallic sodium in 15 ml ethanol) and refluxed for 30 minutes. The solvent was removed under reduced pressure and the residue was triturated with a small amount of water. The resulting precipitate was collected by filtration, washed with water, and dried to give the 7-amino-3-benzyl-1-(4-methoxyphenyl)pyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione. M.P. >280 ºC; \(^1\)H NMR (400 MHz, δ ppm, DMSO-d\(_6\)) 8.77 (1 H, s), 7.51 (1 H, s), 7.49 – 7.24 ( 9 H, m), 5.05 ( 2 H, s), 3.83 ( 3 H, s); IR (KBr \(V_{\text{max}} \text{ cm}^{-1}\)) 3491, 3351, 3061, 2957, 1691, 1669, 1612, 1555, 1448, 1275.
Figure

$^1$H NMR spectrum of 7-amino-3-benzyl-1-(4-methoxyphenyl)pyrimido [4,5-d]pyrimidine-2,4(1H,3H)-dione (Compound 4b)

Figure

IR spectrum of 7-amino-3-benzyl-1-(4-methoxyphenyl)pyrimido [4,5-d] pyrimidine-2,4(1H,3H)-dione(Compound 4b)
Synthesis of 7-amino-3-benzyl-1-(3-(trifluoromethyl)phenyl)pyrimido[4,5-d] pyrimidine-2,4(1H,3H)-dione (Compound 4c)

A mixture of the 5-cyano-3-benzyl-1-(3-trifluoromethyl phenyl) uracil (0.5g, 1.35 mmol) and thiourea (0.38 g, 4.95 mmol) were added to ethanolic sodium ethoxide (110 mg metallic sodium in 15 ml ethanol) and refluxed for 30 minutes. The solvent was removed under reduced pressure and the residue was triturated with a small amount of water. The resulting precipitate was collected by filtration, washed with water, and dried to give the 7-amino-3-benzyl-1-(3-(trifluoromethyl)phenyl)pyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione. M.P. >280 ºC; IR (KBr $\nu_{max}$ cm$^{-1}$) 3467, 3279, 3176, 1696, 1676, 1615, 1560, 1453, 1284.

CONCLUSION

In conclusion, our results demonstrate a new, simple and efficient synthesis of novel, complex, diverse pyrido [2,3-d] pyrimidine and pyrimido [4,5-d] pyrimidine derivatives of biological significance with good yields. These results also illustrate that the 5-cyanouracils 1 are useful substrate for the generation of an array of fused nitrogen heterocycles.

ACKNOWLEDGEMENT

Author A.C. Lele is thankful to Council of Scientific and Industrial Research (New Delhi) and N.H.P. Desai is thankful to University Grants Commission (New Delhi) for financial assistance.
REFERENCES