
# An efficient and simple methodology for the synthesis of 2-amino-4-(*N*-alkyl/arylamino)-6-chloropyrimidines

Khalid Mohammed Khan, Sarosh Iqbal, Muhammad Arslan Bashir, Nida Ambreen, Shahnaz Perveen, Volfgang Voelter

PII: S0040-4039(15)00191-4
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.01.153
Reference: TETL 45823

To appear in: *Tetrahedron Letters*

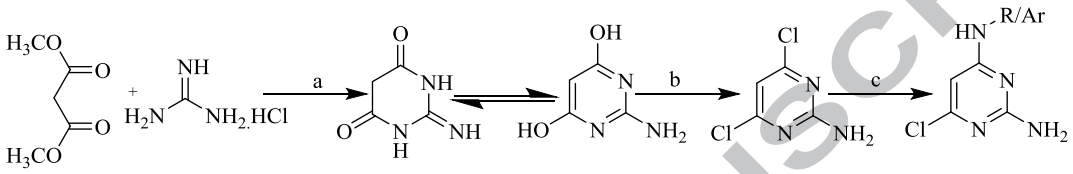
Received Date: 18 July 2014
Revised Date: 28 December 2014
Accepted Date: 22 January 2015

Please cite this article as: Khan, K.M., Iqbal, S., Bashir, M.A., Ambreen, N., Perveen, S., Voelter, V., An efficient and simple methodology for the synthesis of 2-amino-4-(*N*-alkyl/arylamino)-6-chloropyrimidines, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.01.153

## Graphical Abstract

**An efficient and simple methodology for the synthesis of 2-amino-4-(*N*-alkyl/arylamino)-6-chloropyrimidines**

Khalid Mohammed Khan,* Sarosh Iqbal, Muhammad Arslan Bashir, Nida Ambreen, Shahnaz Perveen, Wolfgang Voelter




(a) NaOMe, MeOH, reflux, (b) $POCl_3$, *N,N*-dimethylaniline, 60 °C, (c) $Et_3N$, $H_2NR/Ar$, fusion

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

# An efficient and simple methodology for the synthesis of 2-amino-4-(*N*-alkyl/arylamino)-6-chloropyrimidines

Khalid Mohammed Khan[a,*], Sarosh Iqbal[a], Muhammad Arslan Bashir[a], Nida Ambreen[a], Shahnaz Perveen[b], Volfgang Voelter[c]

[a] *H. E. J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi-75270, Pakistan*
[b] *PCSIR Laboratories Complex, Karachi, Shahrah-e-Dr. Salimuzzaman Siddiqui, Karachi-75280, Pakistan*
[c] *Interfakultäres Institut für Biochemie, Universität Tübingen, Hoppe-Seyler-Str. 4, D-72076 Tübingen, Germany*

ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted
Available online

*Keywords:*
2-Amino-4,6-dichloropyrimidine
Dimethylmalonate
Guanidine hydrochloride
Heterocycles
Nucleophilic substitution

ABSTRACT

In this study, twenty-nine 2-aminopyrimidine derivatives are synthesized in good to excellent yields by fusing 2-amino-4,6-dichloropyrimidine with different amines in the presence of triethylamine without using any solvent or catalyst. Nucleophilic substitution reactions of 2-amino-4,6-dichloropyrimidine with amines have also been performed in ethanol. Comparisons of the yields and reaction times for both solvent and solvent-free conditions have shown that the newly developed solvent-free protocol is high yielding, more efficient, and simpler compared to conventional methods.



Among heterocycles, pyrimidines constitute a pharmaceutically important nucleus which is the key constituent of a variety of bioactive compounds available by synthesis or from Nature, and are often of considerable complexity.[1-9] Amino- and imino-pyrimidines are constituents of various biological systems and play a significant role in many biological processes. They are constituents of DNA, RNA, B group vitamins, antibiotics, and vessel-expanding medicines, and correct heart action and stimulate metabolic processes.[10-14]

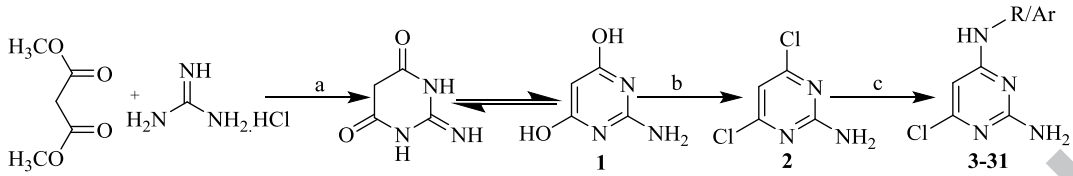
Therefore, syntheses of highly substituted pyrimidine rings have attracted significant attention from organic chemists. A number of protocols have been developed for the synthesis of substituted pyrimidines either by using a variety of substituted starting materials, or by substitution on newly synthesized pyrimidine rings. These procedures include condensation of cyanic acid with *N*-vinyl or *N*-arylamides in the presence of 2-chloropyridine and trifluoromethanesulfonic anhydride,[15] coupling of enamines, triethyl orthoformate and ammonium acetate using $ZnCl_2$ as the catalyst,[16] organolithium-promoted three-component approaches,[17,18] copper iodide and $PdCl_2(PPh_3)$ mediated substitutions on pyrimidine rings,[19,20] etc. Moreover, nucleophilic substitution of 2-amino-4,6-dichloropyrimidine leads to the formation of several complex structures, for example, 7-deazaguanine-based urea (DeUG)[21] and pteridines[22] have been synthesized by using 2-amino-4,6-dichloropyrimidines as intermediates. Some of these methods suffer from shortcomings such as tedious work-ups, low yields, the use of expensive and uncommon starting materials or catalysts, and non-eco-friendly solvents. Consequently, simpler, high yielding, and efficient approaches towards this valuable nucleus are still desirable.

We have developed a new and rapid route for the synthesis of substituted pyrimidine derivatives, *i.e.*, 2-amino-4-(*N*-alkyl/arylamino)-6-chloropyrimidines, without using any solvent or catalyst and starting from 2-amino-4,6-dichloropyrimidine, which was in turn synthesized from cheap and commercially available starting materials: guanidine hydrochloride and dimethyl malonate in the presence of sodium methoxide. 2-Amino-4-(*N*-alkyl/arylamino)-6-chloropyrimidine derivatives were also synthesized using ethanol as the solvent to compare the yields and reaction times of both strategies (see Figures 2 and 3).

2-Amino-4-(*N*-alkyl/arylamino)-6-chloropyrimidine derivatives **3-31** were synthesized in high yields in a three-step sequence. Firstly, commercially available guanidine hydrochloride and dimethyl malonate were reacted in the presence of sodium methoxide to yield 2-amino-4,6-dihydroxypyrimidine (**1**). This was then converted into 2-amino-4,6-dichloropyrimidine (**2**) on treatment with $POCl_3$ in the presence of *N*,*N*-dimethylaniline. Subsequently, a range of 2-amino-4-(*N*-alkyl/arylamino)-6-chloropyrimidine derivatives **3-31** was synthesized by nucleophilic substitution of 2-amino-4,6-dichloropyrimidine (**2**)

* Corresponding author. Tel.: 0092-21-34824910; fax: 0092-21-34819018; e-mail: khalid.khan@iccs.edu

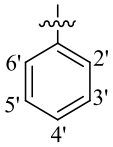
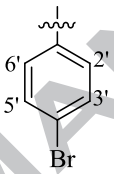
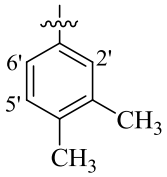
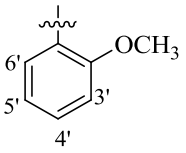
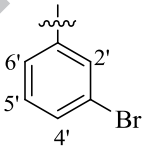
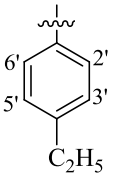
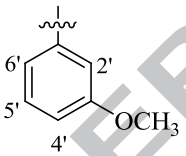
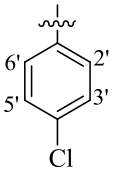
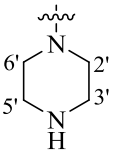
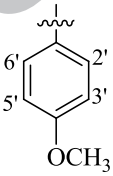
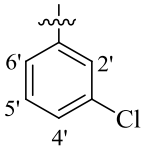
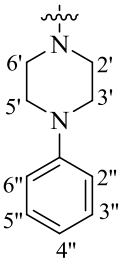
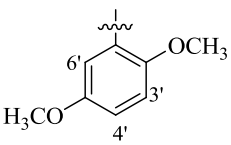
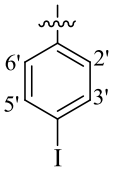
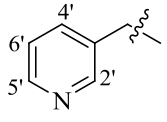
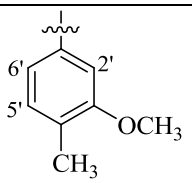
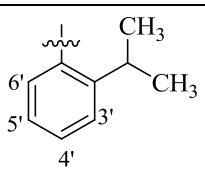
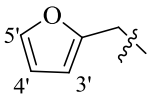
with substituted amines in the presence of triethylamine under solvent-free conditions[23] (Scheme 1). The structures of the compounds synthesized were confirmed by $^{1}H$ and $^{13}C$ NMR spectroscopy and by mass spectrometry.[24] The structures of the synthesized pyrimidine derivatives are shown in Table 1. Of the twenty-nine synthesized 2-amino-4-(*N*-alkyl/arylamino)-6-chloropyrimidine derivatives, compounds **4**, **5**, **7–12**, **14**, **17–22**, **24** and **26**, are novel.

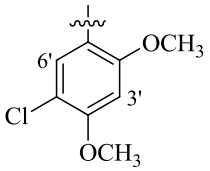
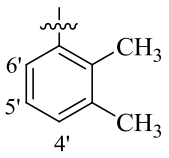
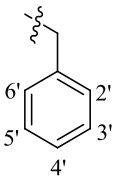
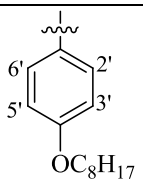
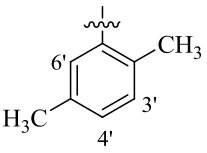
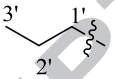
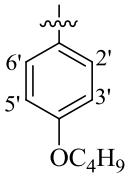
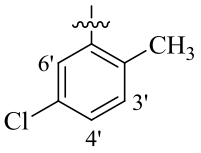
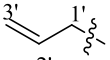
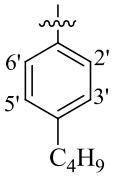
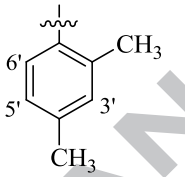



(a) NaOMe, MeOH, reflux, (b) $POCl_3$, *N,N*-dimethylaniline, 60 °C, (c) $Et_3N$, $H_2NR/Ar$, fusion

**Scheme 1**: Synthesis of 2-amino-4-(*N*-alkyl/arylamino)-6-chloropyrimidine derivatives

**Table 1:** Structures of the 2-amino-4-(*N*-alkyl/arylamino)-6-chloropyrimidine derivatives **3-31**

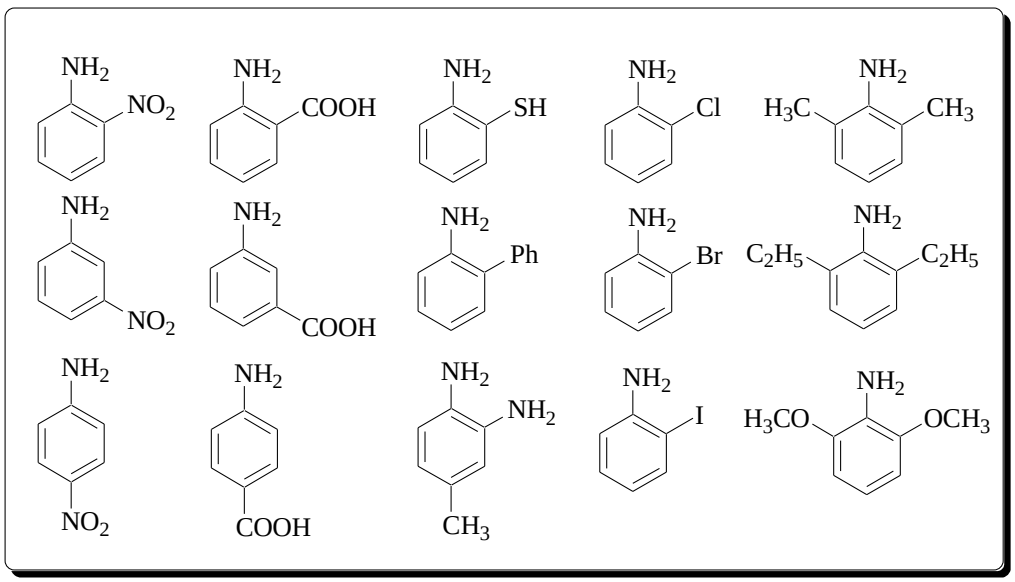
| Product | R | Mp (°C) | Product | R | Mp (°C) | Product | R | Mp (°C) |
|---|---|---|---|---|---|---|---|---|
| **3**[25] |  | 175-177 | **13**[25] |  | 190-192 | **23**[25] |  | 178-180 |
| **4** |  | 240-242 | **14** |  | 180-182 | **24** |  | 172-174 |
| **5** |  | 178-180 | **15**[26] |  | 182-184 | **25**[27] |  | >300 |
| **6**[25] |  | 222-223 | **16**[25] |  | 177-179 | **26** |  | 200-202 |
| **7** |  | 182-184 | **17** |  | 250-252 | **27**[28] |  | 210-212 |
| **8** |  | 245-247 | **18** |  | 170-172 | **28**[28] |  | 140-142 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **9** |  | 185-187 | **19** |  | 176-178 | **29**[29] |  | 255-257 |
| **10** |  | 185-187 | **20** |  | 173-175 | **30**[30] |  | 257-258 |
| **11** |  | 180-182 | **21** |  | 175-177 | **31**[31] |  | 116-118 |
| **12** |  | 175-177 | **22** |  | 178-180 | - | - | - |

During the course of this work, we observed that 2-nitroaniline did not undergo the nucleophilic substitution reaction with 2-amino-4,6-dichloropyrimidine, and we assumed that this may have been due to the electron-withdrawing nature of the nitro group, which decreases the nucleophilicity of the amino group in nitroaniline. In order to confirm our hypothesis, we performed reactions with other anilines possessing electron-withdrawing substituents. We observed that all the nitro- and carboxyl group containing anilines examined failed to produce the required product. In the case of halogen-substituted compounds, we discovered the following behavior of the differently substituted haloanilines: 2-chloro-, 2-bromo-, and 2-iodoanilines did not undergo any reaction, however, 3-bromo-, 4-bromo-, 3-chloro-, 4-chloro-, and 4-iodo- gave the expected products in satisfactory yields.

This interesting situation set a new direction to our research: we assumed that 2-chloro-, 2-bromo-, and 2-iodoanilines were unable to yield the required product due to their electron-withdrawing nature and due to steric hindrance which hampers the approach of the nucleophile to the electrophilic center. To validate our assumption, we focused on anilines with bulky groups at both the 2 and 6 positions. 2,6-Disubstituted anilines, regardless of the electron-withdrawing or electron-donating nature of the substituents, did not undergo any reaction even after prolonged heating. However, if the aniline was only singly 2- or 6-substituted then, depending on the electronic nature and size of the substituent, it underwent nucleophilic substitution. A list of anilines that did not undergo this reaction is given (Figure 1).

**Figure 1:** Examples of anilines that did not undergo the nucleophilic substitution reaction with 2-amino-4,6-dichloropyrimidine



The last step was also repeated using ethanol as the solvent, and was found to be more time-consuming and lower yielding compared to solvent-free conditions. Moreover, in some cases, the reaction was not complete even after 24 hours and therefore column chromatography was performed to purify the resulting crude products. Comparisons of the reaction times and yields are given in Figures 2 and 3.

In conclusion, a simple and efficient protocol for the synthesis of 2-amino-4-(*N*-alkyl/arylamino)-6-chloropyrimidines has been developed using readily available starting materials. The newly developed method shows advantages in terms of its simplicity, short reaction times and high yields. Furthermore, this protocol does not require any expensive catalyst.

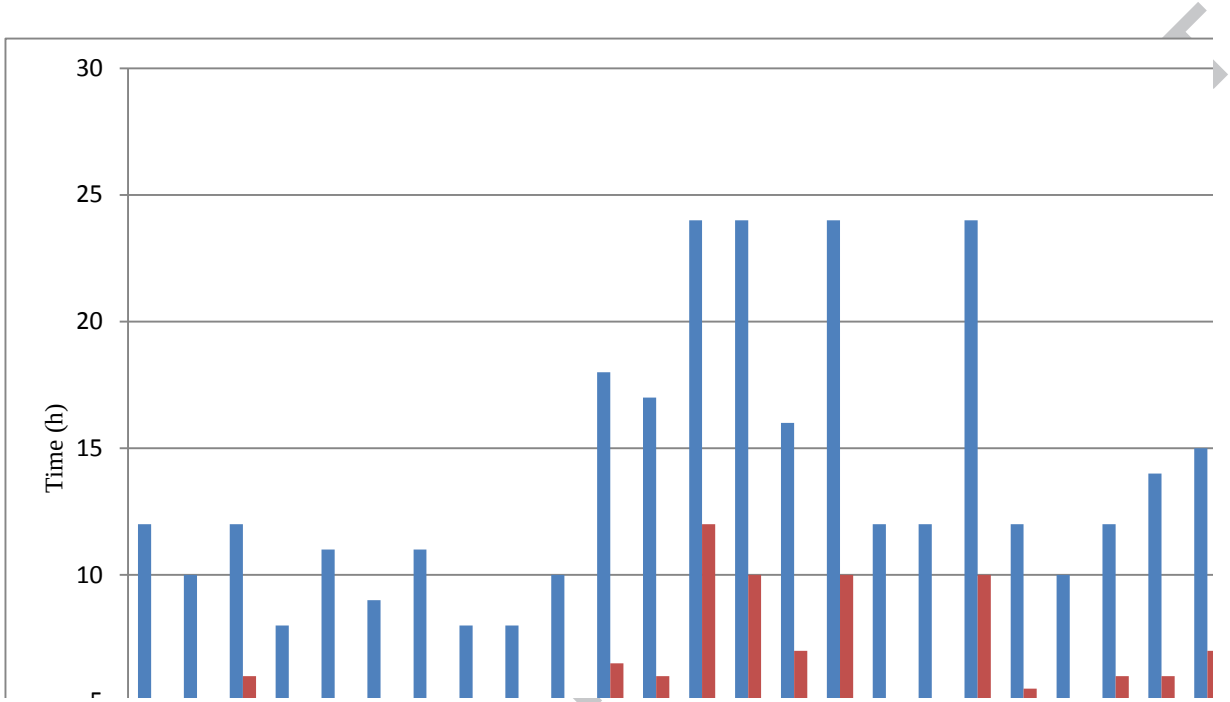



**Figure 2:** Comparison of the reaction time (h) for the syntheses performed in EtOH and under solvent-free conditions, respectively.

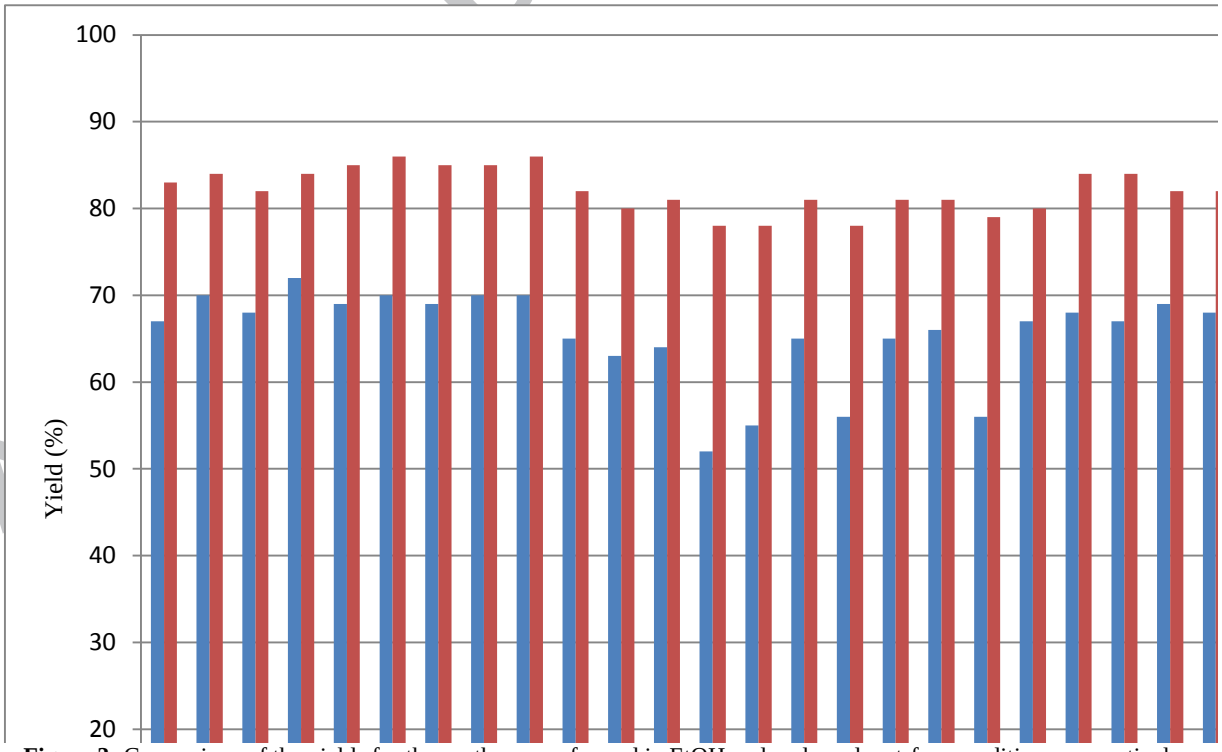



**Figure 3:** Comparison of the yields for the syntheses performed in EtOH and under solvent-free conditions, respectively.

**Acknowledgements:** The authors are thankful to the Organization for Prohibition of Chemical Weapons (OPCW), The Netherlands (Project No. L/ICA/ICB/173681/12) for financial support and DAAD (Deutscher Akademischer Austauschdienst), Bonn, Germany, for granting a fellowship to Prof. Dr. Khalid Mohammed Khan.

**Supplementary data:** supplementary data associated with this manuscript can be found in the online version, at http://dx.doi.org. These data include synthetic procedures and characterization data of all the compounds reported in the manuscript

**References and Notes**


1. Mohammed, S. K.; Soliman, A, M.; El-Remaily, M. A.; Abdel-Ghany, H. *Chem. Sci. J.* **2013**, *110*, 1.
2. Kappe C. O. *Tetrahedron*, **1993**, *49*, 6937.
3. Russowsky, D.; Canto, R. F. S.; Sanches, S. A. A.; D'Oca, M. G. M.; de Fátima, Â.; Pilli, R. A. *Bioorg. Chem.* **2006**, *34*, 173.
4. Cho, H.; Ueda, M.; Shima, K.; Mizuno, A.; Hayashimatsu, M.; Ohnaka, Y. *J. Med. Chem.* **1989**, *32*, 2399.
5. Joffe, A. M.; Fareley, J. D.; Lindon, D.; Goldsand, G. *Am. J. Med.* **1989**, *87*, 332.
6. Rosowsky, A.; Frosch, R. A.; Friesheim, J. H.; Moran, R. G. *J. Med. Chem.* **1989**, *32*, 517.
7. Gangjee, A.; Zeng, Y.; McGuire, J. J.; Mehraein, F.; Kiliuk, R. L. *J. Med. Chem.* **2004**, *47*, 6893.
8. Hu, E. H.; Sidler, D. R.; Dolling, U. H. *J. Org. Chem.* **1998**, *63*, 3454.
9. Chauhan, N.; Nimavat, K.; Vyas, K. *Der. Pharm. Sinica* **2012**, *3*, 394.
10. Borisenko, V. E.; Krekov, S. A.; Niyazova, M. A.; Koll, A.; Lipkowski, P. *Vib. Spectrosc*. **2005**, *37*, 97.
11. El-Gengaighi, S.; Karawya, M. S.; Motawe, H. M.; Ibrahim, N.; Faddah, L. M. *Pharmazie* **1995**, *50*, 361.
12. Fox, J. J.; Bloch, A.; Watanabe, K. A. *Prog. Nucl. Acid Res. Mol. Biol.* **1966**, *5*, 251.
13. Bendiritter, P.; de Araujo Junior, J. X.; Schmidt, M.; Bourgignon, J.-J. *Tetrahedron* **2007**, *63*, 12465.
14. Rospenk, M.; Koll, A. *J. Mol. Struct.* **2007**, *844-845*, 232.
15. Ahmad, O. K.; Hill, M. D.; Movassaghi, M. *J. Org. Chem.* **2009**, *74*, 8460.
16. Sasada, T.; Kobayashi, F.; Sakai, N.; Konakahara, T. *Org. Lett.* **2009**, *11*, 2161.
17. Wang, Z.; Wang, Y.; Zhang, W. X.; Hou, Z.; Xi, Z. *J. Am. Chem. Soc.* **2009**, *131*, 15108.
18. Lechel, T.; Mohl, S.; Reissig, H.-U. *Synlett* **2009**, 1059.
19. Deng, X.; Mani, N. *Org. Lett.* **2006**, *8*, 269.
20. Hockova, D.; Holy, A.; Masojidkova, T.; Votruba, I. *Tetrahedron* **2004**, *60*, 4983.
21. Kuykendall, D. W.; Anderson, C. A.; Zimmerman, S. C. *Org. Lett*. **2009**, *11*, 61.
22. Elion, G. B.; Hitchings, G. H. *J. Am. Chem. Soc.* **1953**, *75*, 4311.
23. General procedure for the synthesis of 2-amino-4-(*N*-alkyl/arylamino)-6-chloropyrimidine derivatives **3**-**31** under solvent-free conditions: finely ground 2-amino-4,6-dichloropyrimidine (**2**) (3 mmol), substituted amine (3 mmol), and $Et_3N$ (6 mmol) were added to a round-bottomed flask and heated. The reaction was monitored by TLC (hexane–EtOAc). After completion, distilled $H_2O$ was added and the precipitate obtained was filtered. In most cases, single spot products were obtained, thereby crystallization was not needed. In a few cases, where precipitates were not formed upon addition of $H_2O$, the solvent was evaporated under vacuum and the resulting crude material was crystallized from EtOH.
24. Characterization data of compound **4**: Yield: 84%; solid, m.p. 240-242 °C; $R_f$: 0.57 (EtOAc–hexanes, 4:6); $^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.49 (s, 1H, NH), 8.01 (d, $J_{6',5'}$ = 8.0 Hz, 1H, H-6'), 7.05 (m, 2H, H-3',4'), 6.92 (dt, $J_{5',4'} = J_{5',6'}$ = 8.0 Hz, $J_{5',3'}$ = 2.4 Hz, 1H, H-5'), 6.58 (s, 2H, $NH_2$), 6.13 (s, 1H, H-5), 3.81 (s, 3H, $OCH_3$). EI-MS *m/z* (rel. int. %): 250.04 ($M^+$, 11.2), 252 ($M^+$ + 2, 3.7), 219 (100), 172 (6.2), 158 (11.6), 128 (6); HR-EIMS calcd for $C_{11}H_{11}ClN_4O$: 250.0621; observed 250.0619.
25. Characterization data of compound **30**: Yield: 89%; solid, m.p. 257-258 °C; $R_f$: 0.52 (EtOAc–hexanes, 3:7); $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.08 (s, 1H, NH), 6.34 (s, 2H, $NH_2$), 5.71 (s, 1H, H-5), 3.17 (br s, 2H, 2×H-1'), 1.50 (m, 2H, H-2'), 0.88 (t, 3H, H-3'); EI MS: *m/z* (rel. abund. %) 186 ($M^+$, 50.7), 188 ($M^+$ + 2, 17.2), 171 (22.3), 157 (100), 128 (11.9); HR-EIMS calcd for $C_7H_{11}ClN_4$: 186.0672; observed: 186.0676.
25. O'Brien, D. E.; Baiocchi, F.; Robins, R. K.; Cheng, C. C. *J. Org. Chem*. **1962**, *27*, 1104.
26. Bhatt, R.; Gong, B.; Hong, F.; Jenkins, S. A.; Klein, J. P.; Kohm, C. T.; Tulinsky, J. US 20040204386, **2004**; *Chem. Abstr*. **2004**, *141*, 350185.
27. Ge, H.-X.; Wang, L.-C.; Jiang, Z.-Z.; Ni, S.-L. *Arzneimittel-Forsch*. **2006**, *56*, 673.
28. Mengel, R.; Schroeder, L.; Stransky, W.; Linden, G.; Schneider, G. DE 3717480, **1988**; *Chem. Abstr*. **1990**, *112*, 7500.
29. Sander, K.; Kottke, T.; Kulu, Y. T.; Proschak, E.; Weizel, L.; Schneider, E. H.; Seifert, R.; Schneider, G.; Stark, H. *Bioorg. Med. Chem*. **2009**, *17*, 7186.
30. Noell, C. W.; Robins, R. K. *J Med. Pharm. Chem*. **1962**, *5*, 558.
31. Konkel, M. J.; Vince, R. *J. Org. Chem*. **1996**, *61*, 6199.