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New HA 14-1 analogues: synthesis of 2-amino-4-cyano-4*H*-chromenes

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ABSTRACT

The synthesis of 2-amino-4-cyano-4*H*-chromene derivatives as new HA 14-1 analogues by a simple and efficient method is reported. In addition, the reaction of 2-amino-2*H*-chromene-3-carbonitriles, salicylaldehydes and amines results in the formation of new chromeno[2,3-*d*]pyrimidine derivatives.

Multicomponent reactions (MCRs), in which multiple reactions are combined into a single synthetic operation have been used extensively to form carbon–carbon bonds in synthetic chemistry.[1,2] Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single step, thus avoiding complicated purification operations and allowing savings of both solvents and reagents.[3,4] Heterocycles containing the chromene moiety show interesting features that make them attractive targets for MCRs.

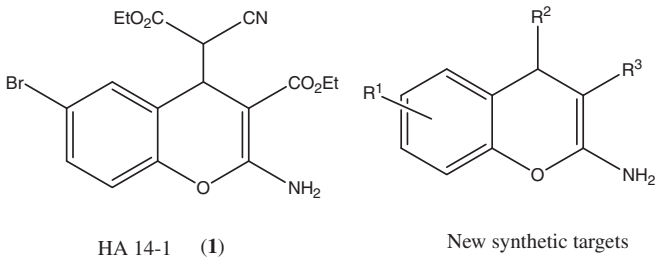
Chromenes constitute a major class of naturally occurring compounds, and interest in their chemistry continues because of their utility as biologically active agents.[5,6] They occur widely in plants, including edible vegetables and fruits.[7] Synthetic chromene analogues have been developed over the years, and some of them have been employed as pharmaceuticals,[8] including antifungal[9] and antimicrobial agents.[10] 2-Aminochromenes are employed as pigments,[11] cosmetics, agrochemicals[12] and are major constituents of many natural products.

Recently, 4*H*-chromene (**1**, Fig. 1) (HA 14-1) was discovered, and was found to display binding activity for the surface pocket of the Bcl-2 protein (IC_{50} = 9 μM) and it induces apoptosis of tumor cells.[13] Bcl-2 and a family of related proteins regulate apoptosis or programmed cell death, and are implicated in a number of human diseases such as cancer.[14,15] Specifically, Bcl-2 can contribute to neoplastic cell expansion by preventing normal cell turnover caused by physiological cell death mechanisms. The discovery of Bcl-2 binding compound **1** provides a promising lead for the development of new analogues as potential anti-cancer agents. Therefore, numerous studies have reported the synthesis of new analogues of HA 14-1 (see general structure, Fig. 1).[16–19]

Multicomponent reactions of salicylaldehydes, malononitrile and various nucleophiles have attracted the interest of researchers in order to prepare different analogues of HA 14-1. The synthesis of indolyl chromenes was reported by Shanthi and Perumal using indoles as the nucleophiles.[20] A recent publication described the preparation of new chromene phosphonic acid diethyl esters by reaction of salicylaldehydes, malononitrile and triethyl phosphite.[21]

As part of our program aimed at developing new methods for the preparation of heterocyclic compounds,[22–30] we report an efficient and simple synthesis of new analogues of HA 14-1.

Iminochromenes **3a**–**n** were prepared via Knoevenagel condensation of salicylaldehydes **1a**–**g** and malononitrile (**2a**) or cyanoacetamide (**2b**) using the known procedure.[31,32] In order to prepare new HA 14-1 analogues, we carried out the reaction of iminochromenes **3a**–**n** with trimethylsilyl cyanide (**4**) (TMSCN) in the presence of $LiClO_4$ (15 mol %) as the catalyst which afforded 2-amino-4-cyano-



HA 14-1 (**1**) New synthetic targets

Figure 1. HA 14-1 and designed analogues.

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E-mail address: a_bazgir@sbu.ac.ir (A. Bazgir).

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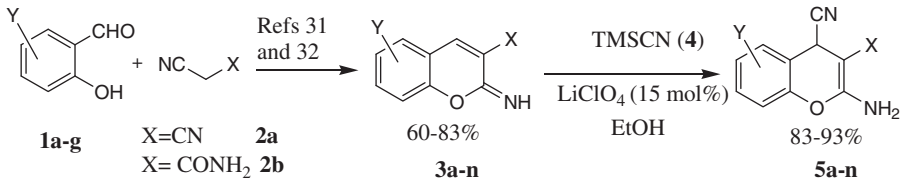


Scheme 1.

Table 1
Two-step synthesis of 2-amino-4-cyano-4*H*-chromenes **5**

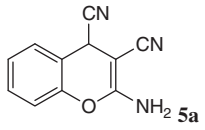
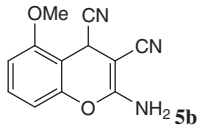
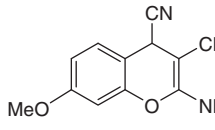
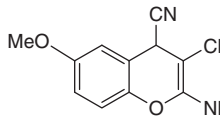
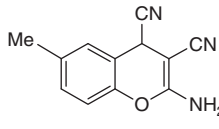
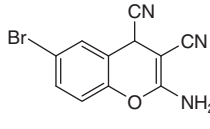
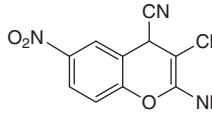
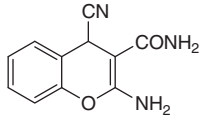
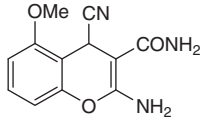
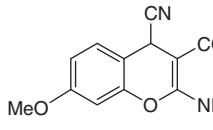
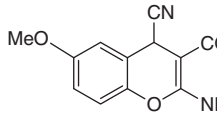
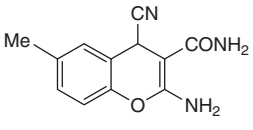
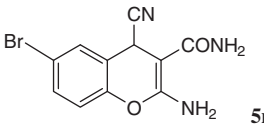
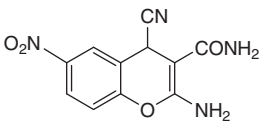
Entry	Product	Time (h)	Yield[a] (%)	Yield[b] (%)
1	 **5a**	3	93	82
2	 **5b**	3.5	89	80
3	 **5c**	4	87	87
4	 **5d**	7	85	83
5	 **5e**	6	83	80
6	 **5f**	6	80	79
7	 **5g**	5	77	73
8	 **5h**	3	91	49
9	 **5i**	5	83	50
10	 **5j**	5	85	48
11	 **5k**	6	88	51

Table 1 (*continued*)

Entry	Product	Time (h)	Yield[a] (%)	Yield[b] (%)
12	 **5l**	5	80	47
13	 **5m**	4.5	81	44
14	 **5n**	4	78	41

[a] Two-step method.
[b] Three-component method.

4*H*-chromenes **5a**–**n** in good yields after 3–7 h in EtOH at room temperature (Scheme 1). The results are summarised in Table 1.

To develop a one-pot, three-component synthesis of 2-amino-4-cyano-4*H*-chromenes **5a**–**n**, we studied the reaction of salicylaldehydes **1a**–**g**, malononitrile (**2a**) or cyanoacetamide (**2b**) and TMSCN (**4**) under similar conditions ($LiClO_4$, EtOH) (Scheme 2).[33] As indicated in Table 1, the desired products were obtained in good yields with **2a**, and moderate yields with **2b** after 24 h. It is noteworthy that without $LiClO_4$ the products were obtained in only trace amounts, even after 48 h.

The nature of these compounds as 1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate *m*/*z* values. Compounds **5a**–**n** are stable solids the structures of which were established by IR, ^1H and ^{13}C NMR spectroscopy and elemental analysis.

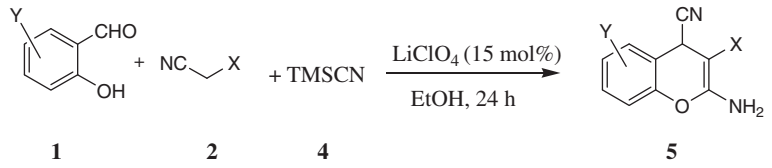
To further explore the potential of this three-component protocol for fused aminochromene synthesis, we replaced salicylaldehyde **1** with 2-hydroxynaphthalene-1-carboxaldehyde (**6**) and obtained 3-amino-1*H*-benzo[*f*]chromenes **7a**, and **b** as the products in good yields (Scheme 3).

To the best of our knowledge, this procedure provides the first example of an efficient and three-component synthesis of 2-amino-4-cyano-4*H*-chromenes.

Mechanistically, it is reasonable to assume that product **5** results from initial Knoevenagel condensation of salicylic aldehydes **1** and cyano compound **2** and subsequent Pinner reaction (**8**→**9**). Next, the resulting intermediate **9** could be attacked by TMSCN **4** to produce the product **5** (Scheme 4).[21]

During our investigation on the synthesis of new chromene derivatives, we found that reaction of 2-imino-2*H*-chromene-3-carbonitrile (**3a**), salicylaldehyde (**1a**) and amines **10a**–**e**, under similar conditions, afforded 2-[4-(alkylamino)-5*H*-chromeno[2,3-*b*]pyrimidin-2-yl]phenols **11a**–**e** in good yields after 15 h (Table 2).[34]

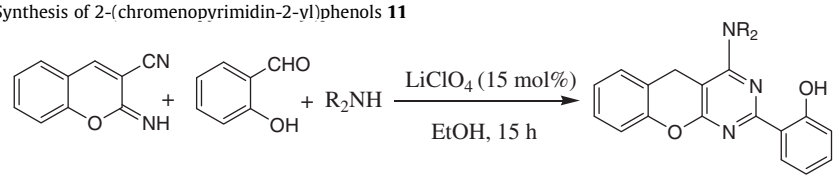
Although we have not established an exact mechanism for the formation of chromenopyridines **11**, a possible explanation is pro-



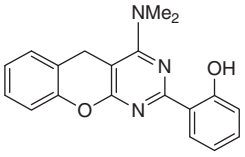
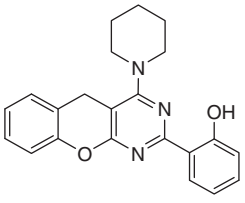
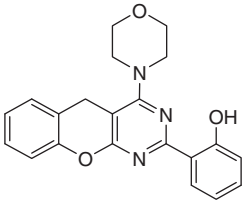
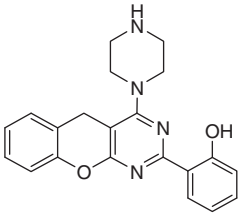
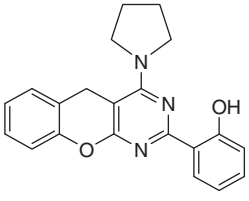
1 **2** **4** **5**

Scheme 2.

Table 2
Synthesis of 2-(chromenopyrimidin-2-yl)phenols **11**

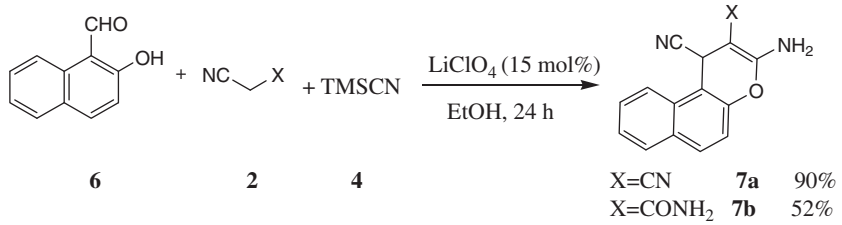


3a **1a** **10a-e** **11a-e**

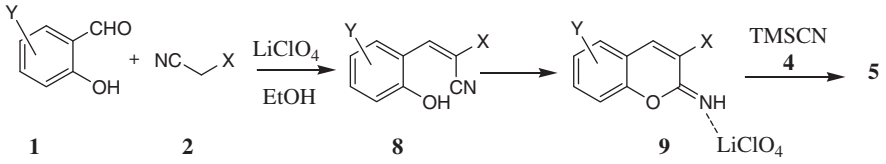
Entry	Product	Yield (%)
1	 **11a**	74
2	 **11b**	79
3	 **11c**	77
4	 **11d**	80
5	 **11e**	76

posed in Scheme 5. The reaction is initiated by nucleophilic attack of amines **10** on the cyano group of **3a**. Next, cyclization with salicylaldehyde (**1a**), followed by tautomerization afforded the products **11**.

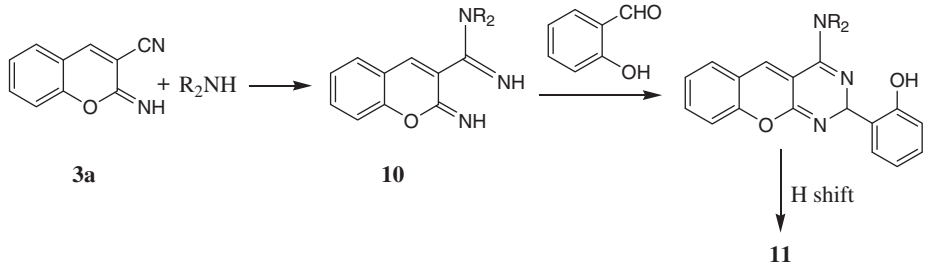
In conclusion, we have described a facile three-component method for the synthesis of 2-amino-4-cyano-4*H*-chromenes by reaction of salicylaldehydes, malononitrile or cyanoacetamide and TMSCN at room temperature. Furthermore, a new synthesis of 2-(chromeno[2,3-*b*]pyrimidin-2-yl)phenol derivatives by the one-pot condensation of 2-imino-2*H*-chromene-3-carbonitrile, salicylaldehyde and amines has been reported.



Scheme 3.



Scheme 4.



Scheme 5.

Acknowledgement

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References and notes

1. Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169.
2. Tietze, L. F.; Modi, A. *Med. Chem. Res.* **2000**, *20*, 304.
3. Nair, V.; Vinod, A. U.; Rajesh, C. *J. Org. Chem.* **2001**, *66*, 4427.
4. List, B.; Castello, C. *Synlett* **2001**, 1687.
5. Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 1765.
6. Kumar, P.; Bodas, M. S. *Org. Lett.* **2000**, *2*, 3821.
7. Curini, M.; Cravotto, G.; Epifano, F.; Giannone, G. *Curr. Med. Chem.* **2006**, *13*, 199.
8. Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. *Curr. Med. Chem.* **2005**, *12*, 887.
9. Tangmouo, J. G.; Meli, A. L.; Komguem, J.; Kuete, V.; Ngounou, F. N.; Lontsi, D.; Beng, V. P.; Choudhary, M. I.; Sondengam, B. L. *Tetrahedron Lett.* **2006**, *47*, 3067.
10. Kraus, G. A.; Kim, I. *J. Org. Chem.* **2003**, *68*, 4517.
11. Ellis, G. P. In *The Chemistry of Heterocyclic Compounds. Chromenes, Chromanes, and Chromones*; Weissberger, A., Taylor, E. C., Eds.; John Wiley: New York, 1977; pp 11–141. Chapter II.
12. Hafez, E. A.; Elnagdi, M. H.; Elagamey, A. G. A.; El-Taweel, F. M. A. A. *Heterocycles* **1987**, *26*, 903.
13. Wang, J. L.; Liu, D.; Zhang, Z.; Shan, S.; Han, X.; Srinvasula, S. M.; Croce, C. M.; Alnemeri, E. S.; Huang, Z. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 7124.
14. Adams, J.; Cory, S. *Science* **1998**, *281*, 1322.
15. Thompson, C. B. *Science* **1995**, *267*, 1456.
16. Yavari, I.; Djahaniani, H.; Nasiri, F. *Tetrahedron* **2003**, *59*, 9409.
17. Costa, M.; Areias, F.; Abrunhosa, L.; Venâncio, A.; Proença, F. *J. Org. Chem.* **2008**, *73*, 1954.
18. Yu, N.; Aramini, J. M.; Germann, M. W.; Huang, Z. *Tetrahedron Lett.* **2000**, *41*, 6993.
19. Grée, D.; Vorin, S.; Manthati, V. L.; Caijo, F.; Viault, G.; Manero, F.; Juin, P.; Grée, R. *Tetrahedron Lett.* **2008**, *49*, 3276.
20. Shanthi, G.; Perumal, P. T. *Tetrahedron Lett.* **2007**, *48*, 6785.
21. Jayashree, P.; Shanthi, G.; Perumal, P. T. *Synlett* **2009**, 917.
22. Bazgir, A.; Mohammadi Khanaposhtani, M.; Abolhasani Soorki, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5800.
23. Bazgir, A.; Seyyedhamzeh, M.; Yasaei, Z.; Mirzaei, P. *Tetrahedron Lett.* **2007**, *48*, 8790.
24. Sayyafi, M.; Seyyedhamzeh, M.; Khavasi, H. R.; Bazgir, A. *Tetrahedron* **2008**, *64*, 2375.
25. Ghahremanzadeh, R.; Imani Shakibaei, G.; Bazgir, A. *Synlett* **2008**, 1129.
26. Jadidi, K.; Ghahremanzadeh, R.; Bazgir, A. *Tetrahedron* **2009**, *65*, 2005.
27. Dabiri, M.; Azimi, S. C.; Khavasi, H. R.; Bazgir, A. *Tetrahedron* **2008**, *64*, 7307.
28. Jadidi, K.; Ghahremanzadeh, R.; Bazgir, A. *J. Comb. Chem.* **2009**, *11*, 341.
29. Ghahremanzadeh, R.; Ahadi, S.; Sayyafi, M.; Bazgir, A. *Tetrahedron Lett.* **2008**, *49*, 4479.
30. Ghahremanzadeh, R.; Sayyafi, M.; Ahadi, S.; Bazgir, A. *J. Comb. Chem.* **2009**, *11*, 393.
31. Borisov, A. V.; Dzhavakhishvili, S. G.; Zhuravel, I. O.; Kovalenko, S. M.; Nikitchenko, V. M. *J. Comb. Chem.* **2007**, *9*, 5.
32. Volmajer, J.; Toplak, R.; Leban, I.; Le Marechal, A. M. *Tetrahedron* **2005**, *61*, 7012.
33. *Typical procedure for the preparation of 2-amino-4H-chromene-3,4-dicarbonitrile* (**5a**). A mixture of 2-hydroxybenzaldehyde (1 mmol), malononitrile (1 mmol), TMSCN (1 mmol) and $LiClO_4$ (15 mol %) in EtOH (5 ml) was stirred for 24 h (the progress of the reaction was monitored by TLC). After completion, the mixture was filtered and the precipitate washed with H_2O (2 × 5 ml) and the residue recrystallised from EtOH to afford pure **5a**. Grey powder (82%); mp: 180 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 3385, 3320, 2193, 1654. MS (EI, 70 eV) *m*/*z*: 197 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 5.35 (1H, s, CH), 7.10–7.45 (4H, m, H-Ar), 7.53 (2H, s, NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 27.4, 47.7, 115.0, 117.2, 119.4, 120.2, 125.9, 129.1, 130.8, 148.6, 161.8. Anal. Calcd for $C_{11}H_7N_3O$: C, 67.00; H, 3.58; N, 21.31. Found: C, 66.89; H, 3.50; N, 21.38. *2-Amino-6-methyl-4H-chromene-3,4-dicarbonitrile* (**5e**). Grey powder (83%); mp: 165–168 °C. IR (KBr) (ν_{max}/cm^{-1}): 3380, 3321, 2197, 1651. MS (EI, 70 eV) *m*/*z*: 211 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.28 (3H, s, CH_3), 5.27 (1H, s, CH), 6.98–7.21 (3H, m, H-Ar), 7.48 (2H, s, NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 20.5, 27.5, 47.7, 114.5, 116.9, 119.5, 120.3, 125.0, 131.3, 135.3, 146.6, 161.9. Anal. Calcd for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.11; H, 4.35; N, 19.80. *2-Amino-4-cyano-5-methoxy-4H-chromene-3-carboxamide* (**5i**). Grey powder; mp: 220 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 3464, 3307, 2228, 1660. MS (EI, 70 eV) *m*/*z*: 245 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.84 (3H, s, CH_3), 5.29 (1H, s, CH), 6.87 (3H, br s, H-Ar and NH_2), 7.09–7.18 (2H, m, H-Ar), 8.12 (2H, s, NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 27.0, 56.3, 69.6, 113.0, 118.2, 119.8, 121.0, 125.4, 138.7, 147.8, 160.2, 170.2. Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.65; H, 4.59; N, 17.03. *2-*

Amino-6-bromo-4-cyano-4H-chromene-3-carboxamide (**5m**). Cream powder; mp: 138 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 3460, 3311, 2221, 1663. MS (EI, 70 eV) *m*/*z*: 294 (M^++2), 292 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 5.32 (1H, s, CH), 6.89 (2H, br s, NH_2), 7.10–7.61 (3H, m, H-Ar), 8.10 (2H, s, NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 26.8, 69.4, 116.9, 119.3, 119.8, 120.6, 131.3, 133.4, 148.6, 159.9, 169.9. Anal. Calcd for $C_{11}H_8BrN_3O_2$: C, 44.92; H, 2.74; N, 14.29. Found: C, 44.83; H, 2.69; N, 14.23. *3-Amino-1H-benzo[f]chromene-1,2-dicarbonitrile* (**7a**). Grey powder; mp: 219 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 3379, 3310, 3196, 2187, 1651. MS (EI, 70 eV) *m*/*z*: 247 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 5.85 (1H, s, CH), 7.29–8.08 (8H, m, H-Ar and NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 25.4, 48.3, 107.6, 117.2, 119.5, 119.9, 123.2, 126.2, 128.5, 129.1, 129.8, 131.0, 131.7, 146.9, 161.6. Anal. Calcd for $C_{15}H_9N_3O_4$: C, 72.87; H, 3.67; N, 16.99. Found: C, 72.75; H, 3.58; N, 16.91.

34. *Typical procedure for the preparation of 2-[4-(dimethylamino)-5H-chromeno[2,3-d]pyrimidin-2-yl]phenol* (**11a**). A mixture of 2-hydroxybenzaldehyde (1 mmol), 2-imino-2*H*-chromene-3-carbonitrile (1 mmol), dimethylamine (1 mmol) and $LiClO_4$ (15 mol %) in EtOH (5 ml) was stirred for 15 h (the progress of the reaction was monitored by TLC). After completion, the mixture was filtered and the precipitate washed with H_2O (2 × 5 ml) and EtOH (5 ml) to afford pure product **11a**. White powder (74%); mp: 177–179 °C. IR (KBr) (ν_{max}/cm^{-1}): 3427, 3048, 1608. MS (EI, 70 eV) *m*/*z*: 319 (M^++1). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.18 (6H, s, $N(CH_3)_2$), 4.15 (2H, s, CH_2), 6.88 (2H, br s, H-Ar), 7.12 (2H, br s, H-Ar), 7.27 (3H, br s, H-Ar), 8.22 (1H, br s, H-Ar), 13.36 (1H, s, OH). Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.58; H, 5.28; N, 13.07. (Due to the very low solubility of product **11a**, we were unable to obtain a ^{13}C NMR spectrum for this product). *2-[4-(Piperidin-1-yl)-5H-chromeno[2,3-d]pyrimidin-2-yl]phenol* (**11b**). White powder (79%); mp: 168–170 °C. IR (KBr) (ν_{max}/cm^{-1}): 3416, 3064, 2933, 1608. MS (EI, 70 eV) *m*/*z*: 359 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.69 (6H, s, $3CH_2$), 3.48 (4H, s, $2CH_2$), 3.99 (2H, s, CH_2), 6.89–6.95 (2H, m, H-Ar), 7.13–7.20 (2H, m, H-Ar), 7.26–7.39 (3H, m, H-Ar), 8.26 (1H, d, $^3J_{HH}$ = 6.0 Hz, H-Ar), 13.28 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 24.3, 25.3, 26.0, 49.2, 97.8, 116.8, 117.8, 118.6, 119.3, 120.6, 125.0, 128.6, 129.1, 129.5, 133.3, 150.4, 160.3, 161.0, 163.8, 146.8. Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.43; H, 5.81; N, 11.76.