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**Graphical abstract:**

**One-Pot Three-Component Synthesis of fully substituted 1H-chromeno[2,3-d]pyrimidine-5-carboxamide derivatives**

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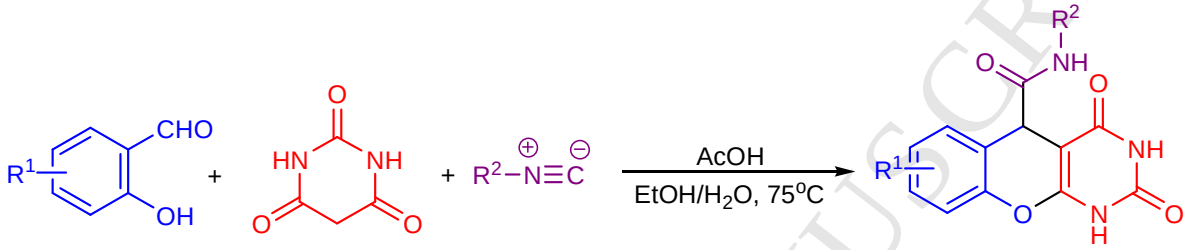

# Novel Isocyanide-Based Three-Component Reaction: A Facile Synthesis of Substituted 1H-chromeno[2,3-d]pyrimidine-5-carboxamides

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**Abstract**

A mild and efficient method for the synthesis of 1H-chromeno[2,3-d]pyrimidine-5-carboxamide derivatives via a one-pot, three-component reaction of an isocyanide, barbituric acid and a salicylaldehyde in the presence of acetic acid in ethanol/water mixture at 75 ˚C is reported. This high atom economy reaction led to the construction of one benzopyran ring, and one amide group in a single synthetic step.

*Keywords:* Chromeno[2,3-d]pyrimidine, Multi-component reactions, Benzopyran, Salicylaldehyde, Barbituric acid, Isocyanide.

## 1. Introduction

Multicomponent reactions (MCRs), because of their productivity, simple procedures, time-saving manner, convergence, and facile execution, are one of the best tools in combinatorial chemistry.[1] MCRs, particularly those performed in aqueous media, have become increasingly useful tools for the synthesis of chemically and biologically important compounds because of their environmentally friendly atom economy and green characteristics.[1] The ability of isocyanide to undergo facile α-addition with a nucleophile and an electrophile under mild conditions made it a popular reactant for the development of novel MCRs.[2] As a result of this orthogonal reactivity, MCRs that involve isocyanides are considered as powerful tools in modern organic synthesis as well as in the field of combinatorial chemistry and drug discovery.[3] Therefore, the design of novel isocyanide-based multicomponent reactions (IMCRs) can be considered as an interesting research topic that also satisfies the practical interest of applied science.[4] As a result, the number of new IMCRs reported in recent years has grown rapidly.[5]

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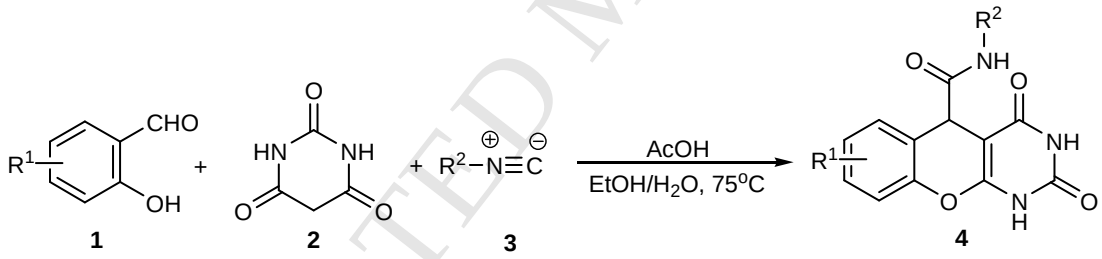
The benzopyrano[2,3-d]pyrimidines are organic compounds which are constructed from two fused benzopyran and pyrimidine rings which exhibit extremely diverse biological and pharmaceutical activities.[6-17] The benzopyrans (4H-chromene) have shown a wide range of biological activities such as anti HBV, cytotoxic,[6] antibacterial,[7] antioxidant,[8] antigenotoxic,[9] ATP sensitive potassium channel openers[10] and antiangiogenic activity [11]. [11] On the other hand, a pyrimidine scaffold is the base of many bioactive molecules such as antitubercular,[12] antibacterial,[13] antitumor,[14] antiinflammatory,[15] antifungal[16] and antileishmanial agent.[17] Consequently, synthetic methodologies for the synthesis of novel benzopyrano[2,3-d]pyrimidine[18] are of particular interests to organic and medicinal chemists.

## 2. Results and discussion

Due to the aforementioned reasons, and as a part of our ongoing research on isocyanide-based MCRs,[5] we report herein the synthesis of 1H-chromeno[2,3-d]pyrimidine-5-carboxamide derivatives **4** through a one-pot, three-component condensation of the salicylaldehydes **1**, barbituric acid **2**, and isocyanides **3** in the presence of acetic acid in ethanol/water mixture (4:1) at 75 ˚C (Scheme 1).

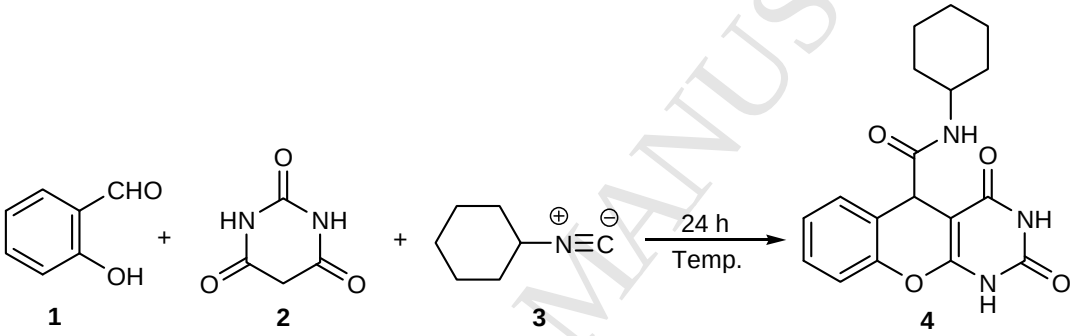



**Scheme 1.** Synthesis of 1H-chromeno[2,3-d]pyrimidine-5-carboxamide

We chose the reaction of salicylaldehyde, barbituric acid, and cyclohexyl isocyanide as a model system for the optimization study. First, we compared the reaction rate in different solvents by measuring the isolated yield using identical amounts of reactants and catalyst for a fixed reaction time of 24 h at 75 ˚C (entries 1-7). The desired products were scarcely obtained in non-polar solvents and even ethanol or water as a polar protic solvent failed to produce the desired product in high (>80%) yield. It was found that addition of water to the ethanol solution can improve the reaction outcome and interestingly (entries 8-12) when the reaction was performed in ethanol /water mixture (4:1) the corresponding product was obtained qualitatively (entry 12). This effect can be explained by a simple acid-catalysis mechanism facilitated by

the strong hydrogen bond interaction at the organic–water interface which stabilizes the reaction intermediate. Next, we studied the model reaction in ethanol/water at different temperatures (entries 13-15). The reaction rate increased as the temperature was raised. At 75 ˚C, the maximum yield (99%) was obtained in a reaction time of 24 h (entry 13). Also, the model reaction was studied in ethanol/water (4:1) at 75 ˚C using different amounts of acetic acid (entries 17-19). The best results were obtained with 100 mol % of acetic acid. Further work indicated that the best results were obtained when the reaction was carried out at 75 ℃ for 24 h in ethanol/water (4:1) using 100 mol % of acetic acid (entry 13).

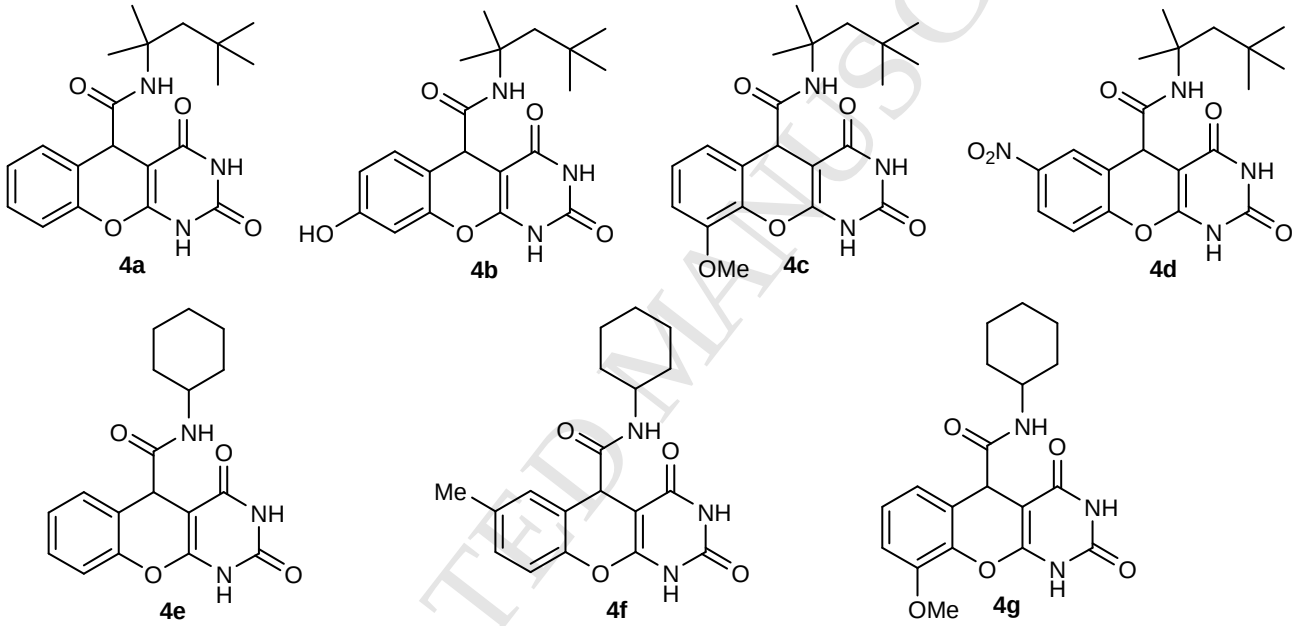
**Table 1:** Optimization of the reaction




| Entry | Solvent | Temperature | Acetic acid (%) | Yield (%) |
|---|---|---|---|---|
| 1 | Water | 75 | 100 | 71 |
| 2 | Ethanol | 75 | 100 | 78 |
| 3 | Methanol | 75 | 100 | 72 |
| 4 | Ethyl acetate | 75 | 100 | 32 |
| 5 | Acetonitrile | 75 | 100 | 44 |
| 6 | Toluene | 75 | 100 | trace |
| 7 | Dichloromethane | 25 | 100 | trace |
| 8 | Water/ Ethanol (1:1) | 75 | 100 | 85 |
| 9 | Water/ Ethanol (2:1) | 75 | 100 | 83 |
| 10 | Water/ Ethanol (1:2) | 75 | 100 | 87 |
| 11 | Water/ Ethanol (1:3) | 75 | 100 | 93 |
| 12 | Water/ Ethanol (1:4) | 75 | 100 | 99 |
| 13 | Water/ Ethanol (1:4) | 75 | 100 | 93 |
| 14 | Water/ Ethanol (1:4) | 50 | 100 | 73 |
| 15 | Water/ Ethanol (1:4) | 25 | 100 | 51 |
| 16 | Water/ Ethanol (1:4) | 75 | 10 | 59 |
| 17 | Water/ Ethanol (1:4) | 75 | 25 | 67 |
| 18 | Water/ Ethanol (1:4) | 75 | 50 | 79 |
| 19 | Water/ Ethanol (1:4) | 75 | 75 | 86 |

With the optimized condition established above, we next attempted to extend the process to two different isocyanides such as 1,1,3,3-tetramethylbutyl isocyanide and cyclohexyl isocyanide, and various types of salicylaldehydes **1** such as salicylaldehyde, 3-methoxysalicylaldehyde, 4-hydroxysalicylaldehyde, 5-methylsalicylaldehyde and 5-nitrosalicylaldehyde. The results in Table 2 show that all reactions proceeded smoothly to afford the expected 1H-chromeno[2,3-d]pyrimidine-5-carboxamide derivatives in good to excellent yields. The structure of the products was deduced from their mass, $^{1}$H NMR, and $^{13}$C NMR spectra (see the experimental section).

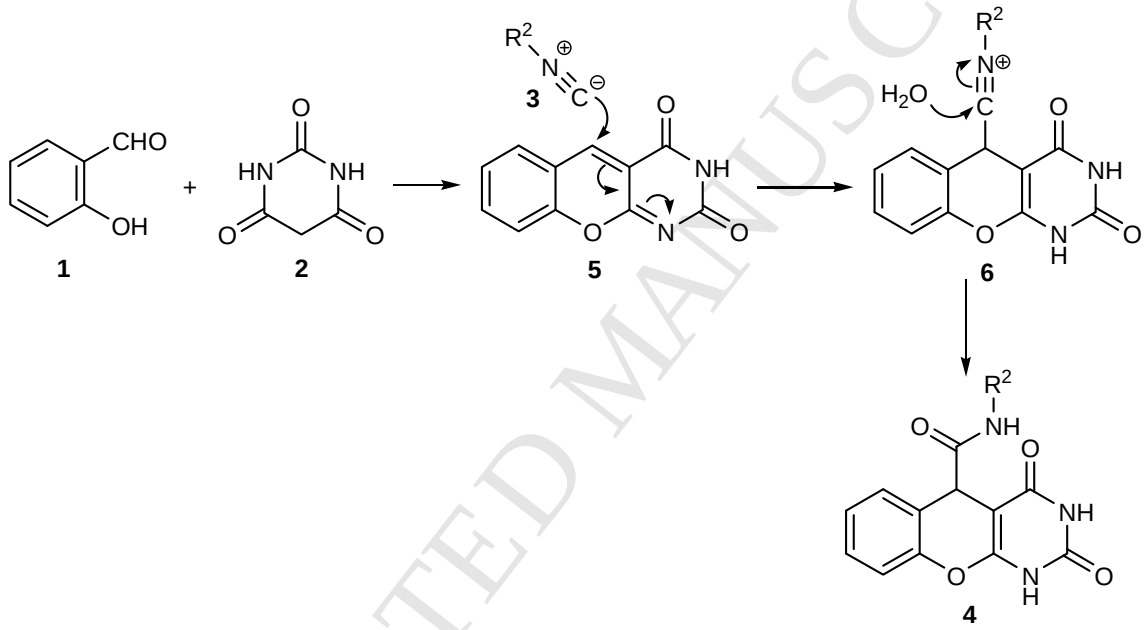
**Table 2.** Synthesis of 1H-chromeno[2,3-d]pyrimidine-5-carboxamide derivatives.




| Entry | $R^1$ | $R^2$ | Product | Yield (%) |
|---|---|---|---|---|
| 1 | H | 1,1,3,3,-Tetramethylbutyl | **4a** | 95 |
| 2 | 4- HO | 1,1,3,3,-Tetramethylbutyl | **4b** | 95 |
| 3 | 3- $CH_3O$ | 1,1,3,3,-Tetramethylbutyl | **4c** | 97 |
| 4 | 5- $O_2N$ | 1,1,3,3,-Tetramethylbutyl | **4d** | 60 |
| 5 | H | Cy | **4e** | 99 |
| 6 | 5- $H_3C$ | Cy | **4f** | 90 |
| 7 | 3- $CH_3O$ | Cy | **4g** | 99 |

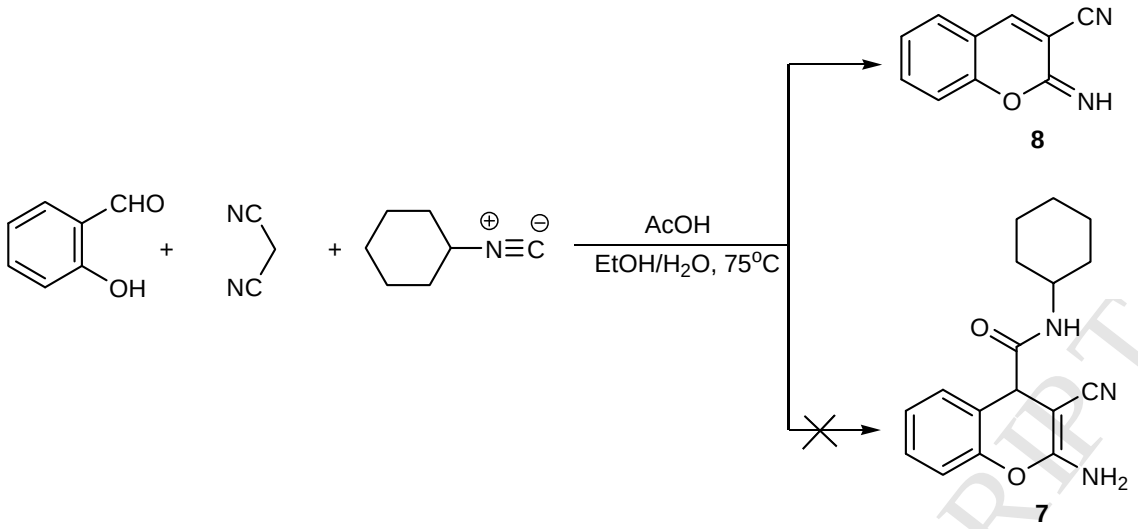
[a]Reaction condition: salicylaldehydes **1** (1 mmol), barbituric acid **2** (1 mmol), and isocyanides **3** (1 mmol), and AcOH (1 mmol) in ethanol/water (4:1) (5 mL) stirred at 75 ˚C for 24 h. [b]Isolated yield.

Mechanistically, it is conceivable that the reaction involves the initial formation of the activated alkene, (benzopyran ring) **5** through a Knoevenagel condensation of salicylaldehydes **1** and barbituric acid **2**.[19] Benzopyran ring **5** undergoes nucleophilic addition with the isocyanide **3** followed by nucleophilic attack on the isocyanide by the water to afford 1H-chromeno[2,3-d]pyrimidine-5-carboxamide derivatives **4.** To clarify the proposed mechanism, first, the benzopyran ring **5** was synthesized according to previous work,[19] by means of reaction between salicylaldehydes **1** and barbituric acid **2**. Next, the reaction of the benzopyran ring **5** with the isocyanide in ethanol/water mixture in the presence of acetic acid afforded the corresponding 1H-chromeno[2,3-d]pyrimidine-5-carboxamide derivatives **4**.




**Scheme 2.** Proposed mechanism

During our investigation, we tried to use the malononitrile instead of barbituric acid. For this, we examined the reaction of malononitrile, and salicylaldehydes with isocyanide in the presence of a acetic acid in ethanol/water (4:1) at 75 ˚C for 24 h. We found that isocyanide was not involved in the reaction, and consequently, the expected product 2-amino-3-cyano-N-cyclohexyl-4H-chromene-4-carboxamide **8** was not obtained. Isolation and characterization of the resulted product showed that under these conditions, the reaction afforded 2-imino-2H-chromene-3-carbonitrile **7** instead, which was reported by was reported by Proenca et al.[20] (Scheme 3).




**Scheme 3.**

## 3. Conclusion

In conclusion, we have developed a new isocyanide based multicomponent reaction for the synthesis of a wide range of 1H-chromeno[2,3-d]pyrimidine-5-carboxamides from salicylaldehydes and barbituric acid and isocyanides. This high yielding reaction has been shown to display a good functional group tolerance, while the product isolation is very straightforward. We hope that this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry programs.

*4. Experimental Section:*

*4.1. General procedure for synthesis of 1H-chromeno[2,3-d]pyrimidine-5-carboxamide derivatives (4a-g)*

A solution of salicylaldehydes (1 mmol), barbituric acid (1 mmol), isocyanide (1 mmol) and AcOH (1 mmol) in ethanol/water (4:1) (5 mL) were stirred for 24 h at 75 ˚C. After completion of the reaction, as indicated by TLC, the solvent was removed under vacuum and the solid residue was washed with ethanol/water mixture (1:1). Then the solid residue was crystallized from ethanol to afford products as colourless crystals.

*4.2. 2,3,4,5-Tetrahydro-N-(2,4,4-trimethylpentan-2-yl)-2,4-dioxo-1H-chromeno[2,3-d]pyrimidine-5-carboxamide (4a)*

White powder (0.35 g, yield 95%); mp 293-295 °C. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3300, 2954, 1694, 1651, 1531, 1488. MS, *m/z*: 372 ($M^+$+1), 216, 202, 172, 129, 83, 69, 57. $^1$H NMR (250 MHz, DSMO-$d_6$): $\delta_H$ (ppm) 0.91

(9H, s, $C(CH_3)_3$), 1.22, 1.27 (6H, 2s, $CH_3$-C-$CH_3$), 1.53 (1H, d, $^2J_{HH}$ = 12.5 Hz, $CH_2$), 1.64 (1H, d, $^2J_{HH}$ = 12.5 Hz, $CH_2$), 4.55 (1H, s, CH), 7.12-7.49 (4H, m, H-Ar), 7.78, 11.05, 11.91 (3H, 3s, 3NH). $^{13}$C NMR (63 MHz, DSMO-*d*$_6$): $\delta_C$ (ppm) 28.7 (*C*$H_3$-C-*C*$H_3$), 28.9 (C(*C*$H_3$)$_3$), 31.0 (*C*$(CH_3)_3$), 31.1 ($CH_2$), 50.2 ($CH_3$-*C*-$CH_3$), 54.1 (CH), 85.5, 116.2, 120.5, 124.9, 128.5, 128.8, 149.0, 149.6 (O-C=C and 6C-Ar), 155.0, 169.6, 171.0 (3C=O). Anal. Calcd for $C_{20}H_{25}N_3O_4$: C, 64.67; H, 6.78; N, 11.31. Found: C, 64.73; H, 6.69; N, 11.33.

*4.3. 2,3,4,5-Tetrahydro-8-hydroxy-N-(2,4,4-trimethylpentan-2-yl)-2,4-dioxo-1H-chromeno[2,3-d]pyrimidine-5-carboxamide (4b)*

White powder (0.37 g, yield 95%); mp 336-339 °C. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3610, 3300, 2953, 1695, 1661, 1544, 1473. MS, *m/z*: 388 ($M^+$+1), 332, 246, 187, 129, 110, 69, 57. $^1$H NMR (250 MHz, DSMO-*d*$_6$): $\delta_H$ (ppm) 0.91 (9H, s, $C(CH_3)_3$), 1.23, 1.27 (6H, 2s, $CH_3$-C-$CH_3$), 1.60 (1H, d, $^2J_{HH}$ = 14.0 Hz, $CH_2$), 1.70 (1H, d, $^2J_{HH}$ = 14.0 Hz, $CH_2$), 4.41 (1H, s, CH), 6.47 (1H, s, H-Ar), 6.62 (1H, d, $^3J_{HH}$ = 7.5 Hz, H-Ar), 7.26 (1H, d, $^3J_{HH}$ = 7.5 Hz, H-Ar), 7.70 (1H, s, OH), 9.84, 11.03, 11.84 (3H, 3s, 3NH). $^{13}$C NMR (63 MHz, DSMO-*d*$_6$): $\delta_C$ (ppm) 28.7 (*C*$H_3$-C-*C*$H_3$), 28.9 (C(*C*$H_3$)$_3$), 30.9 (*C*$(CH_3)_3$), 31.1 ($CH_2$), 50.2 ($CH_3$-*C*-$CH_3$), 54.1 (CH), 85.8, 102.5, 110.6, 112.4, 129.4, 149.0, 149.6, 154.6 (O-C=C and 6C-Ar), 157.3, 163.5, 170.1 (3C=O). Anal. Calcd for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50; N, 10.85. Found: C, 62.01; H, 6.42; N, 10.83.

*4.4. 2,3,4,5-Tetrahydro-9-methoxy-N-(2,4,4-trimethylpentan-2-yl)-2,4-dioxo-1H-chromeno[2,3-d]pyrimidine-5-carboxamide (4c)*

White powder (0.39 g, yield 97%); mp 360-362 °C. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3311, 2959, 1699, 1645, 1532, 1470. MS, *m/z*: 402 ($M^+$), 368, 330, 246, 187, 69, 57. $^1$H NMR (250 MHz, DSMO-*d*$_6$): $\delta_H$ (ppm) 0.90 (9H, s, $C(CH_3)_3$), 1.21, 1.26 (6H, 2s, $CH_3$-C-$CH_3$), 1.58 (1H, d, $^2J_{HH}$ = 12.5 Hz, $CH_2$), 1.70 (1H, d, $^2J_{HH}$ = 14.0 Hz, $CH_2$), 3.84 (1H, s, $OCH_3$), 4.53 (1H, s, CH), 7.00-7.12 (3H, m, H-Ar), 7.72, 11.02, 11.92 (3H, 3s, 3NH). $^{13}$C NMR (63 MHz, DSMO-*d*$_6$): $\delta_C$ (ppm) 28.7 (*C*$H_3$-C-*C*$H_3$), 28.9 (C(*C*$H_3$)$_3$), 31.0 (*C*$(CH_3)_3$), 31.1 ($CH_2$), 50.2 ($CH_3$-*C*-$CH_3$), 54.1 (CH), 55.66 ($OCH_3$), 85.5, 111.3, 119.8, 121.4, 124.6, 138.0, 147.3, 149.5 (O-C=C and 6C-Ar), 154.6, 163.4, 169.7 (3C=O). Anal. Calcd for $C_{21}H_{27}N_3O_5$: C, 62.83; H, 6.78; N, 10.47. Found: C, 62.82; H, 6.75; N, 10.49.

*4.5. 2,3,4,5-Tetrahydro-N-(2,4,4-trimethylpentan-2-yl)-7-nitro-2,4-dioxo-1H-chromeno[2,3-d]pyrimidine-5-carboxamide (4d)*

White powder (0.25 g, yield 60%); mp 360-362 °C. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3307, 2981, 1690, 1655, 1566, 1489. MS, *m/z*: 417 ($M^+$), 370, 261, 217, 97, 83, 57. $^1$H NMR (250 MHz, DSMO-$d_6$): $\delta_H$ (ppm) 0.98 (9H, s, $C(CH_3)_3$), 1.31 (6H, s, $CH_3$-C-$CH_3$), 1.56 (2H, s, $CH_2$), 4.91 (1H, s, CH), 6.70-8.00 (3H, m, H-Ar), 8.04, 8.15, 9.72 (3H, 3s, 3NH). $^{13}$C NMR (63 MHz, DSMO-$d_6$): $\delta_C$ (ppm) 26.6 ($CH_3$-C-$CH_3$), 26.7 ($C(CH_3)_3$), 30.8 ($C(CH_3)_3$), 30.9 ($CH_2$), 51.9 ($CH_3$-$C$-$CH_3$), 54.9 (CH), 80.0, 117.1, 117.6, 123.8, 125.1, 128.5, 137.6, 151.3 (O-C=C and 6C-Ar), 164.5, 165.0, 173.0 (3C=O). Anal. Calcd for $C_{20}H_{24}N_4O_6$: C, 57.68; H, 5.81; N, 13.45. Found: C, 57.73; H, 5.82; N, 13.51.

*4.6. N-Cyclohexyl-2,3,4,5-tetrahydro-2,4-dioxo-1H-chromeno[2,3-d]pyrimidine-5-carboxamide (4e)*

White powder (0.34 g, yield 99%); mp 340-342 °C. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3300, 2963, 2850, 1694, 1539, 1489. MS, *m/z*: 342 ($M^+$+1), 216, 172, 145, 116, 83, 63, 55. $^1$H NMR (300 MHz, DSMO-$d_6$): $\delta_H$ (ppm) 1.16-1.70 (10H, m, 5$CH_2$ of cyclohexyl), 3.40 (1H, m, C*H*-NH of cyclohexyl), 4.48 (1H, s, CH), 7.08-7.45 (4H, m, H-Ar), 8.21 (1H, d, $^3J_{HH}$ = 7.8 Hz, CH-N*H* of cyclohexyl), 11.04, 11.90 (2H, 2s, 2NH). $^{13}$C NMR (63 MHz, DSMO-$d_6$): $\delta_C$ (ppm) 24.3, 25.1, 32.1 (C-cyclohexyl), 47.7 (CH-NH), 50.8 (CH), 83.3, 116.3, 120.3, 128.4, 128.7, 148.3, 149.6, 154.4 (O-C=C and 6C-Ar), 159.7, 163.4, 170.0 (3C=O). Anal. Calcd for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31. Found: C, 63.34; H, 5.53; N, 12.33.

*4.7. N-Cyclohexyl-2,3,4,5-tetrahydro-7-methyl-2,4-dioxo-1H-chromeno[2,3-d]pyrimidine-5-carboxamide (4f)*

White powder (0.32 g, yield 90%); mp 333-336 °C. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3300, 2934, 2850, 1690, 1618, 1539, 1488. MS, *m/z*: 356 ($M^+$+1), 230, 186, 116, 83, 63, 55. $^1$H NMR (250 MHz, DSMO-$d_6$): $\delta_H$ (ppm) 1.22-1.68 (10H, m, 5$CH_2$ of cyclohexyl), 3.40 (1H, m, C*H*-NH of cyclohexyl), 2.26 (3H, s, $CH_3$), 4.43 (1H, s, CH), 7.01-7.24 (4H, m, H-Ar), 8.17, 11.03, 11.93 (3H, 3s, 3NH). $^{13}$C NMR (63 MHz, DSMO-$d_6$): $\delta_C$ (ppm) 21.2 ($CH_3$), 24.3, 25.0, 32.5 (C-cyclohexyl), 43.7 (CH-NH), 47.5 (CH), 85.0, 116.0, 120.0, 128.0, 129.0, 144.5, 147.0, 154.0 (O-C=C and 6C-Ar), 159.0, 165.0, 170.0 (3C=O). Anal. Calcd for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.82. Found: C, 64.22; H, 5.91; N, 11.79.

*4.8. N-cyclohexyl-2,3,4,5-tetrahydro-9-methoxy-2,4-dioxo-1H-chromeno[2,3-d]pyrimidine-5-carboxamide (4g)*

White powder (0.37 g, yield 99%); mp 332-334 °C. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3301, 2943, 2825, 1691, 1533 1488. MS, *m/z*: 372 ($M^+$+1), 246, 202, 126, 83, 63, 55. $^1$H NMR (300 MHz, DSMO-$d_6$): $\delta_H$ (ppm) 1.23-1.88 (10H, m, 5$CH_2$ of cyclohexyl), 3.79 (1H, m, C*H*-NH of cyclohexyl), 3.83 (3H, s, $OCH_3$), 4.48 (1H, s, CH), 6.81-7.13 (3H, m, H-Ar), 8.20, 10.66, 11.00 (3H, 3s, 3NH). $^{13}$C NMR (75 MHz, DSMO-$d_6$): $\delta_C$ (ppm) 23.7, 24.4, 25.1, 30.2, 32.1 (C-cyclohexyl), 47.7 (CH-NH), 49.2 (CH), 55.7 ($OCH_3$), 84.8, 111.2, 119.3, 121.1, 124.8, 138.75, 147.3, 149.6 (O-C=C and 6C-Ar), 155.0, 163.5, 169.8 (3C=O). Anal. Calcd for $C_{19}H_{21}N_3O_5$: C, 61.45; H, 5.70; N, 11.31. Found: C, 61.43; H, 5.71; N, 11.24.

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**References and notes**

1. (a) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, **2005**. (b) *Domino Reactions in Organic Synthesis*; Tietze, L. F., Brasche, G., Gericke, K., Eds.; Wiley-VCH: Weinheim, **2006**. (c) Dömling, U.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168-3210. (d) Soleimani, E.; Khodaei, M. M.; Batooie, N.; Baghbanzadeh, M. *Green Chem*. **2011**, *13*, 566-569
2. (a) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321-3329. (b) Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306-313. (c) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51-80. (d) Orru, R. V. A.; De Greef, M. *Synthesis* **2003**, 1471-1499. (e) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101-4111. (f) Jacobi von Wangelin, A.; Neumann, H.; Gördes, D.; Klaus, S.; Strübing, D.; Beller, M. *Chem. Eur. J.* **2003**, *9*, 4286-4294. (g) Murakami, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 718-720.

3. (a) Weber, L. *Curr. Med. Chem.* **2002**, 9, 1241-1253. (b) Schreiber, S. L. *Science* **2000**, *287*, 1964-1969. (c) Terrett, N. K. *Combinatorial Chemistry*; Oxford University Press: New York, 1998. (d) Weber, L. *Drug Discovery Today* **2002**, *7*, 143-147.

4. For recent reviews on multicomponent reactions, see: (a) Dömling, A. *Chem. Rev*. **2006**, *106*, 17-89. (b) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53-66. (c) Dömling, A. *Curr. Opin. Chem. Biol*. **2000**, *4*, 318-323. (d) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123-131. (e) Zhu, J. *Eur. J. Org. Chem*. **2003**, 1133-1144. (f) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res*. **2003**, *36*, 899-907. (g) Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1-140.

5. (a) Soleimani, E.; Zainali, M. *J. Org. Chem.* **2011,** *76*, 10306-10311. (b) Soleimani, E.; Zainali, M.; Samadi, S. *Tetrahedron Lett.* **2011,** *52*, 4186. (c) Soleimani, E.; Khodaei, M. M.; Taheri Kal Koshvandi, A. Synth. Commun. **2012**, *42*, 1367. (d) Shaabani, A.; Soleimani, E.; Rezayan, A. H.; Sarvary, A.; Khavasi, H. R. *Org. Lett*. **2008**, *10*, 2581-2584. (e) Shaabani, A.; Soleimani, E.; Khavasi, H. R. *J. Comb. Chem*. **2008**, *10*, 442-446.

6. Ren, S. C.; Sheau, F. Y.; Chih, M. L.; Amooru, G.; Damu, T. K.; Cheng, C. P.; Kenneth, F. B.; Hsiung, L. K.; Shung, W. T. *Bioorg. Med. Chem.* **2009**, *17*, 6137-6143.

7. Karnik, A. V.; Kulkarni, A. M.; Malviya, N. J.; Mourya, B. R.; Jadhav, B. L. *Eur. J. Med. Chem.* **2008**, *43*, 2615-2617.

8. Hwan, K. J.; Eun, K. H.; Kyung, J. J.; Hwajung, K.; Jungsook, C.; Heesoon, L. *Arch. Pharm. Res.* **2006**, *29*, 728-734.

9. Fakher, C.; Mehdi, M.; Hedi, B. M.; Leila, C.; Mansour, S. *Eur. J. Med. Chem*. **2007**, *42*, 715-718.

10. Cheng, C. Y.; Chiu, H.; Chang, M. J.; Lin, Y. C.; Tsai, M. C.; Yu, H. C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 463-468.

11. O. A.; Abdou, H. E.; Ahmed, A. A.; Sayed, H. Z.; Yasser, J. Sulf. Chem. 2005, 26, 405-410.

12. Deshmukh, M. B.; Salunkhe, S. M.; Patil, D. R.; Anbhule, P. V. *Eur. J. Med. Chem.* **2009**, *44*, 2651-2654.

13. Cecile, G.; Douguet, D.; Huteau, V.; Gilles, M.; Helene, M. L.; Sylvie, P. *Bioorg. Med. Chem.* **2008**, *16*, 6075-6085.

14. Lin, R.; Sigmond, G.; Johnson, P. J.; Connolly, S. K.; Wetter, E.; Binnun, T. V.; Hughes, W. V.; Murray, N. B.; Pandey, S. J.; Mazza, M. M.; Adams, A. R.; Pesquera, F.; Steven, A. M. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 2333-2337.

15. Falcao, E. P.; da, S.; Melo, S. J.; Srivastava, R. M.; Catanho, M. T.; Nascimento, S. C. Eur. *J. Med. Chem*. **2006**, *41*, 276-282.

16. Chen, Q.; Zhu, X.; Jiang, L.; Yang, L. M.; Fu, G. *Eur. J. Med. Chem*. **2008**, *43*, 595-603.

17. Agarwal, A.; Ashutosh, R.; Goyal, N.; Chauhana, M. S.; Gupta, S. *Bioorg. Med. Chem*. **2005**, *13*, 6678-6684.

18. Agarwal, A.; Ashutosh, R.; Goyal, N.; Chauhana, P. M. S.; Gupta, S.; *Bioorg. Med. Chem*. **2005**, *13*, 6678-6684.

19. Figueroa-Villar, J. D.; Cruz, E. R. *Tetrahedron* **1993**, *49*, 2855-2862.

20. Costa, M.; Areias, F.; Abrunhosa, L.; Venancio, A.; Proenca, F. *J. Org. Chem*. **2008**, *73*, 1954-1962