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Synthesis and in vitro microbiological evaluation of novel series of 8-hydroxy-2-(2-oxo-2*H*-chromen-3-yl)-5-phenyl-3*H*-chromeno [2,3-*d*]pyrimidin-4(5*H*)-one derivatives catalyzed by reusable silica-bonded *N*-propylpiperazine sulfamic acid

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Abstract Silica-bonded propylpiperazine-*N*-sulfamic acid is employed as a recyclable catalyst for the synthesis of a series of 8-hydroxy-2-(2-oxo-2*H*-chromen-3-yl)-5-phenyl-3*H*-chromeno[2,3-*d*]pyrimidin-4(5*H*)-one derivatives by the condensation of 2-amino-3-cyano-7-hydroxy-4-phenyl-4*H*chromene derivatives with coumarin-3-carboxylic acid. The heterogeneous catalyst was used for four runs. This method has the advantages of high yields, a cleaner reaction, simple methodology, short reaction times, and easy work-up. All the compounds were evaluated for their in vitro antimicrobial activity against different bacterial and fungal strains.

Keywords Silica-bonded *N*-propylpiperazine sulfamic acid (SBPPSA) · Chromeno[2,3-*d*]pyrimidin-4(5*H*)-one · 2-amino-4*H*-chromene · 4-(dimethylamino)pyridine (DMAP) · Malononitrile · Microbiological evaluation

Introduction

Coumarins form an important class of compounds, which occupy a special role in nature. They belong to the flavonoid class of plant secondary metabolites, which have been found to exhibit a variety of biological activities, usually associated with low toxicity, and have raised considerable interest because of their potential beneficial effects on human health. [1]. These compounds are considered as

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'privileged structures' in medicinal chemistry due to their immense potentiality. Coumarin derivatives have anti-tuberculosis [2], anti-HIV [3], antibacterial, antioxidant [4], and anti-inflammatory [5] properties, and are used as mushroom tyrosinase inhibitors [6] and cytotoxicity agents [7]. They are also present or used in perfumes and cosmetics [8], alcoholic beverages [9], and laser dyes [10]. Due to their wide range of biological and other applications, in recent times various research groups have made considerable efforts to synthesize these compounds. Coumarin derivatives were first synthesized via the Perkin reaction in 1868, and many simple coumarins are still derived from this method. From the literature, it has been found that a number of methods have been reported so far for the synthesis of coumarin derivatives [11–15]. Most of these procedures require refluxing for hours in organic solvents, the use of expensive catalysts, and tedious work-up. In view of these observations, there is further scope to develop a synthetic methodology using a less expensive and environmentally benign catalyst.

In recent times, it has been found that heterogeneous catalysts have gained in interest since they are less expensive, non-toxic, easily available, and environmentally acceptable. They can be conveniently handled and removed from the reaction mixture, thus making the experimental procedure simple and eco-friendly. Recently, silica-bonded propylpiperazine *N*-sulfamic acid (SBPPSA) has emerged as mild, water-tolerant, inexpensive, and environmentally compatible heterogeneous catalyst, reported by Niknam et al. [16] for the synthesis of 1,2,4,5-tetrasubstituted imidazoles. SBPPSA has also been used as a catalyst for the synthesis of α-aminonitriles [17] and for cyanation reactions [18].

As part of continuing effort in our laboratory towards the development of environmentally friendly procedures for the synthesis of biologically active heterocyclic molecules [19–24], we now describe the synthesis of 8-hydroxy-2-(2-oxo-2*H*-chromen-3-yl)-5-phenyl-3*H*-chromeno[2,3-*d*]pyrimidin-4(5*H*)-one derivatives using SBPPSA as an efficient novel heterogeneous catalyst. These compounds were synthesized using 2-amino-3-cyano-7-hydroxy-4-phenyl-4*H*chromene derivatives and coumarine-3-carboxylic acid using 4-(dimethylamino)pyridine (DMAP) as an efficient catalyst.

Experimental

Apparatus and analysis

Chemicals were purchased from Merck, Fluka, and Aldrich. All yields refer to isolated products unless otherwise stated. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were obtained using a Bruker DRX-500 Avance at ambient temperature, using TMS as internal standard. FT-IR spectra were obtained as KBr discs on a Shimadzu spectrometer. Mass spectra were determined on a Varion–Saturn 2000 GC/MS instrument. Elemental analysis was measured by means of Perkin Elmer 2400 CHN elemental analyzer flowchart.

Preparation of the catalyst (SBPPSA)

Silica-bonded propylpiperazine-*N*-sulfamic acid was prepared by the reaction of 3-piperazine-*N*-propylsilica (3-PNPS) and chlorosulfonic acid in chloroform as reported in the literature [16], and 0.2 g of SBPPSA is equal to 0.24 mmol of H^+.

General procedure for the synthesis of 2-amino-3-cyano-7-hydroxy-4-substituted-4*H*chromene derivatives

A mixture of resorcinol (0.110 g, 1 mmol), aldehyde derivatives (1 mmol), malononitrile (0.066 g, 1 mmol), ethanol (5 mL), and DMAP (10 mol %) was stirred at 60 °C for the appropriate time. After completion of the reaction (TLC monitoring), the DMAP was filtered off and the solvent was evaporated. The catalyst was washed with dichloromethane and vacuumed to remove CH_2Cl_2, and the resulting catalyst was reused directly for the next run. The filtrate was concentrated to dryness, and the crude solid product was crystallized from EtOH to afford the pure 2-amino-3-cyano-7-hydroxy-4-substituted-4*H*-chromene derivatives.

Spectral data for new compounds **(4a–j)**

*2-Amino-3-cyano-7-hydroxy-4-phenyl-4Hchromene (**4a**)*

IR (KBr, cm^{-1}): 3,433 (OH), 3,350 (NH_2), 2,202 (CN), 1,666 (C=C vinyl nitrile), 1,591 (C=C aromatic); ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.95 (s, 1H, CH), 6.24 (s, 2*H*, NH_2), 6.57 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.75 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.88 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.18–7.34 (m, 5*H*, Ar–H), 9.60 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 30.4, 58.5, 103.5, 111.0, 117.5, 124.4, 126.3, 127.8, 129.6, 130.4, 143.3, 155.7, 159.5, 176.3 ppm. MS (ESI): *m/z* 265 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.54; N, 10.60 %. Found: C, 72.66; H, 4.52; N, 10.61 %.

*2-Amino-3-cyano-7-hydroxy-4-(4-chlorophenyl)-4Hchromene (**4b**)*

IR (KBr, cm^{-1}): 3,442 (OH), 3,344 (NH_2), 2,212 (CN), 1,662 (C=C vinyl nitrile), 1,588 (C=C aromatic); ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.88 (s, 1H, CH), 6.29 (s, 2*H*, NH_2), 6.62 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.73 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.91 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.28 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 7.48 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 9.56 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 29.8, 59.2, 104.6, 110.5, 118.0, 123.9, 125.7, 128.4, 129.0, 131.0, 144.0, 156.0, 158.9, 177.1 ppm. MS (ESI): *m/z* 299.45 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{11}ClN_2O_2$: C, 64.33; H, 3.68; N, 9.38 %. Found: C, 64.22; H, 3.60; N, 9.30 %.

*2-Amino-3-cyano-7-hydroxy-4-(4-bromophenyl)-4Hchromene (**4c**)*

IR (KBr, cm^{-1}): 3,428 (OH), 3,340 (NH_2), 2,196 (CN), 1,672 (C=C vinyl nitrile), 1,590 (C=C aromatic); ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.99 (s, 1H, CH), 6.16 (s,

2*H*, NH_2), 6.64 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.78 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.95 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.36–7.50 (m, 4H, Ar–H), 9.52 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 30.7, 58.7, 103.9, 111.2, 117.4, 124.3, 126.4, 127.5, 129.2, 131.3, 143.8, 155.8, 159.3, 177.4 ppm. MS (ESI): *m*/*z* 343.9 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{11}BrN_2O_2$: C, 55.99; H, 3.21; N, 8.16 %. Found: C, 55.88; H, 3.15; N, 8.11 %.

*2-Amino-3-cyano-7-hydroxy-4-(4-fluorophenyl)-4Hchromene (**4d**)*

IR (KBr, cm^{-1}): 3,440 (OH), 3,330 (NH_2), 2,199 (CN), 1,659 (C=C vinyl nitrile), 1,580 (C=C aromatic); ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.09 (s, 1H, CH), 6.22 (s, 2*H*, NH_2), 6.62 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.77 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.90 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.20–7.44 (m, 4H, Ar–H), 9.59 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 30.5, 59.0, 104.4, 110.8, 118.6, 123.8, 125.8, 127.9, 129.4, 130.9, 144.1, 156.4, 158.7, 176.8 ppm. MS (ESI): *m*/*z* 283 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{11}FN_2O_2$: C, 68.08; H, 3.90; N, 9.93 %. Found: C, 68.02; H, 3.84; N, 9.94 %.

*2-Amino-3-cyano-7-hydroxy-4-(4-methylphenyl)-4Hchromene (**4e**)*

IR (KBr, cm^{-1}): 3,430 (OH), 3,352 (NH_2), 2,214 (CN), 1,660 (C=C vinyl nitrile), 1,575 (C=C aromatic); ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.18 (s, 3*H*, CH_3), 4.85 (s, 1H, CH), 6.12 (s, 2*H*, NH_2), 6.58 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.69 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.80 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.22 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 7.49 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 9.60 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 18,9, 29.7, 58.3, 103.2, 111.8, 117.4, 123.5, 126.2, 128.2, 128.9, 131.4, 143.5, 155.9, 158.5, 177.2 ppm. MS (ESI): *m*/*z* 279 $(M+H)^+$. Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.38; H, 5.03; N, 10.07 %. Found: C, 73.25; H, 5.01; N, 10.01 %.

*2-Amino-3-cyano-7-hydroxy-4-(4-methoxyphenyl)-4Hchromene (**4f**)*

IR (KBr, cm^{-1}): 3,426 (OH), 3,335 (NH_2), 2,206 (CN), 1,674 (C=C vinyl nitrile), 1,578 (C=C aromatic); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.66 (s, 3*H*, OCH_3), 5.04 (s, 1H, CH), 6.20 (s, 2*H*, NH_2), 6.63 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.77 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.84 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.30 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 7.46 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 9.55 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 29.2, 55,8, 59.5, 104.5, 110.6, 118.1, 124.6, 125.5, 127.7, 128.7, 131.1, 144.2, 156.1, 159.0, 176.5 ppm. MS (ESI): *m*/*z* 295 $(M+H)^+$. Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.39; H, 4.76; N, 9.52 %. Found: C, 69.27; H, 4.71; N, 9.42 %.

*2-Amino-3-cyano-7-hydroxy-4-(4-nitrophenyl)-4Hchromene (**4g**)*

IR (KBr, cm^{-1}): 3,448 (OH), 3,341 (NH_2), 2,200 (CN), 1,655 (C=C vinyl nitrile), 1,581 (C=C aromatic); ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.07 (s, 1H, CH), 6.17 (s,

2*H*, NH_2), 6.56 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.72 (dd, $J = 4.0$ Hz, $J = 8.0$, 1H, Ar–H), 6.90 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.22 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 7.51 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 9.59 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 30.9, 58.8, 103.9, 111.0, 117.9, 123.7, 126.5, 127.3, 129.5, 130.8, 144.3, 155.5, 158.6, 177.3 ppm. MS (ESI): *m/z* 310 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{11}N_3O_4$: C, 62.13; H, 3.56; N, 13.59 %. Found: C, 62.01; H, 3.54; N, 13.56 %.

*2-Amino-3-cyano-7-hydroxy-4-(4-hydroxyphenyl)-4Hchromene (**4h**)*

IR (KBr, cm^{-1}): 3,427 (OH), 3,444 (OH), 3,337 (NH_2), 2,195 (CN), 1,668 (C=C vinyl nitrile), 1,594 (C=C aromatic); ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.85 (s, 1H, CH), 6.22 (s, 2*H*, NH_2), 6.64 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.74 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.83 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.34 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 7.57 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 9.52 (s, 1H, OH), 9.69 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 29.3, 59.1, 104.0, 110.8, 118.4, 123.9, 125.9, 128.3, 129.1, 131.6, 143.6, 156.3, 158.8, 176.6 ppm. MS (ESI): *m/z* 281 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.28; N, 10.00 %. Found: C, 68.50; H, 4.22; N, 10.02 %.

*2-Amino-3-cyano-7-hydroxy-4-(3-hydroxyphenyl)-4Hchromene (**4i**)*

IR (KBr, cm^{-1}): 3,438 (OH), 3,452 (OH), 3,348 (NH_2), 2,198 (CN), 1,657 (C=C vinyl nitrile), 1,586 (C=C aromatic); ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.98 (s, 1H, CH), 6.25 (s, 2*H*, NH_2), 6.66 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.76 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.92 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.22–7.38 (m, 4H, Ar–H), 9.48 (s, 1H, OH), 9.65 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 30.0, 59.7, 103.7, 111.5, 117.7, 124.0, 125.4, 127.6, 129.7, 130.7, 144.2, 156.7, 159.4, 176.8 ppm. MS (ESI): *m/z* 281 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.28; N, 10.00 %. Found: C, 68.59; H, 4.27; N, 10.01 %.

*2-Amino-3-cyano-7-hydroxy-4-(4-N,N-dimethylaminophenyl)-4Hchromene (**4j**)*

IR (KBr, cm^{-1}): 3,440 (OH), 3,343 (NH_2), 2,210 (CN), 1,670 (C=C vinyl nitrile), 1,576 (C=C aromatic); ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.58 (s, 6H, CH_3), 4.88 (s, 1H, CH), 6.18 (s, 2*H*, NH_2), 6.61 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.71 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.87 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.25 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 7.51 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 9.60 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 29.5, 44.4, 58.0, 105.0, 110.1, 118.8, 123.1, 126.2, 128.0, 128.9, 131.0, 143.7, 155.2, 158.4, 177.5 ppm. MS (ESI): *m/z* 308 $(M+H)^+$. Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.35; H, 5.54; N, 13.68 %. Found: C, 70.30; H, 5.51; N, 13.66 %.

General procedure for the synthesis of 8-hydroxy-2-(2-oxo-2*H*-chromen-3-yl)-5-phenyl-3*H*-chromeno[2,3-*d*]pyrimidin-4(5*H*)-one derivatives by SBPPSA

A mixture of 2-amino-3-cyano-7-hydroxy-4-phenyl-4*H*chromene **4a–j** (1 mmol), coumarin-3-carboxylic acid (1 mmol), and SBPPSA (0.2 g, equal to 0.24 mmol of

H^+) were heated at 60 °C for about 3.0–3.5 h (Scheme 2). After completion of the reaction as indicated by TLC, 2 mL of water was added and stirred at room temperature for 20 min. The precipitated product was filtered, washed with water, dried, and purified over column chromatography using silica gel (230–400 mesh) with *n*-hexane and ethyl acetate (8:2) as eluent. The aqueous layer containing catalyst was recovered, washed with acetone, dried and reused for subsequent reactions without loss in its activity and product yield.

Recycling and reusing of the catalyst

The catalyst was recovered by evaporation of the water, washed with hexane, dried at 50 °C under vacuum for 1 h and reused in another reaction without appreciable reduction in the catalytic activity.

Spectral data for the synthesized compounds **(6a–j)**

*8-Hydroxy-2-(2-oxo-2H-chromen-3-yl)-5-phenyl-3H-chromeno[2,3-d]pyrimidin-4(5H)-one **(6a)***

IR (KBr, cm^{-1}): 3,466 (OH), 3,418 (NH), 1,703 (CO of lactone), 1,651 (CO of ketone), 1,622 (CO of lactam), 1,600 (CN), 1,202 (C–O–C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.12 (s, 1H, CH), 6.66 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.78 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.88 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.18 (d, $J = 7.2$ Hz, 2*H*, Ar–H), 7.36–7.55 (m, 3*H*, Ar–H), 7.72–7.82 (m, 4H, Ar–H), 8.22 (s, 1H, Coumarin H), 9.28 (s, 1H, NH), 9.44 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.4, 102.6, 104.8, 110.3 117.1, 121.4, 124.8, 125.7, 126.1, 126.9, 127.5, 128.1, 128.5, 129.6, 130.6, 143.5, 146.7, 150.6, 156.0, 158.1, 162.1, 162.5, 164.4, 168.1 ppm; MS(ESI): *m/z* 437 $(M+H)^+$; Anal. Calcd for $C_{26}H_{16}N_2O_5$: C, 71.56; H, 3.67; N, 6.42 %. Found: C, 71.44; H, 3.61; N, 6.43 %.

*8-Hydroxy-2-(2-oxo-2H-chromen-3-yl)-5-(4-chlorophenyl)-3H-chromeno[2,3-d]pyrimidin-4(5H)-one **(6b)***

IR (KBr, cm^{-1}): 3,472 (OH), 3,409 (NH), 1,700 (CO of lactone), 1,661 (CO of ketone), 1,629 (CO of lactam), 1,605 (CN), 1,212 (C–O–C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.09 (s, 1H, CH), 6.58 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.74 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.85 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.38 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 7.54 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 7.68–7.80 (m, 4H, Ar–H), 8.46 (s, 1H, Coumarin H), 9.37 (s, 1H, NH), 9.66 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 29.6, 101.7, 105.0, 111.5, 117.7, 121.7, 124.4, 124.9, 126.3, 126.7, 127.0, 128.3, 128.7, 129.3, 131.2, 144.0, 145.9, 151.3, 155.5, 158.7, 162.3, 162.6, 165.0, 167.8 ppm; MS(ESI): *m/z* 471.45 $(M+H)^+$; Anal. Calcd for $C_{26}H_{15}ClN_2O_5$: C, 66.32 H, 3.19; N, 5.95 %. Found: C, 66.26 H, 3.14; N, 5.90 %.

8-Hydroxy-2-(2-oxo-2H-chromen-3-yl)-5-(4-bromophenyl)-3H-chromeno[2,3-d]pyrimidin-4(5H)-one ***(6c)***

IR (KBr, cm^{-1}): 3,468 (OH), 3,415 (NH), 1,708 (CO of lactone), 1,666 (CO of ketone), 1,620 (CO of lactam), 1,590 (CN), 1,207 (C–O–C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.11 (s, 1H, CH), 6.67 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.81 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.91 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.28–7.42 (m, 4H, ArH), 7.60–7.75 (m, 4H, Ar–H), 8.36 (s, 1H, Coumarin H), 9.48 (s, 1H, NH), 9.56 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.6, 101.9, 104.5, 111.7, 117.2, 120.9, 124.3, 125.5, 126.5, 127.0, 127.4, 128.5, 128.8, 129.1, 130.7, 144.3, 145.5, 151.4, 156.2, 158.3, 162.5, 163.0, 164.8, 168.4 ppm; MS(ESI): *m/z* 515.9 $(M+H)^+$; Anal. Calcd for $C_{26}H_{15}BrN_2O_5$: C, 60.59; H, 2.91; N, 5.44 %. Found: C, 60.55; H, 2.88; N, 5.43 %.

8-Hydroxy-2-(2-oxo-2H-chromen-3-yl)-5-(4-fluorophenyl)-3H-chromeno[2,3-d]pyrimidin-4(5H)-one ***(6d)***

IR (KBr, cm^{-1}): 3,478 (OH), 3,411 (NH), 1,711 (CO of lactone), 1,655 (CO of ketone), 1,633 (CO of lactam), 1,588 (CN), 1,215 (C–O–C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.21 (s, 1H, CH), 6.55 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.74 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.87 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.33–7.45 (m, 4H, ArH), 7.77–7.88 (m, 4H, Ar–H), 8.40 (s, 1H, Coumarin H), 9.42 (s, 1H, NH) 9.55 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 29.9, 102.0, 105.2, 112.0, 117.6, 121.1, 124.1, 125.7, 126.2, 126.9, 127.7, 128.7, 128.9, 129.5, 131.3, 144.1, 146.3, 150.9, 156.3, 158.4, 162.2, 163.2, 164.6, 167.7 ppm; MS(ESI): *m/z* 455 $(M+H)^+$; Anal. Calcd for $C_{26}H_{15}FN_2O_5$: C, 68.72; H, 3.30; N, 6.17 %. Found: C, 68.66; H, 3.25; N, 6.15 %.

8-Hydroxy-2-(2-oxo-2H-chromen-3-yl)-5-(4-methylphenyl)-3H-chromeno[2,3-d]pyrimidin-4(5H)-one ***(6e)***

IR (KBr, cm^{-1}): 3,465 (OH), 3,422 (NH), 1,699 (CO of lactone), 1,650 (CO of ketone), 1,638 (CO of lactam), 1,585 (CN), 1,209 (C–O–C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.28 (s, 3*H*, CH_3), 5.18 (s, 1H, CH), 6.62 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.73 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.84 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.40 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 7.52 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 7.69–7.79 (m, 4H, Ar–H), 8.29 (s, 1H, Coumarin H), 9.24 (s, 1H, NH), 9.48 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.7, 30.3, 101.5, 104.9, 112.1, 117.2, 120.7, 123.9, 124.6, 126.4, 127.1, 127.7, 128.0, 128.3, 129.4, 130.9, 143.7, 145.8, 151.2, 155.9, 158.6, 161.8, 162.7, 165.1, 168.5 ppm; MS(ESI): *m/z* 451 $(M+H)^+$; Anal. Calcd for $C_{27}H_{18}N_2O_5$: C, 72.00; H, 4.00; N, 6.22 %. Found: C, 72.03; H, 4.00; N, 6.17 %.

8-Hydroxy-2-(2-oxo-2H-chromen-3-yl)-5-(4-methoxyphenyl)-3H-chromeno[2,3-d]pyrimidin-4(5H)-one ***(6f)***

IR (KBr, cm^{-1}): 3,478 (OH), 3,410(NH), 1,710 (CO of lactone), 1,662 (CO of ketone), 1,631 (CO of lactam), 1,603 (CN), 1,222 (C–O–C); ^{1}H NMR (500 MHz,

$CDCl_3$) δ: 3.54 (s, 3*H*, OCH_3), 5.15 (s, 1H, CH), 6.68 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.79 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.88 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.28 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 7.41 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 7.76–7.90 (m, 4H, Ar–H), 8.35 (s, 1H, Coumarin H), 9.40 (s, 1H, NH), 9.40 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 29.5, 56.3, 102.1, 105.3, 110.9, 117.4, 121.3, 123.7, 125.0, 125.8, 126.5, 127.0, 127.9, 128.6, 129.8, 131.4, 144.4, 146.0, 151.4, 156.1, 157.9, 161.9, 162.6, 165.4, 167.3 ppm; MS(ESI): *m/z* 467 $(M+H)^+$; Anal. Calcd for $C_{27}H_{18}N_2O_6$: C, 69.53; H, 3.86; N, 6.01 %. Found: C, 69.44; H, 3.82; N, 6.00 %.

8-Hydroxy-2-(2-oxo-2H-chromen-3-yl)-5-(4-nitrophenyl)-3H-chromeno[2,3-d]pyrimidin-4(5H)-one ***(6g)***

IR (KBr, cm^{-1}): 3,460 (OH), 3,413 (NH), 1,705 (CO of lactone), 1,667 (CO of ketone), 1,625 (CO of lactam), 1,591 (CN), 1,218 (C–O–C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.05 (s, 1H, CH), 6.65 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.80 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.93 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.39 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 7.54 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 7.67–7.84 (m, 4H, Ar–H), 8.40 (s, 1H, Coumarin H), 9.33 (s, 1H, NH), 9.51 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 29.8, 101.9, 104.7, 111.6, 117.3, 120.5, 124.2, 125.4, 126.1, 126.7, 127.3, 127.8, 128.7, 129.7, 131.6, 143.6, 145.4, 150.9, 155.8, 157.8, 161.7, 162.4, 164.3, 168.0 ppm; MS(ESI): *m/z* 482 $(M+H)^+$; Anal. Calcd for $C_{26}H_{15}N_3O_7$: C, 64.86; H, 3.19; N, 8.73 %. Found: C, 64.78; H, 3.16; N, 8.75 %.

8-Hydroxy-2-(2-oxo-2H-chromen-3-yl)-5-(4-hydroxyphenyl)-3H-chromeno[2,3-d]pyrimidin-4(5H)-one ***(6h)***

IR (KBr, cm^{-1}): 3,480 (OH), 3,461 (OH), 3,417 (NH), 1,692 (CO of lactone), 1,653 (CO of ketone), 1,629 (CO of lactam), 1,595 (CN), 1,210 (C–O–C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.22 (s, 1H, CH), 6.56 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.76 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.86 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.34 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 7.45 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 7.59–7.81 (m, 4H, Ar–H), 8.37 (s, 1H, Coumarin H), 9.41 (s, 1H, NH), 9.44 (s, 1H, OH) 9.62 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.6, 102.3, 105.4, 110.8, 116.8, 121.5, 124.5, 125.6, 126.3, 126.9, 127.6, 128.2, 128.8, 129.0, 130.6, 144.5, 146.2, 151.0, 155.6, 157.7, 162.4, 162.9, 164.7, 168.2 ppm; MS(ESI): *m/z* 453 $(M+H)^+$; Anal. Calcd for $C_{26}H_{16}N_2O_6$: C, 69.03; H, 3.54; N, 6.19 %. Found: C, 69.00; H, 3.50; N, 6.20 %.

8-Hydroxy-2-(2-oxo-2H-chromen-3-yl)-5-(3-hydroxyphenyl)-3H-chromeno[2,3-d]pyrimidin-4(5H)-one ***(6i)***

IR (KBr, cm^{-1}): 3,477 (OH), 3,455 (OH), 3,420 (NH), 1,698 (CO of lactone), 1,663 (CO of ketone), 1,636 (CO of lactam), 1,608 (CN), 1,206 (C–O–C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.03 (s, 1H, CH), 6.67 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.77 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.87 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.36–7.45 (m, 4H, ArH), 7.61–7.74 (m, 4H, Ar–H), 8.27 (s, 1H, Coumarin H), 9.28 (s, 1H, NH), 9.38 (s, 1H, OH), 9.60 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.2,

101.8, 104.6, 111.5, 116.7, 120.9, 123.9, 124.7, 126.5, 126.8, 127.4, 128.4, 128.9, 129.9, 130.3, 143.9, 145.8, 150.7, 156.2, 158.4, 162.3, 163.1, 164.5, 167.6 ppm; MS(ESI): *m/z* 453 $(M+H)^+$; Anal. Calcd for $C_{26}H_{16}N_2O_6$: C, 69.05; H, 3.53; N, 6.11 %. Found: C, 69.03; H, 3.54; N, 6.19 %.

8-Hydroxy-2-(2-oxo-2H-chromen-3-yl)-5-(4-N,N-dimethylaminophenyl)-3H-chromeno[2,3-d]pyrimidin-4(5H)-one ***(6j)***

IR (KBr, cm^{-1}): 3,468 (OH), 3,408 (NH), 1,701 (CO of lactone), 1,658 (CO of ketone), 1,627 (CO of lactam), 1,597 (CN), 1,214 (C–O–C); ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 2.65 (s, 6H, CH_3), 5.13 (s, 1H, CH), 6.61 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.76 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar–H), 6.87 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.33 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 7.44 (d, $J = 7.4$ Hz, 2*H*, Ar–H), 7.66–7.78 (m, 4H, Ar–H), 8.39 (s, 1H, Coumarin H), 9.45 (s, 1H, NH), 9.59 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 29.7, 43.9, 101.8, 104.8, 112.2, 117.8, 120.6, 124.0, 125.6, 126.7, 127.2, 127.8, 128.5, 128.8, 129.4, 131.0, 144.2, 146.4, 150.8, 155.7, 158.5, 162.0, 162.5, 164.0, 168.7 ppm; MS(ESI): *m/z* 480 $(M+H)^+$; Anal. Calcd for $C_{28}H_{21}N_3O_5$: C, 70.15; H, 4.38; N, 8.77 %. Found: C, 70.05; H, 4.33; N, 8.75 %.

Results and discussion

The synthetic pathways of the compounds **6a–j** were achieved via 2-amino-3-cyano-7-hydroxy-4-phenyl-4*H*chromene derivatives (**4a–j**). 4*H*-Chromenes possess potent biological activities like antitumor, antibacterial, antiviral, spasmolytic, and anti-anaphylactic [25–30]. Therefore, various synthetic procedures have been developed for the preparation of 4*H*-chromene derivatives [31–41]. However, these methods often suffer from different drawbacks and most of them give moderate yields even after prolonged reaction times. This clearly indicates that there is still scope to develop an efficient and eco-sustainable method for the synthesis of 4*H*-chromene derivatives. The 4*H*-chromene derivatives were obtained by the three-component condensation of resorcinol, aldehydes, and malononitrile using DMAP as catalyst in ethanol.

A diverse array of Lewis bases (e.g., tertiary phosphines, tertiary amines, pyridines, and imidazoles) have been shown to serve as nucleophilic catalysts. The acylation of alcohols by anhydrides, catalyzed by 4-(dimethylamino)pyridine (DMAP), is perhaps the most frequently encountered example of nucleophilic catalysis. In the presence of DMAP, acylations typically occur several orders of magnitude more rapidly than in its absence [42].

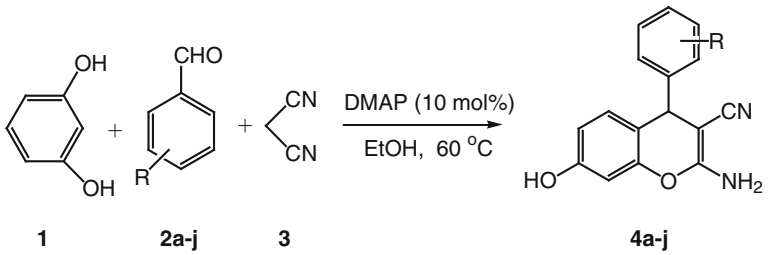
The accelerating pace of reported applications for DMAP and the availability of DMAP in commercial quantities, at modest prices, has continued to stimulate great interest in its use as a catalyst in the fields of organic, polymer, analytical, and biochemistry. Today, there are thousands of examples of the use of DMAP in far-ranging fields of chemistry in both patents and the research literature. Many full-scale production processes utilizing DMAP have been and are being operated. Several pharmaceutical and agricultural products that rely on DMAP's superior

catalytic properties in their synthetic sequences have been produced for years. Since 1976 ,more than 11,000 US patents have been granted which mention DMAP or dimethylaminopyridine [43]. Moreover, DMAP is non-hygroscopic, and is available commercially. Also, it is easy to filter. However, to the best of our knowledge, there is no report which utilizes DMAP as a basic catalyst in the synthesis of 2-amino-3-cyano-7-hydroxy-4-substituted-4*H*chromene derivatives.

To discover the suitable conditions for the reaction, a series of experiments were performed with the standard reaction of resorcinol **1**, benzaldehyde **2a**, and malononitrile **3** as a model reaction (Scheme 1).

Our initial work started with the screening of solvent and catalyst so as to identify optimal reaction conditions for the synthesis of chromene derivatives. To evaluate the effect of the catalyst, we studied the reaction of benzaldehyde, resorcinol, and malononitrile in different pyridine analogues, like DMAP, 4-carboxypyridine, 4-cyanopyridine, and pyridine, in ethanol. DMAP showed better catalytic activity than 4-carboxypyridine, 4-cyanopyridine, and pyridine. The conversion of the products increased in the order of 4-carboxy-pyridine < 4-cyanopyridine < pyridine < DMAP. The electron-donating group-substituted pyridine exhibited higher activity than the electron-withdrawing group-substituted pyridine.

Further, the reaction is carried out in methanol, water ,and under neat condition in the presence of DMAP (10 mol %). Ethanol is proven to be the most suitable solvent for this condensation in terms of yield and reaction time (Table 1, entry 4). We also evaluated the amount of DMAP required for the reaction. The reaction was significantly affected by decreasing the amount of DMAP from 10 to 5 mol%, whereas no improvement could be observed upon increasing the catalyst loading to 15 mol% (Table 1, entries 11, 12). Thus, the best result was obtained with 10 mol% of DMAP in ethanol at 60 °C (Table 1, entry 4). Encouraged by this successful three-component reaction, the synthesis of diverse 2-amino-3-cyano-7-hydroxy-4-phenyl-4*H*chromene derivatives **4a–j** was undertaken. The aromatic aldehydes bearing electron-withdrawing and electron-donating groups were found to be equally effective in producing 2-amino-3-cyano-7-hydroxy-4-phenyl-4*H*chromene derivatives **4a–j** in very good yields (Table 2). The catalyst can be used at least four times without a significant decrease in catalytic activity for the synthesis of 2-amino-3-cyano-7-hydroxy-4-phenyl-4*H*chromene (Table 2, entry 1).



Scheme 1 Synthesis of various 2-amino-3-cyano-7-hydroxy-4-phenyl-4*H*chromene derivatives from resorcinol, benzaldehydes, and malononitrile catalyzed by DMAP (10 mol %)

Table 1 Optimization of the reaction conditions on the synthesis of 2-amino-3-cyano-7-hydroxy-4-phenyl-4*H*chromene (**4a**): solvent screening and catalyst loading

Entry	Solvent	Catalyst	Amount (mol %)	Time (h)	Yield (%)[a]
1	EtOH	4-Carboxy pyridine	10	2	43
2	EtOH	4-Cyano pyridine	10	2	55
3	EtOH	Pyridine	10	2	63
4	EtOH	DMAP	10	1	88
5	None	DMAP	10	2	48
6	MeOH	DMAP	10	2	76
7	Water	DMAP	10	2	72
8	Dichlorometane	DMAP	10	2	32
9	Cyclohexane	DMAP	10	2	29
10	Acetonitrile	DMAP	10	2	42
11	EtOH	DMAP	5	1	75
12	EtOH	DMAP	15	1	88

Reaction conditions: resorcinol (1 mmol), benzaldehyde (1 mmol), malononitrile (1 mmol) at 60 °C

[a] Isolated yield

Table 2 Synthesis of various 2-amino-3-cyano-7-hydroxy-4-phenyl-4*H*chromene derivatives from resorcinol, benzaldehydes, malononitrile catalysed by DMAP (10 mol %)

Entry	R	Product	Time (h)	Yield (%)[a]	Mp (°C)
1	H	**4a**	1.0	88 (86, 84, 82)[b]	232–234
2	4-Cl	**4b**	1.0	87	160–162
3	4-Br	**4c**	1.0	88	228–230
4	4-F	**4d**	1.0	90	186–188
5	4-CH_3	**4e**	1.5	82	182–184
6	4-OCH_3	**4f**	1.5	83	112–114
7	4-NO_2	**4g**	1.0	89	234–236
8	4-OH	**4h**	1.5	83	220–222
9	3-OH	**4i**	1.5	80	216–218
10	4-$N(CH_3)_2$	**4j**	1.5	83	230–232

Reaction conditions: resorcinol (1 mmol), benzaldehydes (1 mmol), malononitrile (1 mmol); DMAP 10 mol % in ethanol at 60 °C

[a] Isolated yield

[b] Reusability of catalyst

After the synthesis of 2-amino-3-cyano-7-hydroxy-4-phenyl-4*H*chromene, we synthesized 8-hydroxy-2-(2-oxo-2*H*-chromen-3-yl)-5-phenyl-3*H*-chromeno[2,3-*d*]pyrimidin-4(5*H*)-one derivatives. Initially, the reaction between compound **4a** and coumarin-3-carboxylic acid was carried out under neat conditions at 60 °C without and with different acid catalysts (sulfamic acid, silica perchloric acid, xanthene sulfuric acid, melamine trisulfonic acid, SBPPSA; each 0.24 mmol) and we observed maximum yield with SBPPSA (Table 3, entry 5).

The solvents played an important role in the synthesis of 8-hydroxy-2-(2-oxo-2*H*-chromen-3-yl)-5-phenyl-3*H*-chromeno[2,3-*d*]pyrimidin-4(5*H*)-one derivatives. Various reaction media were screened (ethanol, *t*-BuOH, acetonitrile, methanol, THF, and 1,4-dioxane) using the model reaction (Table 4, entries 1–6). It was found that the best results were obtained with 0.24 mmol of SBPPSA under solvent-free

Table 3 Preparation of 8-hydroxy-2-(2-oxo-2*H*-chromen-3-yl)-5-phenyl-3*H*-chromeno[2,3-*d*]pyrimidin-4(5*H*)-one: catalyst screening

Entry	Catalyst	Amount of catalyst (mmol)	Time (h)	Yield (%)[a]
1	Sulfamic acid	0.24	4.0	68
2	Silica perchloric acid	0.24	4.0	73
3	Xanthene sulfuric acid	0.24	4.0	69
4	Melamine trisulfonic acid	0.24	4.0	58
5	SBPPSA	0.24	3.0	89
6	None	0	4.0	Trace
7	SBPPSA	0.30	3.0	89
8	SBPPSA	0.18	3.0	76

Reaction conditions: **4a** (1 mmol) and coumarin-3-carboxylic acid (1 mmol) at 60 °C

[a] Isolated yield

condition (Table 4, entry 7). The reaction was completed in 3 h and the expected product was obtained in 90 % yield.

At these optimised conditions (solvent-free, 60 °C, 0.24 mmol of SBPPSA), we synthesized various 8-hydroxy-2-(2-oxo-2*H*-chromen-3-yl)-5-phenyl-3*H*-chromeno[2,3-*d*]pyrimidin-4(5*H*)-one derivatives **6a–j** (Table 5) (Scheme 2). After completion of the reaction, the catalyst was recovered by evaporating the aqueous layer, which was washed with acetone, dried, and reused for four subsequent reactions without significant loss of its activity (Table 5, entry 1; Fig. 1). All the synthesized compounds were confirmed by their analytical and spectroscopic data.

Biological activity

All the compounds were screened for their antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*, and for antifungal activity against *Aspergillus flavus*, *Rhizopus schipperae*, *Aspergillus niger*, and *Candida albicans*. Compounds **6b–j** with various substituents in the aromatic ring will be useful in understanding the influence of steric and electronic effects on the biological activity.

Antibacterial activity

For evaluating antibacterial activity ,Ciprofloxacin was used as the standard drug. Serial dilutions of the drug in Muller Hinton broth were placed in tubes and their pH was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacterium was inoculated and incubated for 16–18 h at 37 °C. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth. The observed MIC are given in Table 6. In general, all the synthesized compounds exerted a wide range of modest antibacterial activity in vitro against the tested organisms. Compound **6a** without any substituent in the aryl moiety exhibits antibacterial activity in vitro at 75 μg/mL against *P. aeruginosa*. It exhibits antibacterial activity against the other tested organisms only at 150 μg/mL. However, **6b**, in which the hydrogen at the *para* position of the aryl moiety is replaced by chlorine, shows activity against all the

Table 4 Preparation of 8-hydroxy-2-(2-oxo-2*H*-chromen-3-yl)-5-phenyl-3*H*-chromeno[2,3-*d*]pyrimidin-4(5*H*)-one: solvent screening

Entry	Solvent	Amount of catalyst (mmol)	Time (h)	Yield (%)[a]
1	Ethanol	0.24	4.0	77
2	*t*-BuOH	0.24	4.0	29
3	Acetonitrile	0.24	4.0	41
4	Methanol	0.24	4.0	69
5	THF	0.24	4.0	46
6	1,4-Dioxane	0.24	4.0	57
7	None	0.24	3.0	90

Reaction conditions: **4a** (1 mmol) and coumarin-3-carboxylic acid (1 mmol) in the presence of SBPPSA (0.2 g, equal to 0.24 mmol of H^+) at 60 °C

[a] Isolated yields

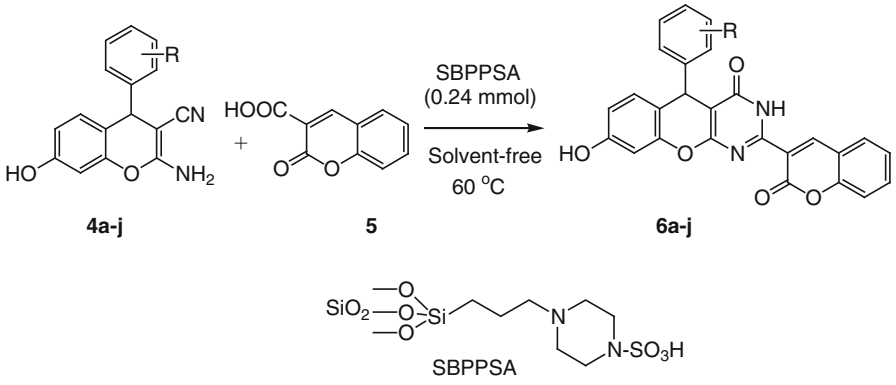
Table 5 Preparation of various 8-hydroxy-2-(2-oxo-2*H*-chromen-3-yl)-5-phenyl-3*H*-chromeno[2,3-*d*]pyrimidin-4(5*H*)-one derivatives

Entry	R	Product	Time (h)	Yield (%)[a]	Mp (°C)
1	H	**6a**	3.0	90 (88, 86, 85)[b]	218–220
2	4-Cl	**6b**	3.0	86	226–228
3	4-Br	**6c**	3.0	88	242–244
4	4-F	**6d**	3.0	87	202–204
5	4-CH_3	**6e**	3.5	85	208–210
6	4-OCH_3	**6f**	3.5	84	246–248
7	4-NO_2	**6g**	3.0	91	234–236
8	4-OH	**6h**	3.0	93	220–222
9	3-OH	**6i**	3.5	90	214–216
10	4-$N(CH_3)_2$	**6j**	3.5	81	230–232

Reaction conditions: **4a–j** (1 mmol) and coumarin-3-carboxylic acid (1 mmol) in the presence of SBPPSA (0.24 mmol) at 60 °C

[a] Isolated yield

[b] Reusability of catalyst



Scheme 2 Synthesis of various 8-hydroxy-2-(2-oxo-2*H*-chromen-3-yl)-5-phenyl-3*H*-chromeno[2,3-*d*]pyrimidin-4(5*H*)-one derivatives from **4a–j** and coumarin-3-carboxylic acid catalyzed by SBPPSA

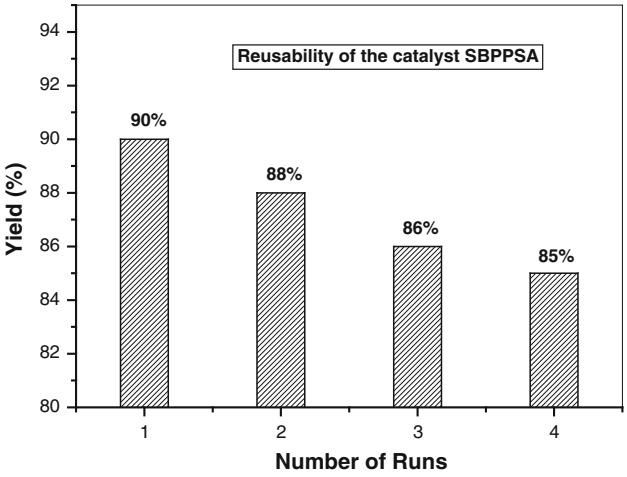


Fig. 1 Reusability of the catalyst SBPPSA for the synthesis of 8-hydroxy-2-(2-oxo-2*H*-chromen-3-yl)-5-phenyl-3*H*-chromeno[2,3-*d*]pyrimidin-4(5*H*)-one

Table 6 In vitro antibacterial activity of compounds **6a–j**

Compounds	Minimum inhibitory concentration (MIC) in μg/mL			
	E. coli	*P. aeruginosa*	*K. pneumonia*	*S. aureus*
6a	150	75	150	150
6b	50	25	50	25
6c	50	25	50	25
6d	25	12.5	25	25
6e	75	50	75	75
6f	75	50	75	50
6g	12.5	12.5	12.5	12.5
6h	75	50	75	50
6i	50	25	50	25
6j	75	50	75	50
Ciprofloxacin	25	12.5	25	25

tested organisms in the range of 25–50 μg/mL. Compound **6c**, which has the bromine in the *para* position, has the same activity as **6b**, which has the chlorine in the *para* position. Indeed, the compounds **6b–j**, bearing a substituent in the aryl group, are more active than the parent compound **6a**. Only **6g** which has a nitro group at the *para* position and **6d** which has a fluorine group in the *para* position are more active than the reference drug Ciprofloxacin.

Antifungal activity

For evaluating antifungal activity, Amphotericin B was used as the standard drug. Newly prepared compounds were also screened for their antifungal activity against

Table 7 In vitro antifungal activity of compounds **6a–j**

Compounds	Minimum inhibitory concentration (MIC) in μg/mL			
	A. flavus	*R. schipperae*	*A. niger*	*C. albicans*
6a	150	100	100	100
6b	75	50	75	25
6c	75	50	75	25
6d	50	50	50	25
6e	100	75	100	100
6f	100	75	100	75
6 g	25	25	25	12.5
6h	100	75	100	50
6i	75	50	75	25
6j	75	75	100	50
Amphoterecin-B	50	25	50	25

each fungal strain in DMSO by the serial plate dilution method. Sabourauds agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of some of the fungal strains for lawning. A loopful of a particular fungal strain was transferred to 3 mL saline to get a suspension of the corresponding species. Twenty milliliters of agar media was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 °C for 1 h. Using a punch, wells were made in these seeded agar plates. The observed MIC are given in Table 7. It is seen that **6a** shows antifungal activity against all the tested fungi in the range of 100–150 μgmL^{-1}. Compounds **6b–j** which have substituents in the 4-aryl group are more active than the parent compound **6a** against all the tested fungi. The *para*-chloro compound **6b** and the *para*-bromo compound **6c** have the same activity. Compounds **6d** and **6g** are more active than the standard drug Amphotericin B against all the tested organisms.

Influence of aromatic substituents

The results suggest that the antibacterial and antifungal activities are markedly influenced by the aromatic substituents. Thus, **6b**, **6c**, and **6g** with electron-withdrawing substituents in the aromatic ring show greater antibacterial activity than the other compounds against all the tested organisms. Also, compounds **6d** and **6g** show greater antifungal activity than all the other compounds against all the tested organisms. The aromatic substituents in **6b**, **6c**, and **6g** have positive values for the Hammett substituent constant σ_p [Cl (+0.23), Br (+0.23) and NO_2 (+0.78)]. The aromatic substituents in **6e**, **6f**, and **6j** have negative values for the Hammett substituent constant σ_p [CH_3 (−0.17), OCH_3 (−0.27) and $N(CH_3)_2$ (−0.83)]. The 4-fluoro compound **6d** is the most active compound, though the σ_p value of F (+0.06) is less than that of the other substituents. Probably, the 4-fluoro compound

is able to interact with the microorganisms more effectively due to some intermolecular hydrogen bonding. Fluorine has the greatest ability to form hydrogen bonding, and hence **6d** is more active than the other compounds. The Hammett substituent constant σ for the aromatic substituents in **6h** and **6i** are σ_p OH (−0.37) and σ_m OH (+0.12), respectively. Hence, **6i** is more active than **6h**.

Conclusions

In summary, we have developed a direct and efficient method for the preparation of 8-hydroxy-2-(2-oxo-2*H*-chromen-3-yl)-5-phenyl-3*H*-chromeno[2,3-*d*]pyrimidin-4(5*H*)-one derivatives by the condensation of 2-amino-3-cyano-7-hydroxy-4-phenyl-4*H*chromene derivatives with coumarin-3-carboxylic acid in the presence of 0.24 mmol of SBPPSA as catalyst under solvent-free conditions. This method tolerates most of the substrates, and the catalyst can be used at least four times without significant loss of activity. All the compounds were screened for their antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *S. aureus* and antifungal activity against *Aspergillus flavus*, *Rhizopus schipperae*, *Aspergillus niger*, and *C. albicans.*

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