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Synthesis of some novel coumarin-pyrimidine hybrid compounds from 8- and 6-acetyl-7-hydroxy-4-methylcoumarin

Thanh Ngoc Nguyen[1]*, Giang Thu Thi Pham[1], and Van Thuy Ngo[1]

[1]*Faculty of Chemical Technology, Hanoi University of Industry, Bac Tu Liem District, Hanoi 10000, Vietnam*
Email: thanhnn@haui.edu.vn

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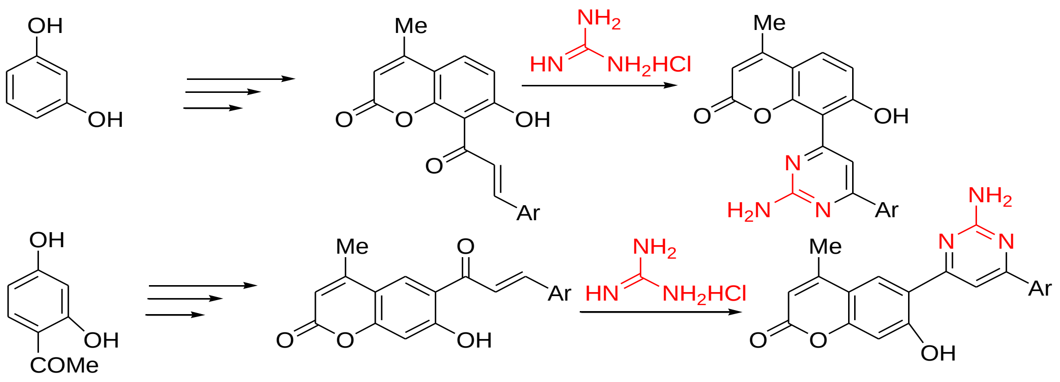
Abstract

Coumarins are heterocyclic compounds which can exhibit a wide range of significant biological and pharmacological properties. Coumarin-pyrimidine hybrids integrate structural elements of both coumarin and pyrimidine, often exhibiting enhanced biological activities due to the synergistic interaction of the two pharmacophores. Starting from 6- and 8-acetyl-7-hydroxy-4-methylcoumarin, a total of twenty-one novel compounds, identified as 8- and 6-(2-amino-6-arylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarins, were successfully synthesized. The synthesized pyrimidines demonstrated significant antimicrobial activity, effectively inhibiting *Klebsiella pneumoniae*, *Staphylococcus epidermidis*, and, more prominently, *Candida albicans*, with aseptic zone diameters reaching up to 30 mm at concentrations of 150 µg/ µl.



Keywords: Coumarin-pyrimidine hybrids, coumarin, ethyl acetoacetate, 2-aminopyrimidine, α,β- unsaturated ketones

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Introduction

Coumarin compounds are naturally-occurring phytochemicals as well as newly synthesized bioactive molecules. These compounds contain heterocycles that exhibit a wide range of significant biological and pharmacological activities, including antidiabetic,[1] anticancer,[2,3] antifungal,[4] anti-HIV, and antibacterial properties.[5] In recent years, various coumarins and their derivatives, with diverse bioactive functions, have been identified.[6]

Several clinically-used drugs contain the coumarin scaffold, such as Warfarin, Acenocoumarol, and Phenprocoumon, which function as anticoagulants by inhibiting vitamin K.[7] Additionally, Novobiocin, a coumarin-based antibiotic, targets bacterial DNA gyrase, exhibiting potent antibacterial activity.[8] Some coumarin-based drugs have also been explored for anticancer properties, such as 4-hydroxycoumarin, which has demonstrated potential activity against various cancer cell lines.[9]

Numerous coumarin derivatives, either isolated from natural sources or synthesized, have demonstrated the ability to inhibit platelet aggregation[10] and the steroid 5α-reductase.[11] Furthermore, coumarins hold potential for other applications, such as optical-brightening agents,[12] photosensitive agents,[13] fluorescent and laser dyes,[13,14] and additives in perfumes and cosmetics.[15]

Pyrimidine derivatives possess significant medicinal properties, as the pyrimidine base is a key component of thymine-, cytosine-, and uracil-essential DNA and RNA building blocks.[16] Electron-rich nitrogen heterocycles, like pyrimidine, play a vital role in various biological activities, including antibacterial,[17] anticancer,[18] and antidiabetic effects.[19,20]

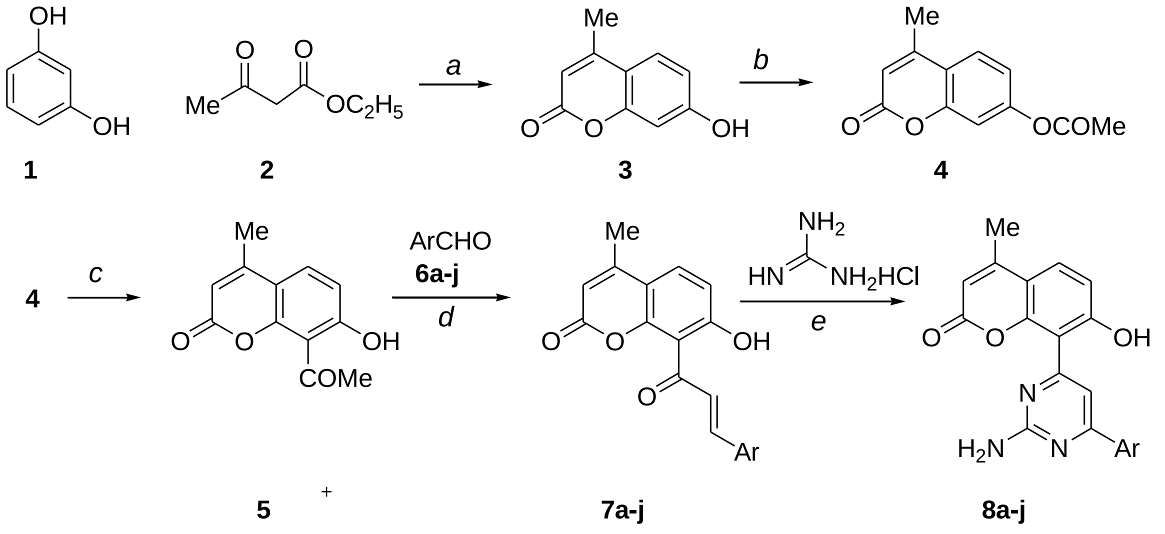
Several pyrimidine-containing drugs are widely used in clinical practice. Notable examples include 5-Fluorouracil (5-FU), Capecitabine, and Pemetrexed, which are extensively employed in anticancer therapy.[21] Additionally, Zidovudine (AZT) and Lamivudine (3TC), two pyrimidine-based antiviral drugs, are crucial in HIV/AIDS treatment.[22] Furthermore, Sofosbuvir, a pyrimidine-based NS5B polymerase inhibitor, is widely prescribed for hepatitis C treatment.[23]

Coumarin-pyrimidine hybrids integrate structural elements of both coumarin and pyrimidine, often exhibiting enhanced biological activities due to the synergistic interaction of these two pharmacophores.[20,24,25] The specific biological effects of a coumarin-pyrimidine hybrid depend on its molecular structure and interactions with biological targets. Experimental studies are essential to fully understand and define the pharmacological profiles of these hybrids.

Results and Discussion

Coumarin has been synthesized by various authors through different pathways.[22,26] This paper presents the synthesis of coumarin derivatives from resorcinol and 2,4-dihydroxyacetophenone according to Schemes 1 and 3.

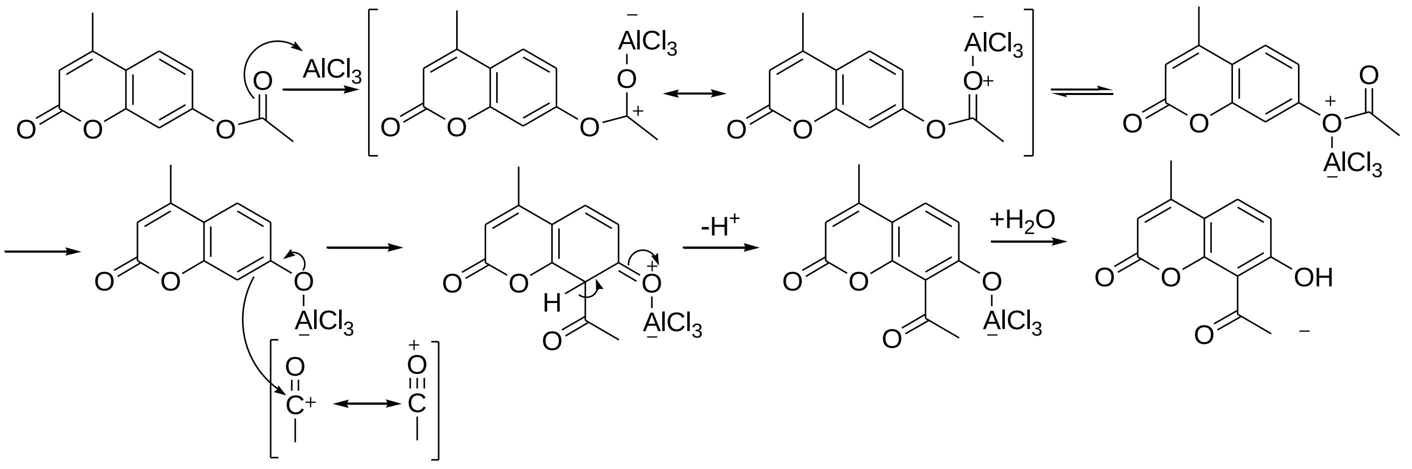
8-Acetyl-7-hydroxy-4-methylcoumarin (**5**) was synthesized starting from resorcinol, as outlined in Scheme 1.



Ar=C_6H_5 (**a**); 4-$CH_3C_6H_4$ (**b**); 4-$CH_3OC_6H_4$ (**c**); 4-$(CH_3)_2NC_6H_4$ (**d**); 4-ClC_6H_4 (**e**);
3-ClC_6H_4 (**f**); 3-$O_2NC_6H_4$ (**g**); 4-BrC_6H_4 (**h**); 4-HO-3-$CH_3OC_6H_3$ (**i**); 3,4-$O_2CH_2C_6H_3$ (**j**)

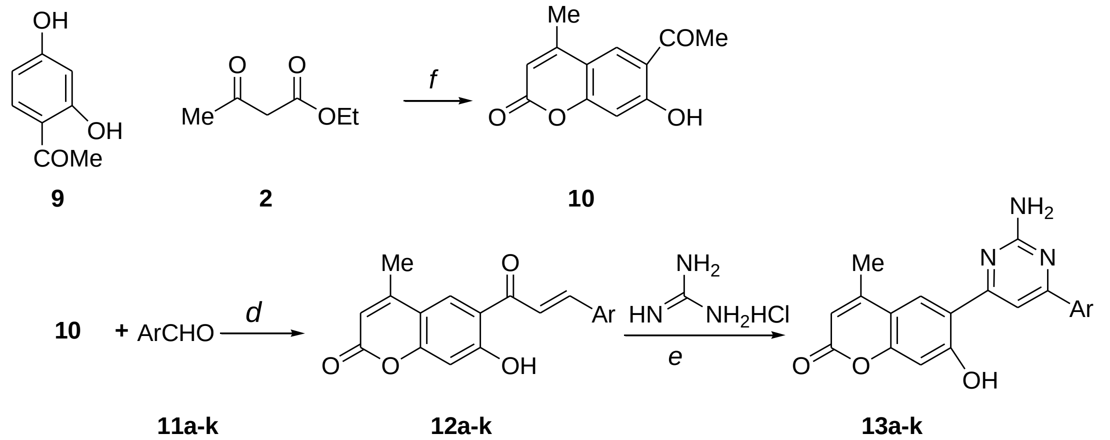
Scheme 1. Synthetic path to coumarin-pyrimidine hybrid compounds **8a–j** from resorcinol. Reaction conditions: (a) H_2SO_4, room temperature for 24 hours; (b) $(CH_3CO)_2O$, under reflux conditions, 1.5 hours; (c) $AlCl_3$ (catalyst), 2 h, 160 °C; (d) Piperidine (catalyst), abs. EtOH, 20–40 h, under reflux conditions; (e) $NaHCO_3$, DMF, 48-70 h, 70 °C.

The process began with the synthesis of 7-hydroxy-4-methylcoumarin (**3**) via the Pechmann reaction, catalyzed by H_2SO_4, using resorcinol and ethyl acetoacetate as starting materials. Compound (**3**) was then acetylated to produce 7-acetoxy-4-methylcoumarin (**4**). Finally, the Fries rearrangement of compound (**4**) was carried out at 160 °C, using dry $AlCl_3$ as a catalyst, to yield 8-acetyl-7-hydroxy-4-methylcoumarin (**5**).[27,28] The transformation of **(4)** into (**5**) occurs via the Fries rearrangement, which involves the migration of the acetyl group under Lewis acid ($AlCl_3$) catalysis (Scheme 2). The Fries rearrangement of the acetyl group mainly occurs at position 8, consistent with the calculated atomic charges on the carbon atoms. Specifically, the charge at C-8 is -0.246, while at C-6 it is -0.184.[29,30]



Scheme 2. Fries rearrangement of 7-acetoxy-4-methylcoumarin.

The synthesis of 6-acetyl-7-hydroxy-4-methylcoumarin (**10**) was achieved using Pechmann condensation, starting from 2,4-dihydroxyacetophenone and ethyl acetoacetate, following a procedure described in the literature.[31] The reaction was conducted in the presence of $POCl_3$ as a catalyst and nitrobenzene as the solvent (Scheme 3).



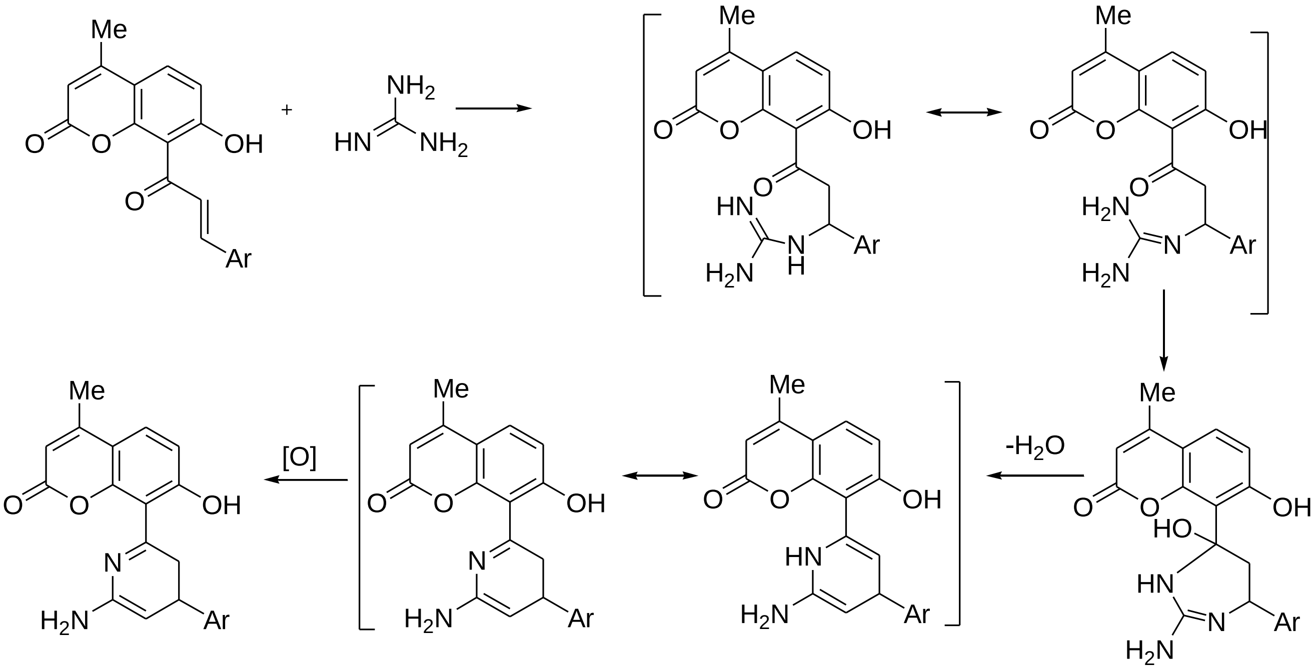
Ar=C_6H_5 (**a**); 4-$CH_3C_6H_4$ (**b**); 4-$CH_3OC_6H_4$ (**c**); 4-$(CH_3)_2NC_6H_4$ (**d**); 4-ClC_6H_4 (**e**);
3-ClC_6H_4 (**f**); 3-$O_2NC_6H_4$ (**g**); 4-BrC_6H_4 (**h**); 4-HO-3-$OCH_3C_6H_3$ (**i**); 3-Pyridyl (**j**) Indol-3-yl (**k**)

Scheme 3. Synthetic path to coumarin-pyrimidines hybrid compounds **13a–k** from 2,4-dihydroxyacetophenone. Reaction conditions (f) $POCl_3$, nitrobenzene, room temperature for seven days.

Compounds 8- and 6-[(2*E*)-3-(aryl)-prop-2-enoyl]-7-hydroxy-4-methylcoumarin (**7a–j** and **12a–k**) were synthesized through the Claisen-Schmidt reaction of 8- and 6-acetyl-7-hydroxy-4-methylcoumarin (**5**, **10**) with various aromatic and heteroaromatic aldehydes (**6a–j** and **11a–k**), following a previously established procedure (Schemes 1 and 3).[20,32] Weak bases such as piperidine, trimethylamine, and pyridine were employed as catalysts in chloroform or ethanol solvents for this reaction. In contrast, using stronger inorganic bases like KOH and NaOH, resulted in lower yields due to the opening of the coumarin ring under these conditions.[20]

The condensation reaction of *α,β*-unsaturated ketones (**7a–j** and **12a–k**) with guanidine hydrochloride yielded 4,6-disubstituted-2-aminopyrimidines (**8a–j** and **13a–k**) as shown in Schemes 1 and 3. Sodium bicarbonate was utilized as a base to neutralize HCl from guanidine hydrochloride, forming the guanidine base. The reaction was carried out under reflux in dry DMF as the solvent. While literature reports suggest that other bases such as KOH in MeOH [33] or NaH in DMF [34] can be employed for this ring-closure reaction, DMF was chosen in this study due to the poor solubility of ketones **7a–j** and **12a–k** in alcohol-based solvents.

The syntheses of the 2-aminopyrimidines were relatively slow, requiring extended reaction times of 48–70 hours under reflux at 70 °C, as monitored by TLC. The molar ratio of *α,β*-unsaturated ketones to guanidine hydrochloride was maintained at 1:1. The synthesis of 2-aminopyrimidines commences with the nucleophilic attack of guanidine on the activated double bond of *α,β*-unsaturated ketones (a Michael-type addition). This is followed by dehydration to yield either 2-arylamino-1,6-dihydropyrimidine or 2-arylamino-1,4-dihydropyrimidine. Subsequent oxidation by atmospheric oxygen results in the formation of aromatic pyrimidines (Scheme 4).[35]



Scheme 4. The reaction mechanism for synthesizing pyrimidine compounds.

The resulting coumarin–pyrimidine hybrids were solids with high melting points (247 °C to > 350 °C) and low solubility in common organic solvents such as ethanol, acetone, and chloroform. The successful formations of 2-aminopyrimidine derivatives were confirmed through spectral analyses, including IR, NMR, and ESI-MS.

The IR spectra of the 2-aminopyrimidine derivatives exhibited characteristic absorption peaks corresponding to the C=C and C=N groups of the pyrimidine ring, appearing in the range of 1519–1611 cm^{-1}. The amino group in the pyrimidine ring was identified by two distinct bands in the regions of 3123–3241 cm^{-1} and 3321–3377 cm^{-1}, respectively. Additionally, the IR spectra confirmed the disappearance of the characteristic absorption bands for the out-of-plane bending vibrations of the C−H group in the *trans*-alkene, typically observed in the 960–990 cm^{-1} region.

In the ^{1}H-NMR spectra of all of the coumarin–pyrimidine hybrid compounds, the appearances of new resonance signals in the regions of δ = 7.03–7.37 ppm and 7.88–8.04 ppm as singlets, each integrating for 2H, were assigned to the two protons of the 2-amino group and the 5-H proton of the pyrimidine ring, respectively. These signals provide clear evidence for the successful ring-closure of enones **7a–j** and **12a–k** with guanidine hydrochloride.

The ^{13}C-NMR spectra displayed distinct signals at δ = 160.8–163.8 ppm and 162.4–166.0 ppm, corresponding to the 4-C and 6-C carbons of the pyrimidine ring, further confirming the structure.

Additionally, the ESI-MS spectra of certain 2-amino-4,6-diarylpyrimidines showed ion-molecule peaks consistent with the calculated molecular formulas, adhering to the nitrogen rule. The presence of chlorine in the molecule or ion was easily identified by observing the characteristic intensity ratios of ions differing by 2 amu.

All synthesized compounds (**8a–j** and **13a–k**) were evaluated for their antimicrobial activity against the gram-negative bacterium *Klebsiella pneumoniae*, the gram-positive bacterium *Staphylococcus epidermidis*, and the fungus *Candida albicans* at 19-8 Hospital (Vietnam) using the disc-diffusion method.[36]

All of the compounds **8a-j and 13a-k** show activity against *K. pneumoniae*, *S. epidermidis*, and especially *C. albicans* at 150 μg/μl with aseptically circle diameters up to 30 mm (compounds **8a, 8h** and **8j**). The details of the results are presented in Table 1.

Table 1. Antibacterial and antifungal activity of **8a-j and 13a-k**

Compd	*K.pneumoniae*			*S.epidamisdis*			*C.albicans*		
	50μg/μl	100μg/μl	150μg/μl	50μg/μl	100μg/μl	150μg/μl	50μg/μl	100μg/μl	150μg/μl
8a	0	14	18	0	17	24	14	26	30
8b	0	12	11	0	0	17	11	20	23
8c	0	8	12	0	0	18	12	22	27
8d	0	8	13	0	0	20	11	22	25
8e	0	15	14	0	0	18	8	20	24
8f	0	14	15	0	0	20	11	21	26
8g	0	14	22	8	16	24	14	23	28
8h	0	12	19	12	20	25	12	22	30
8i	0	14	22	12	24	26	14	26	30
8j	0	12	21	14	22	25	17	24	29
13a	0	14	13	0	0	20	10	21	25
13b	0	10	14	0	0	18	9	20	24
13c	0	8	12	0	0	14	12	24	27
13d	0	14	17	14	19	25	14	23	27
13e	0	13	12	0	0	18	12	19	24
13f	0	8	14	9	17	21	9	23	28
13g	0	9	12	0	0	17	11	20	23
13h	0	8	12	0	0	17	12	22	26
13i	0	8	13	0	0	20	11	22	25
13j	0	15	14	0	0	18	8	20	24
13k	0	14	15	0	0	20	11	21	26

Conclusions

In this study, a series of novel coumarin-pyrimidine hybrid compounds were successfully synthesized from 8- and 6-acetyl-7-hydroxy-4-methylcoumarin. The synthetic pathway was optimized, and the structures of the obtained compounds were confirmed using IR, NMR, and HRMS spectral analyses.The biological evaluation demonstrated that these compounds exhibited significant antimicrobial activity against *Klebsiella pneumoniae*, *Staphylococcus epidermidis*, and *Candida albicans*. Several showed particularly strong inhibitory effects against *C. albicans*, with circle diameters of up to 30 mm at concentrations of 150 μg/μl. These findings suggest that the synergistic integration of coumarin and pyrimidine pharmacophores plays a crucial role in enhancing antimicrobial potency.

Overall, this study provides valuable insights into the synthetic development and biological potential of coumarin-pyrimidine hybrids. Future research will focus on mechanistic studies, molecular docking, and in vivo evaluations to further explore their therapeutic applications and optimize their drug-like properties.

Experimental Section

General. The melting points of the synthetic compounds were confirmed using a Stuart SMP3 apparatus. The IR spectra were recorded with an Impact 410-Nicolet Spectrometer using KBr pellets. NMR spectra were obtained at 500 MHz for ^{1}H and 125 MHz for ^{13}C using an Avance AV500 Spectrometer (Bruker, Germany), with DMSO-d_6 as the solvent and TMS as the internal standard. ESI-MS data were acquired using an LC-MS-ORBITRAP-XL system. Thin-layer chromatography (TLC) was performed using Merck Kieselgel 60F254 pre-coated plates. The R*f values of the compounds were determined using a chloroform/ethyl acetate mixture (1:4 for **8a–j**) and n-hexane/ethyl acetate (1:1.2 for **13a–k**). All chemical reagents, purchased from Merck Chemical Company, were of high purity and suitable for organic synthesis.

General procedure for the synthesis of 8- and 6-(2-amino-6-arylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**8a–j**; **13a–k**). A mixture of 7a–j and 12a–k (1 mmol), guanidine hydrochloride (1 mmol, 95.5 mg), and $NaHCO_3$ (1 mmol, 84 mg) was dissolved in 30 ml of DMF. The solution was heated under reflux in a water bath at 70°C for 48–70 hours, and the progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and poured onto crushed ice with continuous stirring, leading to the precipitation of the crude product. The solid was collected by filtration, thoroughly washed with cold water to remove residual impurities, and dried under vacuum.

For purification, the crude product was recrystallized using a mixture of DMF and 96% ethanol. Specifically, the solid was first dissolved in a minimal amount of hot DMF to ensure complete dissolution. Then, 96% ethanol was slowly added under stirring until the solution reached saturation. The mixture was allowed to cool gradually to room temperature, and crystallization was induced by either slow evaporation. The formed crystals were collected by filtration, washed with cold ethanol to remove any remaining impurities, and dried under vacuum, yielding the purified compounds **8a–j** and **13a–k** in high purity.

8-(2-Amino-6-phenylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**8a**). From **7a** (Ar=C_6H_5, 1mmol, 306 mg): Reaction time: 60 h, yield 158.7 mg (46%) of **8a**, crystallized from a mixture of DMF and 96% ethanol (1:2) as brown crystals. Mp 286-288^{o}C, R^*_f value 0.78. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1711, $\upsilon_{OH,\ NH}$ at 3227, 3341, 3454, $\upsilon_{C=C,\ C=N}$ at 1594, 1537, and δ_{NH} at 1648. ^{1}H-NMR (500 MHz, DMSO-d_6), δ (ppm): 6.21 (1H, d, *J* 1.0 Hz, 3-H cou); 2.41 (3H, d, *J* 1.0 Hz, 4-CH_3 cou); 7.72 (1H, d, *J* 9.0 Hz, 5-H cou); 6.95 (1H, d, *J* 9.0 Hz, 6-H cou); 14.17 (1H, s, 7-OH cou); 7.20 (2H, s, 3-NH_2 pyrim); 7.96 (1H, s, 5-H pyrim); 8.10-8.07 (2H, m, Ar-H) and 7.56-7.52 (3H, m, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6), δ (ppm): 159.4 (2-C cou); 109.9 (3-C cou); 111.7 (4a-C cou); 153.3 (4-C cou); 18.55 (4-CH_3 cou); 127.9 (5-C cou); 114.3 (6-C cou); 154.1 (7-C cou); 108.2 (8-C cou); 162.7 (8a-C cou); 161.5 (4-C pyrim); 161.4 (2-C pyrim); 165.3 (6-C pyrim); 106.0 (5-C pyrim); 137.1 (Ar-C), 126.8 (Ar-C); 128.8 (Ar-C); 130.8 (Ar-C); 128.8 (Ar-C) and 126.8 (Ar-C).

8-(2-Amino-6-*p*-tolylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**8b**). From **7b** (Ar=*p*-$CH_3C_6H_4$, 1mmol, 320 mg): Reaction time: 54 h, yield 172.3 mg (48%) of **8a**, crystallized from a mixture of DMF and 96% ethanol (1:2) as yellow crystals. Mp 289-291^{o}C, R^*_f value 0.80. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1701, $\upsilon_{OH,\ NH}$ at 3227, 3342, 3435, $\upsilon_{C=C,\ C=N}$ at 1594, 1540, and δ_{NH} at 1652. ^{1}H-NMR (500 MHz, DMSO-d_6), δ (ppm): 6.21 (1H, d, *J* 1.0 Hz, 3-H cou); 2.41 (3H, d, *J* 1.0 Hz, 4-CH_3 cou); 7.71 (1H, d, *J* 8.5 Hz, 5-H cou); 6.93 (1H, d, *J* 8.5 Hz, 6-H cou); 14.30 (1H, s, 7-OH cou); 7.16 (2H, s, 3-NH_2 pyrim); 7.95 (1H, s, 5-H pyrim); 7.99 (2H, d, *J* 8.5 Hz, Ar-H), 7.34 (2H, d, *J* 8.5 Hz, Ar-H), and 2.38 (3H, s, Ar-CH_3). ^{13}C-NMR (125 MHz, DMSO-d_6), δ (ppm): 159.3 (2-C cou); 109.8 (3-C cou); 111.7 (4a-C cou); 153.3 (4-C cou); 18.50 (4-CH_3 cou); 127.9 (5-C cou); 114.3 (6-C cou); 154.0 (7-C cou); 108.0 (8-C cou); 162.9 (8a-C cou); 161.3 (4-C pyrim); 161.2 (2-C pyrim); 165.2 (6-C pyrim); 105.6 (5-C pyrim); 140.7 (Ar-C), 126.7 (Ar-C); 129.3 (Ar-C); 134.2 (Ar-C); 129.3 (Ar-C); 126.7 (Ar-C) and 20.89 (Ar-CH_3). ESI-MS: *m/z* 382.79 $[M+Na]^+$, 100%. Anal. Calcd for $C_{21}H_{17}N_3O_3$, M= 359.1270 Da.

8-(2-Amino-6-*p*-methoxyphenylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**8c**). From **7c** (Ar=*p*-$CH_3OC_6H_4$, 1mmol, 336 mg): Reaction time: 48 h, yield 198.7 mg (53%) of **8c**, crystallized from a mixture of DMF and 96% ethanol (1:2) as light-yellow crystals. Mp 276-278°C, R^*_f value 0.68. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1730, $\upsilon_{OH, NH}$ at 3231, 3345, 3451, $\upsilon_{C=C, C=N}$ at 1606, 1556, and δ_{NH} at 1650. ^{1}H-NMR (500 MHz, DMSO-d_6), δ (ppm): 6.21 (1H, d, *J* 1.0 Hz, 3-H cou); 2.41 (3H, d, *J* 1.0 Hz, 4-CH_3 cou); 7.71 (1H, d, *J* 8.5 Hz, 5-H cou); 6.93 (1H, d, *J* 8.5 Hz, 6-H cou); 7.12 (2H, s, 3-NH_2 pyrim); 7.94 (1H, s, 5-H pyrim); 8.07 (2H, d, *J* 7.0 Hz, Ar-H), 7.08 (2H, d, *J* 7.0 Hz, Ar-H), and 3.84 (3H, s, Ar-OCH_3). ^{13}C-NMR (125 MHz, DMSO-d_6), δ (ppm): 161.1 (2-C cou); 109.7 (3-C cou); 111.6 (4a-C cou); 153.3 (4-C cou); 18.56 (4-CH_3 cou); 127.9 (5-C cou); 114.4 (6-C cou); 154.1 (7-C cou); 108.0 (8-C cou); 163.1 (8a-C cou); 161.5 (4-C pyrim); 161.3 (2-C pyrim); 164.9 (6-C pyrim); 105.1 (5-C pyrim); 129.4 (Ar-C), 114.2 (Ar-C); 128.4 (Ar-C); 159.4 (Ar-C); 128.4 (Ar-C); 114.2 (Ar-C) and 55.35 (Ar-OCH_3). ESI-MS: *m/z* 376.44 $[M+H]^+$, 100%. Anal. Calcd for $C_{21}H_{17}N_3O_4$, M= 375.1219 Da.

8-(2-Amino-6-*p-N,N*-dimethylaminophenylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**8d**). From **7d** (Ar=*p*-$(CH_3)_2NC_6H_4$, 1mmol, 349 mg): Reaction time: 48 h, yield 217.8 mg (56%) of **8d**, crystallized from a mixture of DMF and 96% ethanol (1:2) as yellow crystals. Mp 290-292°C, R^*_f value 0.72. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1722, $\upsilon_{OH, NH}$ at 3223, 3322, 3442, $\upsilon_{C=C, C=N}$ at 1589, 1550, and δ_{NH} at 1633. ^{1}H-NMR (500 MHz, DMSO-d_6), δ (ppm): 6.21 (1H, s, 3-H cou); 2.41 (3H, s, 4-CH_3 cou); 7.70 (1H, d, *J* 8.5 Hz, 5-H cou); 6.92 (1H, d, *J* 8.5 Hz, 6-H cou); 15.08 (1H, s, 7-OH cou); 7.03 (2H, s, 3-NH_2 pyrim); 7.99 (1H, s, 5-H pyrim); 7.98 (2H, d, *J* 8.5 Hz, Ar-H), 6.80 (2H, d, *J* 8.5 Hz, Ar-H), and 3.00 (6H, s, Ar-$N(CH_3)_2$). ^{13}C-NMR (125 MHz, DMSO-d_6), δ (ppm): 159.4 (2-C cou); 109.6 (3-C cou); 154.1 (4-C cou); 18.58 (4-CH_3 cou); 127.8 (5-C cou); 114.6 (6-C cou); 153.5 (7-C cou); 107.3 (8-C cou); 163.8 (8a-C cou); 160.8 (4-C pyrim); 160.1 (2-C pyrim); 165.4 (6-C pyrim); 104.1 (5-C pyrim); 111.5 (Ar-C); 128.0 (Ar-C); 152.1 (Ar-C); 128.0 (Ar-C); 114.5 (Ar-C) and 40.01 (Ar-$N(CH_3)_2$).

8-(2-Amino-6-*p*-chlorophenylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**8e**). From **7e** (Ar=*p*-ClC_6H_4, 1mmol, 340.5 mg): Reaction time: 70 h, yield 159.4 mg (42%) of **8e**, crystallized from a mixture of DMF and 96% ethanol (1:2) as light brown crystals. Mp 346-348°C, R^*_f value 0.69. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1730, $\upsilon_{OH, NH}$ at 3235, 3355, 3497, $\upsilon_{C=C, C=N}$ at 1602, 1550, and δ_{NH} at 1644. ^{1}H-NMR (500 MHz, DMSO-d_6), δ (ppm): 6.19 (1H, s, 3-H cou); 2.40 (3H, s, 4-CH_3 cou); 7.71 (1H, d, *J* 9.0 Hz, 5-H cou); 6.93 (1H, d, *J* 9.0 Hz, 6-H cou); 13.89 (1H, s, 7-OH cou); 7.20 (2H, s, 3-NH_2 pyrim); 7.88 (1H, s, 5-H pyrim); 8.08 (2H, d, *J* 8.5 Hz, Ar-H), 7.60 (2H, d, *J* 8.5 Hz, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6), δ (ppm): 158.8 (2-C cou); 109.4 (3-C cou); 111.3 (4a-C cou); 153.4 (4-C cou); 17.93 (4-CH_3 cou); 127.4 (5-C cou); 114.1(6-C cou); 153.1 (7-C cou); 107.8 (8-C cou); 162.6 (8a-C cou); 161.4 (4-C pyrim); 161.2 (2-C pyrim); 163.8 (6-C pyrim); 105.7 (5-C pyrim); 135.3 (Ar-C); 128.1 (Ar-C); 128.4 (Ar-C); 135.6 (Ar-C); 128.4 (Ar-C) and 128.1 (Ar-C). ESI-MS: *m/z* 380.50 $[M+H]^+$, 100%. Anal. Calcd for $C_{20}H_{14}ClN_3O_3$, M= 379.0724 Da.

8-(2-Amino-6-*m*-chlorophenylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**8f**). From **7f** (Ar=*m*-ClC_6H_4, 1mmol, 340.5 mg): Reaction time: 66 h, yield 162.3 mg (43%) of **8f**, crystallized from a mixture of DMF and 96% ethanol (1:2) as light brown crystals. Mp 277-279°C, R^*_f value 0.82. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1725, $\upsilon_{OH, NH}$ at 3193, 3350, 3493, $\upsilon_{C=C, C=N}$ at 1594, 1539, and δ_{NH} at 1661. ^{1}H-NMR (500 MHz, DMSO-d_6), δ (ppm): 6.22 (1H, s, 3-H cou); 2.42 (3H, s, 4-CH_3 cou); 7.73 (1H, d, *J* 9.0 Hz, 5-H cou); 6.96 (1H, d, *J* 9.0 Hz, 6-H cou); 13.71 (1H, s, 7-OH cou); 7.24 (2H, s, 3-NH_2 pyrim); 7.92 (1H, s, 5-H pyrim); 8.15 (H, t, *J* 1.5 and 2.0 Hz, Ar-H); 7.60 (H, t, *J* 8.5

and 1.5 Hz, Ar-H); 7.57 (1H, t, *J* 8.5 and 8.5 Hz, Ar-H) and 8.02 (1H, d, *J* 8.5 Hz, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6), δ (ppm): 158.8 (2-C cou); 109.5 (3-C cou); 111.5 (4a-C cou); 153.3 (4-C cou); 17.95 (4-CH_3 cou); 127.5 (5-C cou); 114.0 (6-C cou); 153.1 (7-C cou); 107.7 (8-C cou); 162.4 (8a-C cou); 161.5 (4-C pyrim); 161.2 (2-C pyrim); 163.4 (6-C pyrim); 105.9 (5-C pyrim); 138.9 (Ar-C); 130.3 (Ar-C); 133.4 (Ar-C); 130.0 (Ar-C); 124.9 (Ar-C) and 126.2 (Ar-C).

8-(2-Amino-6-*m*-nitrophenylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**8g**). From **7g** (Ar=*m*-$O_2NC_6H_4$, 1mmol, 349 mg): Reaction time: 68 h, yield 159 mg (41%) of **8g**, crystallized from a mixture of DMF and 96% ethanol (1:2) as pale yellow crystals. Mp 247-249°C, R^*_f value 0.66. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1742, $\upsilon_{OH,\ NH}$ at 3193, 3329, 3471, $\upsilon_{C=C,\ C=N}$ at 1611, 1528, δ_{NH} at 1665, $\nu_{s,\ as}$ (NO_2) at 1527, 1352. ^{1}H-NMR (500 MHz, DMSO-d_6), δ (ppm): 6.19 (1H, s, 3-H cou); 2.42 (3H, s, 4-CH_3 cou); 7.72 (1H, d, *J* 9.0 Hz, 5-H cou); 6.94 (1H, d, *J* 9.0 Hz, 6-H cou); 7.27 (2H, s, 3-NH_2 pyrim); 7.95 (1H, s, 5-H pyrim); 8.95 (H, s, Ar-H); 8.38 (H, dd, *J* 8.5 and 2.0 Hz, Ar-H); 7.84 (1H, t, *J* 8.5 and 8.5 Hz, Ar-H) and 8.47 (1H, d, *J* 8.5 Hz, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6), δ (ppm): 161.5 (2-C cou); 109.3 (3-C cou); 111.4 (4a-C cou); 153.3 (4-C cou); 17.91 (4-CH_3 cou); 127.4 (5-C cou); 114.1 (6-C cou); 153.1 (7-C cou); 107.9 (8-C cou); 162.3 (8a-C cou); 162.1 (4-C pyrim); 161.8 (2-C pyrim); 162.4 (6-C pyrim); 106.3 (5-C pyrim); 138.5 (Ar-C); 132.3 (Ar-C); 148.2 (Ar-C); 130.0 (Ar-C); 120.9 (Ar-C) and 124.6 (Ar-C).

8-(2-Amino-6-*p*-bromophenylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**8h**). From **7h** (Ar=*p*-BrC_6H_4, 1mmol, 383 mg): Reaction time: 54 h, yield 219.4 mg (52%) of **8h**, crystallized from a mixture of DMF and 96% ethanol (1:2) as pale yellow crystals. Mp 346-348°C, R^*_f value 0.87. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1733, $\upsilon_{OH,\ NH}$ at 3223, 3357, 3491, $\upsilon_{C=C,\ C=N}$ at 1606, 1541, and δ_{NH} at 1646. ^{1}H-NMR (500 MHz, DMSO-d_6), δ (ppm): 6.16 (1H, d, *J* 1.0 Hz, 3-H cou); 2.42 (3H, d, *J* 1.0 Hz, 4-CH_3 cou); 7.73 (1H, d, *J* 9.0 Hz, 5-H cou); 6.93 (1H, d, *J* 9.0 Hz, 6-H cou); 6.94 (2H, s, 3-NH_2 pyrim); 7.94 (1H, s, 5-H pyrim); 8.03 (2H, d, *J* 8.0 Hz, Ar-H); 7.72 (2H, dd, *J* 8.0 Hz, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6), δ (ppm): 158.9 (2-C cou); 109.1 (3-C cou); 111.4 (4a-C cou); 153.4 (4-C cou); 17.94 (4-CH_3 cou); 127.4 (5-C cou); 114.2 (6-C cou); 153.1 (7-C cou); 108.2 (8-C cou); 162.8 (8a-C cou); 161.6 (4-C pyrim); 161.3 (2-C pyrim); 163.8 (6-C pyrim); 105.9 (5-C pyrim); 136.1 (Ar-C); 128.3 (Ar-C); 131.3 (Ar-C); 123.9 (Ar-C); 131.3 (Ar-C) and 128.3 (Ar-C).

8-(2-Amino-6-(4-hydroxy-3-methoxyphenyl)pyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**8i**). From **7i** (Ar=4-HO-3-$OMeC_6H_3$, 1mmol, 350 mg): Reaction time: 48h, yield 226.7 mg (58%) of **8i**, crystallized from a mixture of DMF and 96% ethanol (1:2) as light-yellow crystals. Mp 297-299°C, R^*_f value 0.90. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1729, $\upsilon_{OH,\ NH}$ at 3124, 3331, 3430, $\upsilon_{C=C,\ C=N}$ at 1594, 1541, and δ_{NH} at 1655. ^{1}H-NMR (500 MHz, DMSO-d_6), δ (ppm): 6.21 (1H, s, 3-H cou); 2.42 (3H, d, 4-CH_3 cou); 7.72 (1H, d, *J* 8.5 Hz, 5-H cou); 6.92 (1H, d, *J* 8.5 Hz, 6-H cou); 7.08 (2H, s, 3-NH_2 pyrim); 8.04 (1H, s, 5-H pyrim); 7.60 (1H, dd, *J* 8.5 and 1.5 Hz, Ar-H); 6.93 (1H, d, *J* 8.5 Hz, Ar-H); 7.69 (1H, d, *J* 1.5 Hz, Ar-H); 9.64 (1H, s, Ar-OH) and 3.88 (3H, s, Ar-OCH_3). ^{13}C-NMR (125 MHz, DMSO-d_6), δ (ppm): 160.9 (2-C cou); 109.6 (3-C cou); 111.6 (4a-C cou); 154.1 (4-C cou); 18.53 (4-CH_3 cou); 127.9 (5-C cou); 114.5 (6-C cou); 153.4 (7-C cou); 107.5 (8-C cou); 163.4 (8a-C cou); 162.4 (4-C pyrim); 161.1 (2-C pyrim); 165.2 (6-C pyrim); 104.9 (5-C pyrim); 147.7 (Ar-C); 128.0 (Ar-C); 120.3 (Ar-C); 159.4 (Ar-C); 149.6 (Ar-C); 111.5 (Ar-C) and 55.54 (Ar-OCH_3). ESI-MS: *m/z* 392.29 $[M+1]^+$, 100%. Anal. Calcd for $C_{21}H_{17}N_3O_5$, M= 391.1168 Da.

8-(2-Amino-6-(3,4-methylenedioxyphenyl)pyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**8j**). From **7j** (Ar=3,4-$O_2CH_2MeC_6H_3$, 1mmol, 348 mg): Reaction time: 48h, yield 229 mg (59%) of **8i**, crystallized from a mixture of DMF and 96% ethanol (1:2) as light-yellow crystals. Mp 341-343°C, R^*_f value 0.79. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1717, $\upsilon_{OH,\ NH}$ at 3222, 3343, 3465, $\upsilon_{C=C,\ C=N}$ at 1584, 1536, and δ_{NH} at 1624. ^{1}H-NMR (500 MHz, DMSO-d_6), δ (ppm): 6.23 (1H, s, 3-H cou); 2.42 (3H, d, 4-CH_3 cou); 7.73 (1H, d, *J* 9.0 Hz, 5-H cou); 6.95 (1H, d, *J* 9.0 Hz, 6-H cou); 7.13 (2H, s, 3-NH_2 pyrim); 7.90 (1H, s, 5-H pyrim); 7.68 (1H, dd, *J* 8.0 and 1.5 Hz, Ar-H); 7.08 (1H, d, *J* 8.0 Hz, Ar-H); 7.61 (1H, d, *J* 1.5 Hz, Ar-H); and 6.12 (3H, s, Ar-O_2CH_2). ^{13}C-NMR (125 MHz, DMSO-d_6), δ (ppm): 158.8 (2-C cou); 109.4 (3-C cou); 111.4 (4a-C cou); 153.4 (4-C cou); 17.98 (4-CH_3 cou); 127.4 (5-C cou); 114.1 (6-C cou); 153.1 (7-

C cou); 107.4 (8-C cou); 162.9 (8a-C cou); 160.8 (4-C pyrim); 160.7 (2-C pyrim); 164.5 (6-C pyrim); 105.1 (5-C pyrim); 130.9 (Ar-C); 107.9 (Ar-C); 121.2 (Ar-C); 147.6 (Ar-C); 149.3 (Ar-C); 106.3 (Ar-C) and 101.2 (Ar-O_2CH_2).

6-(2-Amino-6-phenylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**13a**). From **12a** (Ar=C_6H_5, 1mmol, 306 mg): Reaction time: 62 h, yield 186.4 mg (54%) of **13a**, crystallized from a mixture of DMF and 96% ethanol (1:2) as brown-yellow crystals. Mp 341-342°C, R^*_f value 0.83. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1720, $\upsilon_{OH,\ NH}$ at 3216, 3336, 3428, $\upsilon_{C=C,\ C=N}$ at 1572, 1547, and δ_{NH} at 1621. ^{1}H-NMR (500 MHz, DMSO-*d*$_6$), δ (ppm): 6.18 (1H, s, 3-H cou); 2.55 (3H, s, 4-CH_3 cou); 8.40 (1H, s, 5-H cou); 14.76 (1H, s, 7-OH cou); 6.82 (1H, s, 8-H cou); 7.09 (2H, s, 3-NH_2 pyrim); 7.86 (1H, s, 5-H pyrim); 8.24-8.23 (2H, m, Ar-H) and 7.56-7.54 (3H, m, Ar-H). ^{13}C-NMR (125 MHz, DMSO-*d*$_6$), δ (ppm): 159.6 (2-C cou); 111.0 (3-C cou); 153.6 (4-C cou); 112.3 (4a-C cou); 18.41 (4-CH_3 cou); 125.6 (5-C cou); 115.4 (6-C cou); 156.1 (7-C cou); 104.2 (8-C cou); 163.9 (8a-C cou); 163.8 (4-C pyrim); 161.1 (2-C pyrim); 166.0 (6-C pyrim); 100.6 (5-C pyrim); 137.1 (Ar-C), 127.3 (Ar-C); 128.5 (Ar-C); 130.7 (Ar-C); 128.5 (Ar-C) and 127.3 (Ar-C).

6-(2-Amino-6-*p*-methylphenylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**13b**). From **12b** (Ar=4-$CH_3C_6H_4$, 1mmol, 320 mg): Reaction time: 60 h, yield 219 mg (61%) of **13b**, crystallized from a mixture of DMF and 96% ethanol (1:2) as pale yellow crystals. Mp 344-346°C, R^*_f value 0.86. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1722, $\upsilon_{OH,\ NH}$ at 3191, 3320, 3491, $\upsilon_{C=C,\ C=N}$ at 1579, 1549, and δ_{NH} at 1659. ^{1}H-NMR (500 MHz, DMSO-*d*$_6$), δ (ppm): 6.20 (1H, s, 3-H cou); 2.55 (3H, s, 4-CH_3 cou); 8.41 (1H, s, 5-H cou); 15.10 (1H, s, 7-OH cou); 6.83 (1H, s, 8-H cou); 7.27 (2H, s, 3-NH_2 pyrim); 7.85 (1H, s, 5-H pyrim); 8.17 (2H, d, *J* 8.0 Hz, Ar-H); 7.35 (2H, d, *J* 8.0 Hz, Ar-H) and 2.39 (3H, s, Ar-CH_3). ^{13}C-NMR (125 MHz, DMSO-*d*$_6$), δ (ppm): 159.8 (2-C cou); 110.9 (3-C cou); 153.9 (4-C cou); 112.2 (4a-C cou); 18.52 (4-CH_3 cou); 125.6 (5-C cou); 115.1 (6-C cou); 156.0 (7-C cou); 104.2 (8-C cou); 163.9 (8a-C cou); 163.7 (4-C pyrim); 160.9 (2-C pyrim); 165.9 (6-C pyrim); 99.85 (5-C pyrim); 134.1 (Ar-C), 127.3 (Ar-C); 129.2 (Ar-C); 140.9 (Ar-C); 129.2 (Ar-C; 127.3 (Ar-C) and 20.99 (Ar-CH_3).

6-(2-Amino-6-*p*-methoxyphenylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**13c**). From **12c** (Ar=4-$CH_3OC_6H_4$, 1mmol, 320 mg): Reaction time: 60 h, yield 219 mg (61%) of **13c**, crystallized from a mixture of DMF and 96% ethanol (1:2) as pale yellow crystals. Mp 324-326°C, R^*_f value 0.79. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1722, $\upsilon_{OH,\ NH}$ at 3203, 3324, 3447, $\upsilon_{C=C,\ C=N}$ at 1577, 1541, and δ_{NH} at 1648. ^{1}H-NMR (500 MHz, DMSO-*d*$_6$), δ (ppm): 6.16 (1H, s, 3-H cou); 2.55 (3H, s, 4-CH_3 cou); 8.36 (1H, s, 5-H cou); 14.95 (1H, s, 7-OH cou); 6.79 (1H, s, 8-H cou); 7.00 (2H, s, 3-NH_2 pyrim); 7.78 (1H, s, 5-H pyrim); 8.22 (2H, d, *J* 8.5 Hz, Ar-H); 7.08 (2H, d, *J* 8.5 Hz, Ar-H) and 3.86 (3H, s, Ar-OCH_3). ^{13}C-NMR (125 MHz, DMSO-*d*$_6$), δ (ppm): 159.3 (2-C cou); 110.6 (3-C cou); 153.2 (4-C cou); 111.9 (4a-C cou); 17.95 (4-CH_3 cou); 125.1 (5-C cou); 115.1 (6-C cou); 155.8 (7-C cou); 103.9 (8-C cou); 163.6 (8a-C cou); 163.3 (4-C pyrim); 161.4 (2-C pyrim); 165.2 (6-C pyrim); 99.37 (5-C pyrim); 129.0 (Ar-C), 113.7 (Ar-C); 128.6 (Ar-C); 160.6 (Ar-C); 128.6 (Ar-C; 113.7 (Ar-C) and 55.08 (Ar-OCH_3).

6-(2-Amino-6-*p*-*N,N*-dimethylaminophenylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**13d**). From **12d** (Ar=4-$(CH_3)_2NC_6H_4$, 1mmol, 349 mg): Reaction time: 64 h, yield 252.2 mg (65%) of **13d**, crystallized from a mixture of DMF and 96% ethanol (1:2) as yellow crystals. Mp 347-349°C, R^*_f value 0.74. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1713, $\upsilon_{OH,\ NH}$ at 3234, 3348, 3412, $\upsilon_{C=C,\ C=N}$ at 1566, 1541, and δ_{NH} at 1654. ^{1}H-NMR (500 MHz, DMSO-*d*$_6$), δ (ppm): 6.20 (1H, d, *J* 1.5 Hz, 3-H cou); 2.55 (3H, d, *J* 1.5 Hz, 4-CH_3 cou); 8.39 (1H, s, 5-H cou); 15.40 (1H, s, 7-OH cou); 6.81 (1H, s, 8-H cou); 7.11 (2H, s, 3-NH_2 pyrim); 7.77 (1H, s, 5-H pyrim); 8.16 (2H, d, *J* 9.0 Hz, Ar-H); 6.80 (2H, d, *J* 9.0 Hz, Ar-H) and 3.01 (6H, s, Ar-$N(CH_3)_2$). ^{13}C-NMR (125 MHz, DMSO-*d*$_6$), δ (ppm): 159.8 (2-C cou); 110.8 (3-C cou); 153.9 (4-C cou); 111.3 (4a-C cou); 18.46 (4-CH_3 cou); 125.3 (5-C cou); 115.2 (6-C cou); 155.9 (7-C cou); 104.2 (8-C cou); 164.1 (8a-C cou); 162.9 (4-C pyrim); 160.6 (2-C pyrim); 165.7 (6-C pyrim); 98.40 (5-C pyrim); 123.4 (Ar-C), 112.1 (Ar-C); 128.6 (Ar-C); 152.2 (Ar-C); 128.6 (Ar-C); 112.1 (Ar-C) and 40.09 (Ar-$N(CH_3)_2$).

6-(2-Amino-6-*p*-chlorophenylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**13e**). From **12e** (Ar=4-ClC_6H_4, 1mmol, 340.5 mg): Reaction time: 70 h, yield 216.3 mg (57%) of **13e**, crystallized from a mixture of DMF and

96% ethanol (1:2) as brown-yellow crystals. Mp >350°C, R^*_f value 0.69. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1715, $\upsilon_{OH,\ NH}$ at 3213, 3377, 3499, $\upsilon_{C=C,\ C=N}$ at 1578, 1546, and δ_{NH} at 1624. ^1H-NMR (500 MHz, DMSO-d_6), δ (ppm): 6.20 (1H, s, 3-H cou); 2.54 (3H, s, 4-CH_3 cou); 8.40 (1H, s, 5-H cou); 14.98 (1H, s, 7-OH cou); 6.82 (1H, s, 8-H cou); 7.35 (2H, s, 3-NH_2 pyrim); 7.92 (1H, s, 5-H pyrim); 8.27 (2H, d, *J* 8.5 Hz, Ar-H); 7.62 (2H, d, *J* 8.5 Hz, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6), δ (ppm): 159.2 (2-C cou); 110.5 (3-C cou); 153.1 (4-C cou); 111.9 (4a-C cou); 17.84 (4-CH_3 cou); 125.2 (5-C cou); 115.1 (6-C cou); 155.8 (7-C cou); 103.9 (8-C cou); 163.9 (8a-C cou); 163.6 (4-C pyrim); 160.8 (2-C pyrim); 164.2 (6-C pyrim); 100.3 (5-C pyrim); 135.3 (Ar-C), 128.7 (Ar-C); 128.2 (Ar-C); 135.5 (Ar-C); 128.2 (Ar-C) and 128.7 (Ar-C).

6-(2-Amino-6-*m*-chlorophenylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**13f**). From **12f** (Ar=3-ClC_6H_4, 1mmol, 340.5 mg): Reaction time: 70 h, yield 201 mg (53%) of **13f**, crystallized from a mixture of DMF and 96% ethanol (1:2) as brown-yellow crystals. Mp: 326-328°C, R^*_f value 0.71. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1737, $\upsilon_{OH,\ NH}$ at 3233, 3340, 3419, $\upsilon_{C=C,\ C=N}$ at 1576, 1546, and δ_{NH} at 1659. ^1H-NMR (500 MHz, DMSO-d_6), δ (ppm): 6.20 (1H, s, 3-H cou); 2.55 (3H, s, 4-CH_3 cou); 8.42 (1H, s, 5-H cou); 14.88 (1H, s, 7-OH cou); 6.83 (1H, s, 8-H cou); 7.37 (2H, s, 3-NH_2 pyrim); 7.93 (1H, s, 5-H pyrim); 8.28 (1H, s, Ar-H); 7.63-7.57 (2H, m, Ar-H) and 8.23 (1H, d, *J* 7.0 Hz, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6), δ (ppm): 159.7 (2-C cou); 111.0 (3-C cou); 153.8 (4-C cou); 112.3 (4a-C cou); 18.51 (4-CH_3 cou); 125.8 (5-C cou); 115.0 (6-C cou); 156.1 (7-C cou); 104.3 (8-C cou); 164.1 (8a-C cou); 163.9 (4-C pyrim); 160.9 (2-C pyrim); 164.3 (6-C pyrim); 100.5 (5-C pyrim); 133.6 (Ar-C), 126.8 (Ar-C); 139.1 (Ar-C); 130.6 (Ar-C); 130.5 (Ar-C) and 126.0 (Ar-C).

6-(2-Amino-6-*m*-nitrophenylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**13g**). From **12g** (Ar=3-$O_2NC_6H_4$, 1mmol, 351 mg): Reaction time: 62 h, yield 230 mg (59%) of **13g**, crystallized from a mixture of DMF and 96% ethanol (1:2) as brown-yellow crystals. Mp > 350°C, R^*_f value 0.89. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1740, $\upsilon_{OH,\ NH}$ at 3227, 3342, 3413, $\upsilon_{C=C,\ C=N}$ at 1577, 1539; δ_{NH} at 1658 and $\nu_{s,\ as}$ (NO_2) at 1516, 1358. ^1H-NMR (500 MHz, DMSO-d_6), δ (ppm): 6.18 (1H, s, 3-H cou); 2.56 (3H, s, 4-CH_3 cou); 8.42 (1H, s, 5-H cou); 14.88 (1H, s, 7-OH cou); 6.82 (1H, s, 8-H cou); 7.26 (2H, s, 3-NH_2 pyrim); 7.98 (1H, s, 5-H pyrim); 9.00 (1H, s, Ar-H); 8.37 (1H, d, *J* 8.0 Hz Ar-H); 7.85 (1H, t, *J* 8.0 and 8.0 Hz, Ar-H) and 8.67 (1H, d, *J* 8.0 Hz, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6), δ (ppm): 159.3 (2-C cou); 111.6 (3-C cou); 153.2 (4-C cou); 111.9 (4a-C cou); 17.95 (4-CH_3 cou); 125.1 (5-C cou); 115.1 (6-C cou); 155.8 (7-C cou); 103.9 (8-C cou); 163.6 (8a-C cou); 163.3 (4-C pyrim); 160.6 (2-C pyrim); 165.2 (6-C pyrim); 99.37 (5-C pyrim); 129.0 (Ar-C), 128.7 (Ar-C); 161.4 (Ar-C); and 113.7 (Ar-C).

6-(2-Amino-6-*p*-bromophenylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**13h**). From **12h** (Ar=4-BrC_6H_4, 1mmol, 385 mg): Reaction time: 62 h, yield 254.4 mg (60%) of **13h**, crystallized from a mixture of DMF and 96% ethanol (1:2) as pale yellow crystals. Mp > 350°C, R^*_f value 0.84. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1719, $\upsilon_{OH,\ NH}$ at 3218, 3362, 3491, $\upsilon_{C=C,\ C=N}$ at 1571, 1547; δ_{NH} at 1623. ^1H-NMR (500 MHz, DMSO-d_6), δ (ppm): 6.15 (1H, s, 3-H cou); 2.53 (3H, s, 4-CH_3 cou); 8.35 (1H, s, 5-H cou); 14.65 (1H, s, 7-OH cou); 6.79 (1H, s, 8-H cou); 7.11 (2H, s, 3-NH_2 pyrim); 7.82 (1H, s, 5-H pyrim); 8.17 (2H, d, *J* 8.5 Hz Ar-H); 7.72 (2H, d, *J* 8.5 Hz, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6), δ (ppm): 159.2 (2-C cou); 110.7 (3-C cou); 153.2 (4-C cou); 112.0 (4a-C cou); 17.95 (4-CH_3 cou); 125.2 (5-C cou); 114.9 (6-C cou); 155.8 (7-C cou); 103.9 (8-C cou); 163.9 (8a-C cou); 163.4 (4-C pyrim); 160.8 (2-C pyrim); 164.3 (6-C pyrim); 100.1 (5-C pyrim); 124.2 (Ar-C), 131.2 (Ar-C); 128.9 (Ar-C); 135.9 (Ar-C); 128.9 (Ar-C) and 113.7 (Ar-C).

6-(2-Amino-6-(4-hydroxy-3-methoxyphenylpyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**13i**). From **12i** (Ar=4-HO-3-OMeC_6H_3, 1mmol, 352 mg): Reaction time: 60 h, yield 223 mg (57%) of **13h**, crystallized from a mixture of DMF and 96% ethanol (1:2) as light-yellow crystals. Mp: 311-313°C, R^*_f value 0.85. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1721, $\upsilon_{OH,\ NH}$ at 3218, 3333, 3433, $\upsilon_{C=C,\ C=N}$ at 1579, 1523; δ_{NH} at 1645. ^1H-NMR (500 MHz, DMSO-d_6), δ (ppm): 6.18 (1H, d, *J* 1.0 Hz, 3-H cou); 2.54 (3H, d, *J* 1.0 Hz, 4-CH_3 cou); 8.37 (1H, s, 5-H cou); 15.20 (1H, s, 7-OH cou); 6.80 (1H, s, 8-H cou); 7.20 (2H, s, 3-NH_2 pyrim); 7.78 (1H, s, 5-H pyrim); 7.79 (1H, dd, *J* 8.0 and 2.0 Hz, Ar-

H); 6.93 (1H, d, *J* 8.0 Hz, Ar-H); 7.82 (1H, d, *J* 2.0 Hz, Ar-H); 3.89 (3H, s, Ar-OCH_3) and 9.61 (1H, s, Ar-OH). ^{13}C-NMR (125 MHz, DMSO-*d*$_6$), δ (ppm): 159.7 (2-C cou); 110.8 (3-C cou); 153.8 (4-C cou); 112.1 (4a-C cou); 18.43 (4-CH_3 cou); 125.4 (5-C cou); 115.1 (6-C cou); 155.9 (7-C cou); 104.2 (8-C cou); 164.0 (8a-C cou); 163.3 (4-C pyrim); 160.7 (2-C pyrim); 165.6 (6-C pyrim); 99.31 (5-C pyrim); 128.0 (Ar-C), 121.3 (Ar-C); 115.3 (Ar-C); 149.7 (Ar-C); 147.7 (Ar-C); 111.1 (Ar-C) and 55.81 (Ar-OCH_3). ESI-MS: *m/z* 392.94$[M+1]^+$, 40%, 414.83$[M+23]^+$, 100%. Anal. Calcd for $C_{21}H_{17}N_3O_5$, M= 391.1168 Da.

6-(2-Amino-6-(pyridin-3-yl)pyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**13j**). From **12j** (Ar=C_5H_4N, 1mmol, 307 mg): Reaction time: 64 h, yield 235.3 mg (68%) of **13j**, crystallized from a mixture of DMF and 96% ethanol (1:2) as light-yellow crystals. Mp: 346-347°C, R^*_f value 0.79. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1740, $\upsilon_{OH, NH}$ at 3234 (br), $\upsilon_{C=C, C=N}$ at 1584, 1551; δ_{NH} at 1663. ^{1}H-NMR (500 MHz, DMSO-*d*$_6$), δ (ppm): 6.17 (1H, s, 3-H cou); 2.53 (3H, s, 4-CH_3 cou); 8.38 (1H, s, 5-H cou); 14.90 (1H, s, 7-OH cou); 6.79 (1H, s, 8-H cou); 7.36 (2H, s, 3-NH_2 pyrim); 7.93 (1H, s, 5-H pyrim); 8.73 (1H, s, Ar-H); 7.75 (1H, dd, *J* 7.5 and 5.0 Hz, Ar-H); 8.53 (1H, d, *J* 7.5 Hz, Ar-H) and 9.42 (1H, s, Ar-H). ^{13}C-NMR (125 MHz, DMSO-*d*$_6$), δ (ppm): 159.7 (2-C cou); 111.0 (3-C cou); 153.7 (4-C cou); 112.3 (4a-C cou); 18.47 (4-CH_3 cou); 125.6 (5-C cou); 114.9 (6-C cou); 156.1 (7-C cou); 104.3 (8-C cou); 163.8 (8a-C cou); 163.7 (4-C pyrim); 160.9 (2-C pyrim); 164.2 (6-C pyrim); 100.4 (5-C pyrim); 132.4 (Ar-C), 134.6 (Ar-C); 123.6 (Ar-C); 148.5 (Ar-C) and 151.4 (Ar-C). ESI-MS: *m/z* 345.11 $[M-H]^-$, 100%. Anal. Calcd for $C_{19}H_{14}ClN_4O_3$, M= 346.1106 Da.

6-(2-Amino-6-(indol-3-yl)pyrimidin-4-yl)-7-hydroxy-4-methylcoumarin (**13k**). From **12k** (Ar=indol 3-yl, 1mmol, 345 mg): Reaction time: 54 h, yield 238 mg (62%) of **13k**, crystallized from a mixture of DMF and 96% ethanol (1:2) as yellow crystals. Mp: 345-347°C, R^*_f value 0.80. IR (KBr, cm^{-1}): $\upsilon_{C=O}$ at 1722, $\upsilon_{OH, NH}$ at 3234, 3342, 3406, $\upsilon_{C=C, C=N}$ at 1580, 1519; δ_{NH} at 1626. ^{1}H-NMR (500 MHz, DMSO-*d*$_6$), δ (ppm): 6.17 (1H, d, *J* 1.0 Hz, 3-H cou); 2.55 (3H, d, *J* 1.0 Hz, 4-CH_3 cou); 8.34 (1H, s, 5-H cou); 15.64 (1H, s, 7-OH cou); 6.79 (1H, s, 8-H cou); 7.12 (2H, s, 3-NH_2 pyrim); 7.75 (1H, s, 5-H pyrim); 8.59 (1H, d, *J* 2.5 Hz, Ar-H); 7.49 (1H, d, *J* 8.0 Hz, Ar-H); 7.22-7.15 (2H, m, Ar-H); 8.73 (1H, d, *J* 8.0, Ar-H) and 11.85 (1H, s, Ar-NH). ^{13}C-NMR (125 MHz, DMSO-*d*$_6$), δ (ppm): 159.8 (2-C cou); 110.8 (3-C cou); 153.7 (4-C cou); 111.9 (4a-C cou); 18.41 (4-CH_3 cou); 125.5 (5-C cou); 115.2 (6-C cou); 155.8 (7-C cou); 104.2 (8-C cou); 164.3 (8a-C cou); 161.6 (4-C pyrim); 160.6 (2-C pyrim); 164.9 (6-C pyrim); 98.74 (5-C pyrim); 111.9 (Ar-C), 124.8 (Ar-C); 137.1 (Ar-C); 113.7 (Ar-C); 120.5 (Ar-C); 122.9 (Ar-C); 122.2 (Ar-H) and 129.9 (Ar-C). ESI-MS: *m/z* 385.44 $[M+H]^+$, 100%. Anal. Calcd for $C_{22}H_{16}N_4O_3$, M= 384.1222 Da.

Biological activity

Each disc contained 50-150 µg/ml of the tested compounds. The agar was allowed to solidify and then three wells/cups were made using a sterile cork borer for each organism. This was done to ensure the proper distribution of the wells, with three in the periphery and one in the center. Agar plugs were removed, and the test samples (each compound at three concentrations) were poured into the corresponding marked wells using micropipettes. Antibacterial and antifungal activity was assessed by aseptically circle diameter (mm).

Supplementary Material

Copies of NMR and IR spectra associated with this paper are provided in the accompanying Supplementary Material.

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