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An expeditious synthesis of β-pyrimidyl-α,β-didehydro-α-amino acid derivatives and pyrano[2,3-*d*]pyrimidines using microwave-assisted conditions

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ABSTRACT

An expeditious transformation of 5-acyl-2*H*-pyran-2-ones with various amidines as 1,3-binucleophiles into isomerically pure (*E*)-α,β-didehydro-α-amino acid derivatives (DDAAD) containing the 5-pyrimidyl moiety at the β-position is described. The method was performed in ethanolic (or ethanol/water) solutions in the presence of Na_2CO_3 as a nontoxic base and under microwave-assisted conditions. When starting from the 5-ethoxycarbonyl-2*H*-pyran-2-one derivative and in the presence of DBU as a base the corresponding pyrano[2,3-*d*]pyrimidines were prepared.

1. Introduction

The significance of α,β-didehydro-α-amino acid derivatives (DDAAD) is recognized as a result of their occurrence in the structure of various natural products, their biological activity, and their synthetic potential.[1,2] The hydrogenation of β-heteroaryl-α,β-didehydroalanines is one of the most convenient ways to prepare novel types of optically pure nonproteinogenic α-amino acid derivatives.[2] For this reason, the synthesis of novel types of DDAAD opens up new possibilities for investigating this important class of compounds.

Pyrimidines and their fused derivatives also constitute a very important class of compounds including natural products, pharmaceuticals, and functional materials. They are accessible by variety of methods, including classical approaches and novel strategies.[3] Recently, the preparation of some β-pyrimidyl-DDAAD[4] containing the 2-pyrimidyl,[4a] 4-pyrimidyl[4b] or 5-pyrimidyl[4c–e] moiety at the β-position was published, mostly in connection with their biological potential.

2*H*-Pyran-2-ones and fused pyran-2-ones are versatile synthons for the synthesis of different types of products.[1d,5] It is well known, for example, that several kinds of nucleophiles react with the pyran-2-one nucleus at the C-2, C-4, and C-6 positions causing an initial ring opening, followed by a recyclization into a new heterocyclic ring. Among them there are a few reports concerning the transformations of pyran-2-one derivatives with amidines or related compounds (urea, thiourea, guanidine) toward pyrimidine derivatives.[6]

As a part of our continuing interest in the transformations of 2*H*-pyran-2-ones we have developed their efficient transformation with binucleophilic reagents (hydrazine and its derivatives, hydroxylamine) into DDAAD bearing a pyrazolyl or isoxazolyl moiety at the β-position.[1d,7] Having in mind the above-mentioned conversion of 2*H*-pyran-2-one derivatives into pyrimidine derivatives,[6c] we decided to check the possibility of transforming our 3-acylamino-2*H*-pyran-2-one derivatives **1**[7b,8] with a series of amidines **2** as binucleophilic reagents[9] toward β-(5-pyrimidyl)-DDAAD **3**. The idea was to connect a binucleophilic amidine derivative with the C-6 carbon atom of the 2*H*-pyran-2-one ring and the carbonyl function at position 5 of the 2*H*-pyran-2-one ring, leaving the 3-acylamino moiety unreacted. When starting from differently substituted 2*H*-pyran-2-ones and amidines a large library of multifunctional products,[10] diverse, small molecules containing the didehydroamino acid unit and the pyrimidyl ring in their structure, would be accessible.

2. Results and discussion

To find the optimal conditions for the preparation of **3** we first examined the reaction of 2*H*-pyran-2-one **1a** with a slight excess of acetamidine hydrochloride (1.1 equiv) in the presence of a base. When applying an excess of triethylamine (4 equiv) in boiling ethanol 9 h of conventional heating was required to complete the reaction, and the product **3a** was isolated after an acidic work-up in a 76% yield. The relatively long reaction time and the need for an excess of the organic base stimulated us to develop a less-time-consuming and greener process. For this reason we turned, in our test experiments, to reactions that take place under a variety of conditions, from heterogeneous to homogeneous, in conjunction with a microwave-accelerated reaction and the principles of green chemistry.[11,12]

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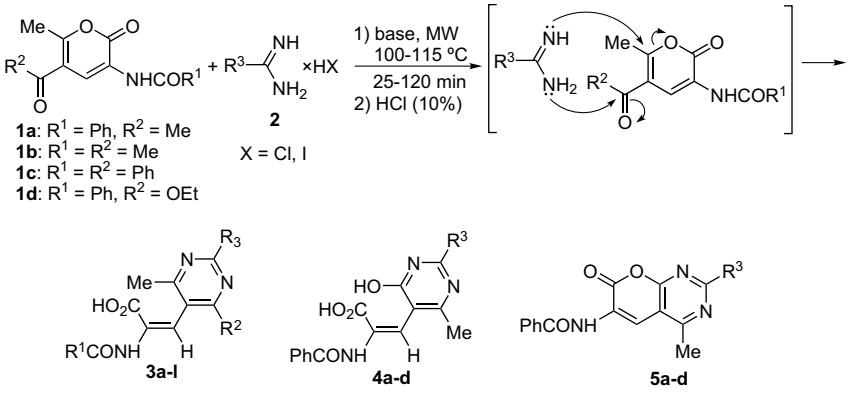


Scheme 1.

The test reactions were run on a 0.5-mmol scale with equimolar amounts of **1a**, acetamidine hydrochloride, and the base in 1.5 mL of solvent in a closed-vessel microwave reactor (10 mL) at 100 °C and stopped after 15 min to find the combination with the highest conversion. After irradiation the solvent was evaporated and the remaining residue was acidified, filtered off, and analyzed by means of ^{1}H NMR spectroscopy. When using triethylamine, pyridine or DABCO (1 equiv) no conversion to the final product **3a** was observed using the ^{1}H NMR spectroscopy in any of the tested solvents (toluene, DME, THF, MeCN, EtOH). Additionally, the screening showed that the reaction in a nonpolar solvent (PhMe, DME) gives no product **3a**, even with sodium carbonate, which was finally chosen as the most appropriate base for the desired transformation. This fact could be attributed to the low solubility of both the base and the amidine salt. As the polarity of the solvent increased (using THF, MeCN, EtOH), the conversion using sodium carbonate as a base also increased. When we tried to perform the reaction toward **3a** under similar conditions, with Na_2CO_3 as a base in water, no product formation was observed, most probably due to the faster decomposition of the acetamidine (prior to the reaction with the pyran-2-one **1a**). Hence, the best combination seemed to be the application of Na_2CO_3 in EtOH, in which most of the starting material (**1a**) disappeared after 15 min and the ^{1}H NMR spectrum of the crude reaction mixture revealed, in addition to the product **3a**, a significant quantity of intermediates that disappeared after prolonged heating. We then tried to optimize the model reaction by using other alkali carbonates (K_2CO_3, Cs_2CO_3) in an ethanolic mixture. Cs_2CO_3 showed, probably due to the better solubility, the highest conversion within 15 min, with no starting material remaining and the smallest quantity of intermediates. Even with only 1 equiv of Cs_2CO_3 the reaction toward **3a** could be completed within 30 min of microwave irradiation at 100 °C and with 75% of isolated yield. Surprisingly, Na_2CO_3 showed a higher conversion than K_2CO_3; nevertheless, a reaction with only 1 equiv of Na_2CO_3 could not be completed after 150 min of irradiation at 100 °C. Using twice the amount of Na_2CO_3 and setting the reaction time to 90 min increased the conversion to 100% and made it possible to isolate the desired product **3a** in an 85% yield (Table 1, run 1). In spite of the fact that Cs_2CO_3 showed better features in the model conversion than Na_2CO_3 we chose the latter in two-equivalent amounts for other syntheses of the products **3** because of its lower price and molecular mass.

Table 1
Reaction conditions and yields of products **3**, **4**, and **5**

Run	SM	Amidine **2** (R^3=)	*T* (°C), r. time (min)	Product	Yield[a] (%)
1	**1a**	Me	100, 90[b]	**3a**	85
2	**1a**	H	100, 60[b]	**3b**	90
3	**1a**	Ph	100, 60[b] (27.5)[c] (30)[d]	**3c**	85 (84)[c] (91)[d]
4	**1a**	3-$O_2NC_6H_4$	100, 60[b]	**3d**	90
5	**1a**	NH_2	100, 30[b]	**3e**	80
6	**1b**	Ph	100, 45[b] (25)[c] (30)[d]	**3f**	80 (75)[c] (92)[d]
7	**1b**	3-$O_2NC_6H_4$	100, 25[b]	**3g**	90[b]
8	**1c**	H	115, 90[b]	**3h**	91
9	**1c**	Me	115, 105[b]	**3i**	86
10	**1c**	Ph	100, 120[b]	**3j**	82
11	**1c**	3-$O_2NC_6H_4$	100, 90[b]	**3k**	90
12	**1c**	NH_2	110, 105[b]	**3l**	88
13	**1d**	Ph	100, 45[e]	**4a**	85
14			110, 120[f]	**5a**	56
15	**1d**	4-MeC_6H_4	100, 45[e]	**4b**	81
16			110, 120[f]	**5b**	54
17	**1d**	4-ClC_6H_4	100, 30[e]	**4c**	80
18			110, 60[f]	**5c**	52
19	**1d**	3-$O_2NC_6H_4$	100, 20[e]	**4d**	81
20			110, 120[f]	**5d**	50

[a] Yields of isolated products are given.
[b] EtOH, Na_2CO_3 (2 equiv), 30 W.
[c] H_2O, K_2CO_3 (1.5 equiv), 30 W.
[d] H_2O, Na_2CO_3 (1.5 equiv), 30 W.
[e] EtOH, H_2O, Na_2CO_3 (2 equiv), 45 W.
[f] EtOH, DBU (1.1 equiv), 45 W.

Under the above, optimal conditions (with small changes to the temperature and the reaction time), 3-acylamino-2*H*-pyran-2-ones **1a–c** reacted with an equimolar amount of amidines **2** in ethanol and in the presence of Na_2CO_3 (2 equiv) to give the appropriate 5-pyrimidyl moiety containing (*E*)-DDAAD **3a–l** with 80–91% yields (Table 1, Scheme 1). The ^{1}H NMR spectra of the crude reaction mixtures under optimized conditions did not reveal any signals that could be referred to the side products. As shown in Table 1, these conditions are compatible with aliphatic and aromatic amidines, and even with guanidine. Additionally, in the reaction of benzamidine hydrochloride with **1a** and **1b** we successfully used water as the solvent and 1.5 equiv of K_2CO_3 or Na_2CO_3. These reaction conditions reduced the reaction time significantly and the yields of **3c** and **3f** were very high, especially with Na_2CO_3 as a base (Table 1, runs 3 and 6). Unfortunately, water cannot be used as a solvent for the reactions with aliphatic amidines and formamidine, because they are not stable under these conditions.

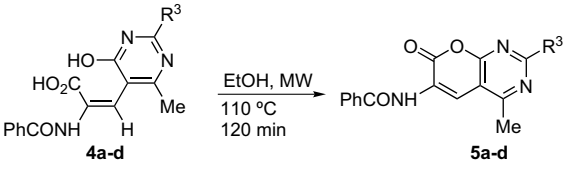
With the above results in hand we wanted to further extend this transformation to the starting 5-ethoxycarbonyl-2*H*-pyran-2-one derivative **1d**. Surprisingly, all the preliminary experiments with acetamidine hydrochloride were unsuccessful. For example, the reaction of **1d** with acetamidine hydrochloride on the 0.5-mmol scale conducted in ethanol at room temperature, 60 °C or 100 °C for 1 h and with different bases (DBU, Na_2CO_3 and Cs_2CO_3; 1 equiv) did not give any major product. On the other hand, when the

suspension of **1d** with 1 equiv of benzamidine hydrochloride and 1 equiv of Na_2CO_3 in ethanol was irradiated for 1 h at 100 °C, a mixture of the DDAAD **4a** and the pyrano[2,3-*d*]pyrimidine **5a** was obtained. Surprisingly, applying DBU as a base instead of Na_2CO_3 and under the above conditions **5a** was obtained as an exclusive product, albeit with a modest yield (35%). The yield of the reaction increased to 56% as the reaction temperature and the time were increased to 110 °C and 120 min. A further increase in the reaction temperature and the time did not result in any improvement of the yield. However, all the aromatic amidines applied gave, under similar reaction conditions, the corresponding pyrano[2,3-*d*]pyrimidines **5a–d** in reasonable yields (50–56%) (Table 1, runs 14, 16, 18, 20). Having in mind the fact that the bicyclic derivatives **5** are just the cyclized form of DDAAD **4** we then focused our investigation on the exclusive synthesis of **4**. Adding water to the reaction mixture proved beneficial to both the purity and the yield of the reaction products **4**. Thus, the reaction of equimolar amounts of **1d** and benzamidine hydrochloride with 2 equiv of Na_2CO_3 as a base in an ethanol/water mixture (2:1) at 100 °C led, after 45 min of microwave irradiation and after an acidic work-up, exclusively to the product **4a** in a high yield (85%). These reaction conditions were successfully applied to the syntheses of the products **4a–d** (Table 1, runs 13, 15, 17, 19). Recalling that the bicyclic derivatives **5** could be formed by the cyclization of DDAAD **4**, we decided to check the possibility of preparing the pyrano[2,3-*d*]pyrimidines **5** from **4** in a condensation reaction, including the elimination of water. We were delighted to find that the transformation of **4a** into the pyrano[2,3-*d*]pyrimidine **5a** could be accomplished in a 92% yield by microwave irradiation of the derivative **4a** in ethanol (in the absence of water) for 120 min at 110 °C, followed by a simple filtration of **5a** from the reaction mixture (Table 2, run 1). In this way the previous 56% yield of **5a**, obtained directly from **1d** in a single step, here increased to 78% as a result of a two-step process starting from **1d**. Similarly, we also successfully synthesized the products **5b–d** in higher yields than with the one-step process (Table 2) (Scheme 2).

Table 2
Reaction conditions and yields of products **5** from **4**

Run	SM	R^3	Product **5**[a]	Yield[b] (%)
1	**4a**	Ph	**5a**	92
2	**4b**	4-MeC_6H_4	**5b**	81
3	**4c**	4-ClC_6H_4	**5c**	80
4	**4d**	3-$O_2NC_6H_4$	**5d**	75

[a] EtOH, MW, 110 °C, 120 min, 45 W.
[b] Yields of isolated products are given.



4a-d **5a-d**

Scheme 2.

The most obvious pathway of the reaction from **1** into DDAAD **3** (or **4**) is an attack of the amidine derivative as a 1,3-binucleophile at the carbonyl moiety of the 5-acyl (or ethoxycarbonyl) group and at the C-6 of the pyran-2-one ring (Scheme 1) followed by the ring opening and the elimination of the water (or ethanol) molecule to yield the product **3** (or **4**). This reaction pathway supports the (*E*)-configuration[7] of the products **3** (or **4**), which was proven in the case of compound **3b** using the 2D NMR technique. Namely, for the product **3b** the long-range coupling constant between the C-1 (δ 164.8) and the H-3 (δ 7.00) was 10.5 Hz, which is consistent with the literature data for related systems having the (*E*)-configuration.[13] In order to further confirm the observed configuration, a NOESY experiment was carried out, which revealed the spatial proximity between the NH proton of the benzamide group (δ 10.27) and the 3-H. Due to the large range of the 3-H chemical shifts (6.78–7.21) of compounds **3**, we decided to further confirm the proposed configuration also in the case of compounds **3l** ($\delta_{H\text{-}3}$ 6.78) and **3g** ($\delta_{H\text{-}3}$ 7.21). The long-range coupling constant between the C-1 and the H-3 was, in both cases, determined as 10.3 Hz (for **3l**) and 10.5 Hz (**3g**), supporting the proposed (*E*)-configuration. Since the H-3 chemical shift of compounds **4** has a very narrow range (6.61–6.67) and is, in addition, shifted upfield from the mean value of the H-3 chemical shifts for compounds **3**, we again carried out a NOESY experiment and determined the coupling constant between the C-1 and the H-3 for **4a**. Both experiments unequivocally confirmed the (*E*)-configuration of compounds **4** (the coupling constant for **4a** being 10.0 Hz).

3. Conclusions

We have developed a novel, convenient, and green methodology for the synthesis of isomerically pure (*E*)-DDAAD **3** and **4** bearing a highly substituted 5-pyrimidyl moiety at the β-position. (*E*)-DDAAD **3a–l** were synthesized from 5-acyl-2*H*-pyran-2-ones **1a–c** and amidines **2** in ethanolic mixtures and in the presence of Na_2CO_3. The 5-ethoxycarbonyl-2*H*-pyran-2-one **1d** exhibited a different reactivity pattern than the 2*H*-pyran-2-ones **1a–c**. Namely, with aromatic amidines from **1d** in ethanolic mixtures in the presence of DBU as the base pyrano[2,3-*d*]pyrimidines **5** were obtained as the final products. When Na_2CO_3 was used as the base and a mixture of EtOH and water (2:1) was applied as a solvent the corresponding β-(4-hydroxypyrimidyl)-DDAAD **4** were isolated. The utilization of microwaves, green solvents (ethanol, water), and nontoxic carbonate bases combined with acceptable reaction times and an easy work-up renders this synthesis environmentally benign and user friendly.

4. Experimental

4.1. General

Melting points were determined on a Kofler micro hot stage. ^{1}H NMR spectra were recorded with a Bruker Avance DPX 300 spectrometer at 29 °C (unless otherwise stated) and 300 MHz using TMS as an internal standard, with the exception of compounds **5**, where the spectra are referenced against the solvent signal (CF_3CO_2D residual solvent singlet at δ=11.5 ppm). ^{13}C NMR spectra were recorded on the same instrument at 75.5 MHz and are referenced against the central line of the solvent signal (DMSO-d_6 septet at δ=39.5 ppm, pyridine-d_5 triplet at δ=149.9 ppm, CF_3CO_2D quartet at δ=164.2 ppm). The coupling constants (*J*) are given in hertz. IR spectra were obtained with a Bio-Rad FTS 3000MX (KBr pellets for all products). MS spectra were recorded with a VG-Analytical AutoSpec Q (EI and FAB) or a Q-TOF Premier instrument (ESI). Elemental analyses (C, H, N) were performed with a Perkin Elmer 2400 Series II CHNS/O Analyzer. TLC was carried out on Fluka silica-gel TLC-cards. Microwave reactions were conducted in air using a focused microwave unit (Discover by CEM Corporation, Matthews, NC). The machine consists of a continuous, focused microwave power-delivery system with an operator-selectable power output from 0 to 300 W. Reactions were performed in glass vessels (capacity 10 mL) sealed with a septum. The pressure was controlled by a load cell connected to the vessel via the septum. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature controller mounted under the reaction vessel. All the mixtures were stirred with a Teflon-coated magnetic stirring bar in the vessel. Temperature, pressure, and

power profiles were recorded using commercially available software provided by the manufacturer of the microwave unit. The starting compounds **1a–d** were prepared as described previously.[7b,8] All other reagents and solvents were used as received from commercial suppliers. Amidines were used in the form of hydrochlorides, with the exception of 4-chlorobenzamidine, which was used as a hydroiodide.

4.2. Microwave-assisted synthesis of 3

A suspension of the starting 3-benzoylamino-2*H*-pyran-2-ones **1a–c** (0.5 mmol), amidine (guanidine) hydrochloride **2** (0.5 mmol), sodium carbonate (1 mmol, 106 mg) in ethanol (1.5 mL) was irradiated in the focused MW equipment (for the reaction time and temperature, see Table 1, Scheme 1). After irradiation, ethanol was removed under a reduced pressure and 2 mL of water was added and acidified with 10% aq HCl to pH ~ 2. The resulting precipitated solid was filtered off, washed with water, and dried.

4.3. Microwave-assisted synthesis of 4

A suspension of the starting 5-ethoxycarbonyl-6-methyl-3-benzoylamino-2*H*-pyran-2-one **1d** (0.5 mmol, 150 mg), amidine hydrochloride or hydroiodide **2** (0.5 mmol), Na_2CO_3 (1 mmol, 106 mg) in a mixture of ethanol and water (2:1, 1.5 mL) was irradiated in the focused MW equipment at 100 °C (see Table 1, Scheme 1). After irradiation, ethanol was removed under a reduced pressure and 2 mL of water was added and acidified with 10% aq HCl to pH ~ 2. The resulting precipitated solid was filtered off, washed with water, and dried.

4.4. Microwave-assisted synthesis of 5

*4.4.1. Synthesis of **5** from **1d**.* A suspension of the starting 5-ethoxycarbonyl-2*H*-pyran-2-one **1d** (0.5 mmol, 150 mg), amidine hydrochloride or hydroiodide (0.5 mmol), DBU (0.55 mmol, 84 mg) in ethanol (1.5 mL) was irradiated in the focused MW equipment at 110 °C (see Table 1, Scheme 1). The resulting precipitated solid was filtered off, washed with ethanol, and dried.

*4.4.2. Synthesis of **5** from **4a–d**.* A suspension of (*E*)-2-[(benzoylamino)-3-(4-hydroxy-6-methylpyrimidin-5-yl)]propenoic acid derivative **4** (0.5 mmol) in EtOH (1.5 mL) was irradiated in the focused MW equipment (see Table 2, Scheme 2). After irradiation, the reaction mixture was cooled and the resulting precipitated product was filtered off and dried.

4.5. Analytical and spectroscopic data of products

*4.5.1. (E)-2-(Benzoylamino)-3-(2,4,6-trimethylpyrimidin-5-yl)propenoic acid (**3a**).* Yield: 132.3 mg (85%); brown powder; mp 198–200 °C (from H_2O/EtOH). IR (KBr): 3385, 3348, 1670, 1512, 1485 cm^{-1}. ^1H NMR[14] (DMSO-d_6) δ 2.34 (s, 6H, two Me), 2.51 (s, 3H, Me), 6.94 (s, 1H, 3-H), 7.58 (m, 3H, Ph), 7.96 (m, 2H, Ph), 10.23 (s, 1H, NH), 12.83 (br s, 1H, OH). ^{13}C NMR[14] (DMSO-d_6) δ 22.4, 25.1, 120.4, 124.4, 127.6, 128.5, 132.0, 132.3, 133.2, 163.2, 164.3, 164.8, 165.4. MS (EI): *m*/*z* 311 (M^+, 6.2%), 105 (100). Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.42; H, 5.66; N, 13.24.

*4.5.2. (E)-2-(Benzoylamino)-3-(4,6-dimethylpyrimidin-5-yl)propenoic acid (**3b**).* Yield: 133.8 mg (90%); white powder; mp 213–216 °C (H_2O/EtOH). IR (KBr): 3389, 1668, 1578, 1518, 1487 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.39 (s, 6H, two Me), 7.00 (s, 1H, 3-H), 7.58 (m, 3H, Ph), 7.97 (m, 2H, Ph), 8.78 (s, 1H, 2′-H), 10.25 (s, 1H, NH), 12.89 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ 22.5, 120.1, 127.6, 127.8, 128.5, 132.0, 132.4, 133.2, 155.7, 163.3, 164.8, 165.4. MS (EI): *m*/*z* 297 (M^+, 6.6%), 105 (100). Anal. Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.68; H, 5.19; N, 13.85.

*4.5.3. (E)-2-(Benzoylamino)-3-(4,6-dimethyl-2-phenylpyrimidin-5-yl)propenoic acid (**3c**).* Yield: 158.7 mg (85%); off-white powder; mp 109–111 °C (H_2O/EtOH). IR (KBr): 3388, 1673, 1637, 1541, 1516, 1485 cm^{-1}. ^1H NMR[14] (DMSO-d_6) δ 2.48 (s, 6H, two Me), 7.04 (s, 1H, 3-H), 7.57 (m, 6H, Ph), 7.98 (m, 2H, Ph), 8.40 (m, 2H, Ph), 10.27 (s, 1H, NH), 12.89 (br s, 1H, OH). ^{13}C NMR[14] (DMSO-d_6) δ 22.8, 120.5, 125.9, 127.5, 127.6, 128.5, 130.4, 132.0, 132.4, 133.3, 137.2, 160.5, 163.8, 164.8, 165.4 (one signal is hidden). MS (EI): *m*/*z* 373 (M^+, 27%), 105 (100). Anal. Calcd for $C_{22}H_{19}N_3O_3 \cdot 1/3H_2O$: C, 69.64; H, 5.22; N, 11.07. Found: C, 69.58; H, 5.39; N, 10.77.

*4.5.4. (E)-2-(Benzoylamino)-3-[4,6-dimethyl-2-(3-nitrophenyl)pyrimidin-5-yl]propenoic acid (**3d**).* Yield: 188.3 mg (90%); off-white powder; mp 209–213 °C (H_2O/EtOH). IR (KBr): 3389, 1736, 1645, 1526 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.50 (s, 6H, two Me), 7.19 (s, 1H, 3-H), 7.60 (m, 3H, Ph), 7.83 (m, 1H, C_6H_4), 7.96 (m, 2H, Ph), 8.37 (m, 1H, C_6H_4), 8.81 (m, 1H, C_6H_4), 9.13 (m, 1H, C_6H_4), 10.27 (s, 1H, NH), 12.96 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ 22.8, 120.1, 121.7, 125.0, 127.1, 127.6, 128.5, 130.4, 132.0, 132.6, 133.2, 133.5, 138.8, 148.3, 158.4, 164.3, 164.8, 165.4. MS (EI): *m*/*z* 418 (M^+, 7.5%), 105 (100). Anal. Calcd for $C_{22}H_{18}N_4O_5$: C, 63.15; H, 4.34; N, 13.39. Found: C, 63.16; H, 4.49; N, 13.28.

*4.5.5. (E)-2-(Benzoylamino)-3-(2-amino-4,6-dimethylpyrimidin-5-yl)propenoic acid (**3e**).* Yield: 124.9 mg (80%); brown powder; mp 268–271 °C (with decay) (H_2O/EtOH). IR (KBr): 3348, 1704, 1665, 1518, 1385 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.17 (s, 6H, two Me), 6.35 (s, 2H, NH_2), 6.78 (s, 1H, 3-H), 7.52 (m, 3H, Ph), 7.95 (m, 2H, Ph), 10.15 (s, 1H, NH), 12.58 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ 22.4, 115.7, 122.0, 127.6, 128.4, 131.5, 131.8, 133.4, 161.5, 164.1, 165.2. MS (EI) *m*/*z* 312 (M^+, 36%), 105 (100). HRMS (EI) calcd for $C_{16}H_{16}N_4O_3$: 312.1222, found: 312.1226.

*4.5.6. (E)-2-(Acetylamino)-3-(4,6-dimethyl-2-phenylpyrimidin-5-yl)propenoic acid (**3f**).* Yield: 124.5 mg (80%); pale-brown powder; mp 209–212 °C (H_2O/EtOH). IR (KBr): 3229, 3182, 3028, 1721, 1657, 1631, 1545 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.04 (s, 3H, Me), 2.41 (s, 6H, two Me), 7.14 (s, 1H, 3-H), 7.50 (m, 3H, Ph), 8.38 (m, 2H, Ph), 9.67 (s, 1H, NH), 12.96 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ 22.8, 23.1, 117.9, 126.3, 127.5, 128.5, 130.3, 131.6, 137.2, 160.3, 163.6, 164.8, 168.9. MS (EI) *m*/*z* 311 (M^+, 82), 269 (100). Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.45; H, 5.62; N, 13.31.

*4.5.7. (E)-2-(Acetylamino)-3-[4,6-dimethyl-2-(3-nitrophenyl)pyrimidin-5-yl]propenoic acid (**3g**).* Yield: 160.3 mg (90%); off-white powder; mp 244–247 °C (H_2O/EtOH). IR (KBr): 3372, 1705, 1524 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.07 (s, 3H, Me), 2.45 (s, 6H, two Me), 7.21 (s, 1H, 3-H), 7.79 (m, 1H, C_6H_4), 8.34 (m, 1H, C_6H_4), 8.76 (m, 1H, C_6H_4), 9.08 (m, 1H, C_6H_4), 9.69 (s, 1H, NH), 13.07 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ 22.7, 23.2, 117.5, 121.7, 124.9, 127.5, 130.3, 131.7, 133.5, 138.8, 148.2, 158.2, 164.1, 164.7, 169.0. MS (EI) *m*/*z* 356 (M^+, 41%), 314 (100). Anal. Calcd for $C_{17}H_{16}N_4O_5$: C, 57.30; H, 4.53; N, 15.72. Found: C, 57.23; H, 4.47; N, 15.63.

*4.5.8. (E)-2-(Benzoylamino)-3-(4-methyl-6-phenylpyrimidin-5-yl)-propenoic acid (**3h**).* Yield: 163.5 mg (91%); pale-brown powder; mp 225–228 °C (H_2O/EtOH). IR (KBr): 3376, 1660, 1530 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.50 (s, 3H, Me), 7.11 (s, 1H, 3-H), 7.52 (m, 6H, Ph), 7.75 (m, 2H, Ph), 7.93 (m, 2H, Ph), 9.01 (s, 1H, 2′-H), 10.08 (s, 1H, NH), 12.83 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ 22.9, 121.2, 126.3, 126.7,

127.6, 128.0, 128.5, 129.2, 129.4, 131.95, 131.98, 133.2, 137.9, 156.1, 161.9, 163.4, 164.6. MS (EI) *m/z* 360 (MH^+, 0.7%), 105 (100). Anal. Calcd for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.69. Found: C, 70.22; H, 4.87; N, 11.40.

*4.5.9. (E)-2-(Benzoylamino)-3-(2,4-dimethyl-6-phenylpyrimidin-5-yl)propenoic acid (**3i**).* Yield: 160.6 mg (86%); white powder; mp 202–204 °C (H_2O/EtOH). IR (KBr): 3353, 1671, 1640, 1542, 1440 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.44 (s, 3H, Me), 2.61 (s, 3H, Me), 7.01 (s, 1H, 3-H), 7.42 (m, 3H, Ph), 7.55 (m, 3H, Ph), 7.70 (m, 2H, Ph), 7.91 (m, 2H, Ph), 10.05 (s, 1H, NH), 12.73 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ 23.7, 26.3, 122.4, 124.4, 128.5, 128.8, 129.4, 130.0, 130.3, 132.8, 132.9, 134.1, 139.1, 163.0, 165.59, 165.62, 165.9, 166.2. MS (EI) *m/z* 374 (MH^+, 0.6%), 105 (100). Anal. Calcd for $C_{22}H_{19}N_3O_3$: C, 70.76; H, 5.13; N, 11.25. Found: C, 70.99; H, 5.17; N, 11.09.

*4.5.10. (E)-2-(Benzoylamino)-3-(4-methyl-2,6-diphenylpyrimidin-5-yl)propenoic acid (**3j**).* Yield: 178.5 mg (82%); off-white powder; mp 125–128 °C (H_2O/EtOH). IR (KBr): 3386, 1709, 1670, 1530, 1489 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.58 (s, 3H, Me), 7.13 (s, 1H, 3-H), 7.37 (m, 3H, Ph), 7.55 (m, 9H, Ph), 7.84 (m, 2H, Ph), 7.93 (m, 2H, Ph), 8.47 (m, 2H, Ph), 10.10 (s, 1H, NH), 12.80 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ 23.3, 119.3, 125.7, 127.4, 127.6, 127.9, 128.53, 128.56, 129.1, 129.5, 130.5, 131.9, 132.7, 133.5, 137.3, 138.5, 160.5, 162.0, 164.8, 165.0, 165.6. MS (EI) *m/z* 453 (M^+, 1.6%), 105 (100). HRMS (EI) calcd for $C_{27}H_{21}N_3O$ (M^+): 435.1583, found: 435.1591. Anal. Calcd for $C_{27}H_{21}N_3O_3 \cdot {}^1/_2$ EtOH: C, 73.35; H, 5.28; N, 9.16. Found: C, 73.29; H, 5.15; N, 9.11.

*4.5.11. (E)-2-(Benzoylamino)-3-[4-methyl-2-(3-nitrophenyl)-6-phenyl pyrimidin-5-yl]propenoic acid (**3k**).* Yield: 216.2 mg (90%); brown powder; mp 243–246 °C (H_2O/EtOH). IR (KBr): 3367, 1733, 1643, 1534, 1341 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.63 (s, 3H, Me), 7.17 (s, 1H, 3-H), 7.55 (m, 6H, Ar), 7.85 (m, 3H, Ar), 7.94 (m, 2H, Ph), 8.40 (m, 1H, Ar), 8.88 (m, 1H, Ar), 9.18 (m, 1H, Ar), 10.14 (s, 1H, NH), 12.66 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ 23.3, 118.7, 121.8, 125.0, 126.9, 127.5, 128.0, 128.5, 129.4, 129.6, 130.4, 131.9, 133.0, 133.4, 133.6, 138.1, 138.9, 148.3, 158.4, 162.3, 164.8, 165.0, 166.2. MS (FAB) *m/z* 481 (MH^+, 2%), 154 (100). Anal. Calcd for $C_{27}H_{20}N_4O_5$: C, 67.49; H, 4.20; N, 11.37. Found: C, 67.26; H, 4.34; N, 11.37.

*4.5.12. (E)-3-(2-Amino-4-methyl-6-phenylpyrimidin-5-yl)-2-(benzoylamino)propenoic acid (**3l**).* Yield: 164.7 mg (88%); brown powder; mp 264–266 °C (H_2O/EtOH). IR (KBr): 3368, 1703, 1669, 1600, 1507 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.27 (s, 3H, Me), 6.56 (s, 2H, NH_2), 6.78 (s, 1H, 3-H), 7.37 (m, 3H, Ph), 7.57 (m, 5H, Ph), 7.90 (m, 3H, Ph), 9.97 (s, 1H, NH), 12.56 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ 22.7, 114.9, 123.1, 127.5, 127.6, 128.4, 128.7, 129.1, 131.0, 131.8, 133.3, 138.9, 161.8, 163.6, 165.10, 165.11, 165.7. MS (EI) *m/z* 374 (M^+, 1.6), 105 (100). Anal. Calcd for $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14.96. Found: C, 67.02; H, 4.70; N, 14.81.

*4.5.13. (E)-2-(Benzoylamino)-3-(4-hydroxy-6-methyl-2-phenylpyrimidin-5-yl)propenoic acid (**4a**).* Yield: 159.8 mg (85%); yellow powder; mp 285–287 °C (H_2O/EtOH). IR: 3417, 1663, 1599, 1561, 1526 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.30 (s, 3H, Me), 6.62 (s, 1H, 3-H), 7.55 (m, 6H, Ph), 7.96 (m, 2H, Ph), 8.13 (m, 2H, Ph), 10.20 (s, 1H, NH), 12.75 (br s, 2H, 2×OH). ^{13}C NMR (pyridine-d_5) δ 23.4, 117.3, 120.2, 128.2, 128.6, 129.18, 129.21, 131.8, 132.2, 133.5, 134.3, 135.7, 155.9, 161.6, 163.8, 166.8, 168.0. MS (ESI^+) *m/z* 376 (MH^+). Anal. Calcd for $C_{21}H_{17}N_3O_4$: C, 67.19; H, 4.56; N, 11.19. Found: C, 66.89; H, 4.57; N, 11.08.

*4.5.14. (E)-2-(Benzoylamino)-3-[4-hydroxy-6-methyl-2-(4-methylphenyl)pyrimidin-5-yl]propenoic acid (**4b**).* Yield: 157.7 mg (81%); pale-yellow powder; mp 321–323 °C (H_2O/EtOH). IR (KBr): 3405, 1663, 1620 (br), 1551, 1511, 1465 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.29 (s, 3H, Me), 2.39 (s, 3H, Me), 6.61 (s, 1H, 3-H), 7.34 and 8.04 (AA′XX′, *J*=8.1 Hz, 4H, C_6H_4), 7.61 (m, 3H, Ph), 7.94 (m, 2H, Ph), 10.17 (s, 1H, NH), 12.60 (br s, 2H, 2×OH). ^{13}C NMR (pyridine-d_5) δ 21.4, 23.4, 117.3, 120.0, 128.1, 128.5, 129.1, 129.9, 131.3, 132.2, 133.3, 135.7, 142.1, 155.6, 161.5, 163.6, 166.7, 167.9. MS (ESI^-): *m/z* 388 (MH^-), 344. Anal. Calcd for $C_{22}H_{19}N_3O_4$: C, 67.86; H, 4.92; N, 10.79. Found: C, 68.00; H, 4.83; N, 10.42.

*4.5.15. (E)-2-(Benzoylamino)-3-[2-(4-chlorophenyl)-4-hydroxy-6-methylpyrimidin-5-yl]propenoic acid (**4c**).* Yield: 163.9 mg (80%); yellow powder; mp 318–323 °C (H_2O/EtOH). IR (KBr): 3409, 1667, 1622, 1551, 1521, 1490 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.31 (s, 3H, Me), 6.64 (s, 1H, 3-H), 7.57 (m, 3H, Ph), 7.60 and 8.14 (AA′XX′, *J*=8.6 Hz, 4H, C_6H_4), 7.94 (m, 2H, Ph), 10.16 (s, 1H, NH), 12.70 (br s, 2H, 2 x OH). ^{13}C NMR (pyridine-d_5) δ 23.6, 117.2, 121.0, 128.9, 130.0, 130.1, 130.9, 133.2, 135.3, 135.7, 138.3, 155.7, 161.8, 165.1, 167.8, 169.3 (one signal is hidden). MS (ESI^-) *m/z* 408 (MH^-), 364. Anal. Calcd for $C_{21}H_{16}ClN_3O_4$: C, 61.54; H, 3.94; N, 10.25. Found: C, 61.35; H, 3.91; N, 10.47.

*4.5.16. (E)-2-(Benzoylamino)-3-[4-hydroxy-6-methyl-2-(3-nitrophenyl)pyrimidin-5-yl]propenoic acid (**4d**).* Yield: 170.3 mg (81%); yellow powder; mp 267–270 °C (H_2O/EtOH). IR (KBr): 3406, 1667, 1620, 1600, 1522 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.36 (s, 3H, Me), 6.69 (s, 1H, 3-H), 7.56 (m, 3H, Ph), 7.84 (m, 1H, C_6H_4), 7.95 (m, 2H, Ph), 8.41 (m, 1H, C_6H_4), 8.60 (m, 1H, C_6H_4), 9.00 (m, 1H, C_6H_4), 10.19 (s, 1H, NH), 12.80 (br s, 2H). ^{13}C NMR (pyridine-d_5) δ 23.3, 117.0, 118.4, 123.2, 125.4, 128.1, 129.2, 130.2, 132.3, 133.3, 134.2, 135.7, 138.3, 149.0, 156.8, 163.5, 166.4, 166.7, 167.8. MS (ESI^-) *m/z* 419 (MH^-), 375. Anal. Calcd for $C_{21}H_{16}N_4O_6$: C, 60.00; H, 3.84; N, 13.33. Found: C, 60.05; H, 3.96; N, 13.18.

*4.5.17. N-(4-Methyl-7-oxo-2-phenyl-7H-pyrano[2,3-d]pyrimidin-6-yl)benzamide (**5a**).* Yield: from **1d** 100.1 mg (56%), from **4a** 164.4 mg (92%); light-brown powder; mp 279–281 °C (DMF/EtOH). IR (KBr): 3352, 1723, 1671, 1624, 1576, 1528 cm^{-1}. ^1H NMR (DMSO-d_6, 100 °C) δ 2.79 (s, 3H, Me), 7.57 (m, 6H, Ph), 7.97 (m, 2H, Ph), 8.42 (m, 2H, Ph), 8.73 (s, 1H, 5-H), 9.57 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 °C) δ 20.43, 109.3, 120.3, 124.9, 127.0, 127.7, 128.11, 128.15, 130.9, 131.8, 133.0, 135.7, 156.8, 160.8, 161.3, 165.6, 166.1. ^1H NMR (CF_3CO_2D) δ 3.13 (s, 3H, Me), 7.47 (m, 2H, Ph), 7.58 (m, 3H, Ph), 7.70 (m, 1H, Ph), 7.81 (m, 2H, Ph), 8.20 (m, 2H, Ph), 9.10 (s, 1H, 5-H). ^{13}C NMR (CF_3CO_2D) δ 19.5, 115.3, 119.1, 130.13, 130.19, 130.5, 131.8, 132.3, 132.9, 134.0, 137.4, 139.0, 159.5, 162.2, 165.97, 166.00, 173.7. MS (EI) *m/z* 357 (M^+, 38%), 105 (100). Anal. Calcd for $C_{21}H_{15}N_3O_3$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.51; H, 4.35; N, 11.54.

*4.5.18. N-[4-Methyl-2-(4-methylphenyl)-7-oxo-7H-pyrano[2,3-d]pyrimidin-6-yl]benzamide (**5b**).* Yield: from **1d** 100.3 mg (54%), from **4b** 150.4 mg (81%); pale-yellow crystals; mp 324–327 °C (DMF/MeOH). IR (KBr): 3378, 1720, 1668, 1626, 1579, 1526 (br) cm^{-1}. ^1H NMR (CF_3CO_2D) δ 2.47 (s, 3H, Me), 3.17 (s, 3H, Me), 7.47 and 8.18 (AA′XX′, *J*=8.3 Hz, 4H, C_6H_4), 7.56 (m, 2H, Ph), 7.69 (m, 1H, Ph), 7.89 (m, 2H, Ph), 9.16 (s, 1H, 5-H). ^{13}C NMR (CF_3CO_2D) δ 19.1, 22.9, 114.4, 127.2, 129.6, 129.8, 131.5, 132.0, 133.4, 133.7, 137.1, 152.0, 159.4, 161.9, 165.4, 165.6, 173.5 (one signal is missing). MS (ESI^+) *m/z* 372 (MH^+). Anal. Calcd for $C_{22}H_{17}N_3O_3$: C, 71.15; H, 4.61; N, 11.31. Found: C, 70.88; H, 4.61; N, 11.30.

*4.5.19. N-[2-(4-Chlorophenyl)-4-methyl-7-oxo-7H-pyrano[2,3-d]pyrimidin-6-yl]benzamide (**5c**).* Yield: from **1d** 101.9 mg (52%), from **4c** 156.7 mg (80%); pale-yellow powder; mp 301–303 °C (DMF/MeOH). IR (KBr): 3386, 1725, 1674, 1622, 1569, 1518 cm^{-1}. ^1H NMR (CF_3CO_2D) δ 3.00 (s, 3H, Me), 7.42 (m, 5H, 3H of Ph and 2H of C_6H_4), 7.70 (m, 2H, Ph), 8.05 (AA′XX′, *J*=8.7 Hz, 2H of C_6H_4), 8.97 (s,

1H, 5-H). ^{13}C NMR (CF_3CO_2D) δ 19.45, 115.4, 118.9, 128.9, 130.1, 130.2, 132.2, 133.0, 133.3, 133.9, 137.4, 146.7, 159.3, 161.0, 165.8, 166.0, 173.6. MS (ESI$^+$) m/z 392 (MH^+), 372. Anal. Calcd for $C_{21}H_{14}ClN_3O_3$: C, 64.38; H, 3.60; N, 10.72. Found: C, 64.35; H, 3.51; N, 10.78.

*4.5.20. N-[4-Methyl-2-(3-nitrophenyl)-7-oxo-7H-pyrano[2,3-d]pyrimidin-6-yl]benzamide (**5d**).* Yield: from **1d** 100.6 mg (50%), from **4d** 150.9 mg (75%); light-brown needles; mp 268–270 °C (DMF/MeOH). IR (KBr): 3389, 1743, 1677, 1626, 1530 (br) cm^{-1}. ^{1}H NMR (CF_3CO_2D) δ 3.28 (s, 3H, Me), 7.60 (m, 2H, Ph), 7.73 (m, 1H, C_6H_4), 7.93 (m, 3H, Ph), 8.64 (m, 1H, C_6H_4), 8.78 (m, 1H, C_6H_4), 9.25 (m, 2H, 5-H and 1H of C_6H_4). ^{13}C NMR (CF_3CO_2D) δ 19.3, 116.2, 118.2, 126.4, 129.8, 130.5, 131.97, 132.04, 132.4, 133.5, 134.1, 137.2, 137.6, 151.3, 158.7, 159.2, 165.5, 166.4, 173.5. MS (ESI$^+$) m/z 403 (MH^+), 372. Anal. Calcd for $C_{21}H_{14}N_4O_5$: C, 62.69; H, 3.51; N, 13.92. Found: C, 62.50; H, 3.37; N, 13.38.

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