One-Step Synthesis of 2-Amino-5-(4,5-diphenylpyrimidin-2-ylamino)pentanoic Acid from Isoflavones and Arginine

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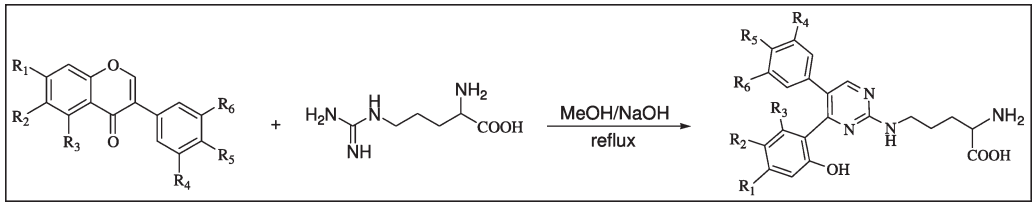

A simple and straightforward methodology toward the synthesis of novel 2-amino-5-(4,5-diphenylpyrimidin-2-ylamino)pentanoic acid has been developed by one-step reaction of isoflavones with arginine. A series of 14 new compounds was reported. All of them were characterized by FTIR, NMR, and elemental analysis. A variety of substrates can participate in the process with good yields and high purities making this methodology suitable for library synthesis in drug discovery.

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INTRODUCTION

Pyrimidines are well known and widely investigated six-membered nitrogen-containing heterocyclic compounds that exhibit important biological activity [1–4]. Amino acid groups are found widely in a large variety of compounds that exhibit important biological activity, such as amino acids, are interesting drug targets because they are found on proteins, are well-known papain inhibitor [5], and present potential anti-HIV [6], anticonvulsant [7], and antiproliferative activity [8]. It is convenient to synthesize substituted pyrimidines by reaction of amidines or guanidines with α,β-unsaturated ketones [9,10], β-diketones [11,12], β-alkoxy- and β-aminovinyl ketones [13–16], and *N*-arylacetyleneic imines [17,18]. Natural isoflavones display a wide range of biological activities [19]. For instance, soybean isoflavones (daidzein and genistein) have shown pharmacological effects as antidysrhythmic [20], antioxidant [21], and anticardio-cerebral vascular disease [22]. Ipriflavone has been reported to be efficient in preventing and treating osteoporosis [23]. It was reported that the chromone fragment present in isoflavones can generate a 1,3-diketone equivalent, which readily reacts with amidines [24], guanidine [2], carbamide [25], and sulfocarbamides [26] to form the corresponding 2-substituted pyrimidines. The use of combinatorial approaches to the high-throughput synthesis of this drug-like scaffold would be a powerful advance in helping to speed up drug discovery. Recently, we have reported the high-throughput synthesis of 3,4-diarylpyrazoles and 4,5-diphenyl-2-pyrimidinylguanidine by using a one-pot reaction of hydrazine [27] or bisguanidine [28] with isoflavones. Herein, we report a new strategy for the preparation of the unknown class of 2-amino-5-(4,5-diphenylpyrimidin-2-ylamino)-pentanoic acid by the cyclocondensation of isoflavones (**1**) with arginine (**2**) (Table 1).

RESULTS AND DISCUSSION

We turned our attention to optimize the condition of the cyclocondensations of isoflavones (**1**) with arginine (**2**) and designed a process by the cyclocondensation of 4′,7-dimethoxylisoflavone (**1a**) with arginine (**2**) as a model substrate (Table 2). As shown in Table 2, we used K_2CO_3 as base and **3a** yield was 37% (Table 2, entry 1). It was also found that triethylamine (TEA) was ineffective in providing the desired condensation product (Table 2, entry 2). A comparative reactivity study of bases in the reaction showed that NaOH proved to be more effective for this cyclocondensation (Table 2, entry 3). As it was shown, solvents MeOH, EtOH, THF, MeCN, *n*-BuOH, and DMF have been attempted, MeOH gave expected result (Table 2, entry 3). Further study with varying NaOH equivalents revealed that 3.0 equiv of base is necessary to obtain a high yield of the condensation product (Table 2, entry 9). Finally, the ratio of **1a** and **2** was also evaluated. The ratio of **1a**:**2** (1:3),

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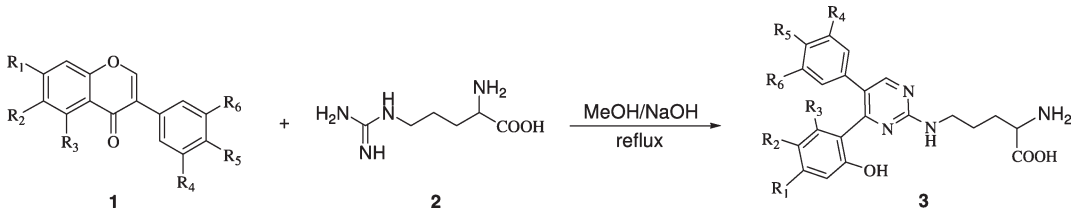
Table 1

Synthesis of 2-amino-5-(4,5-diphenylpyrimidin-2-ylamino)pentanoic acid by reaction of various isoflavones with arginine in MeOH. (For details, See Experimental.)



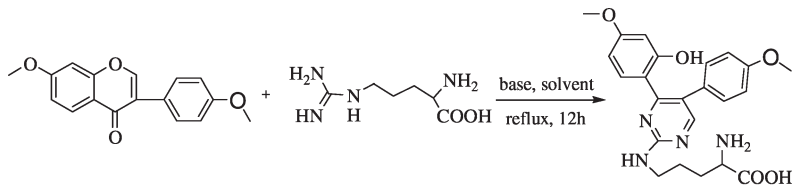
1 **2** **3**

Entry	Substrate	R_1	R_2	R_3	R_4	R_5	R_6	Time (h)	Yield[a] (%)
1	**1a**	OMe	H	H	H	OMe	H	8.0	92
2	**1b**	OMe	H	OMe	H	OMe	H	6.5	90
3	**1c**	O^{i}Pr	H	H	H	H	H	7.2	88
4	**1d**	OMe	H	H	H	H	H	7.0	85
5	**1e**	OMe	OMe	OMe	H	OMe	H	5.0	83
6	**1f**	OMe	H	Me	H	H	H	5.0	81
7	**1g**	OBn	H	H	H	OMe	H	7.5	85
8	**1h**	OMe	H	H	H	OMe	NO_2	7.5	87
9	**1i**	OMe	H	H	^{i}Pr	OH	^{i}Pr	8.3	79
10	**1j**	OMe	H	H	H	OH	H	8.5	77
11	**1k**	OH	H	H	H	OMe	H	9.0	73
12	**1l**	OH	H	H	H	H	H	9.0	70
13	**1m**	OH	H	H	H	OH	H	12.0	57
14	**1n**	OH	H	H	^{i}Pr	OH	^{i}Pr	11.2	65

[a] Isolated yield after silica chromatography.

Table 2

Optimization of cyclocondensation of 4′,7-dimethoxylisoflavone **1a** with arginine **2**.[a]

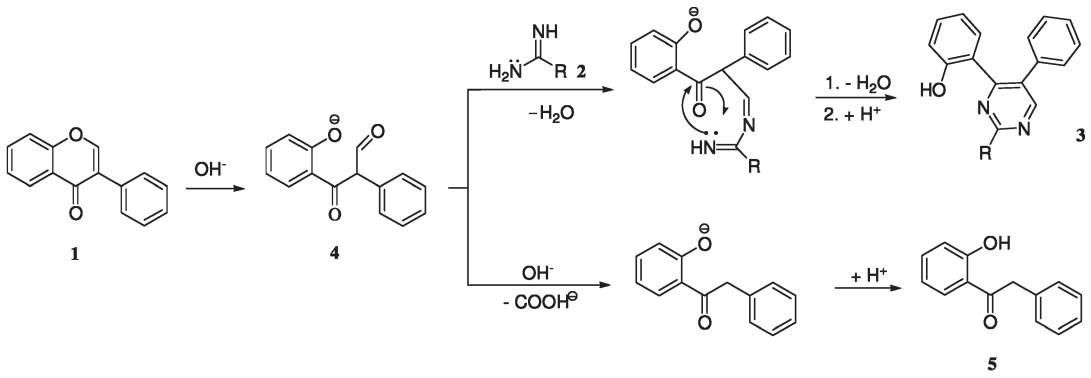


1a **2** **3a**

Entry	Solvent	Base	Molar ratios **1a**/**2a**/base	Yield (%)[b] **3a**
1	MeOH	K_2CO_3	1:1:2	37
2	MeOH	TEA	1:1:2	NR[c]
3	MeOH	NaOH	1:1:2	67
4	EtOH	NaOH	1:1:2	56
5	THF	NaOH	1:1:2	NR[c]
6	MeCN	NaOH	1:1:2	Trace
7	*n*-BuOH	NaOH	1:1:2	Trace
8	DMF	NaOH	1:1:2	NR[c]
9	MeOH	NaOH	1:1:3	79
10	MeOH	NaOH	1:1:4	71
11	MeOH	NaOH	1:2:3	85
12	MeOH	NaOH	1:3:3	92
13	MeOH	NaOH	1:4:3	89

[a] All reaction were carried out in the appropriate solvent (15 mL) using 4′,7-dimethoxylisoflavone (**1a**, 1 mmol), arginine (**2**), and base until complete disappearance of **1a** (refluxing for 8 h, TLC check).
[b] Isolated yield after silica chromatography.
[c] No reaction.

Scheme 1. Proposed mechanism for the formation of **3**.



[a] R= - $NH(CH_2)_3CH(NH_2)COOH$.

the yield of **3a** was high for the cyclocondensation reaction (Table 2, entry 12).

With the optimized reaction conditions and proven results in hand, the condensation of variety of structurally divergent isoflavones (**1**) and arginine (**2**) were studied to illustrate this concise and general method for the synthesis of 2-amino-5-(4,5-diphenylpyrimidin-2-ylamino)pentanoic acid. All substrates reacted smoothly to give the corresponding 2-amino-5-(4,5-diphenylpyrimidin-2-ylamino)pentanoic acid in 5–12 h in good to excellent yields, and the results were summarized in Table 1. All products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis.

In general, isoflavone **1** substituted with alkoxy, benzyoxyl groups gave high yields. In contrast, the presence of the hydroxyl groups gave lower yields. As shown in Table 1, isoflavones **1a–h** (Table 1, entries 1–8) that do not contain hydroxyl groups, gave yields of **3** about 85%. Isoflavones with one hydroxyl group, **1i–l** (Table 1, entries 9–12) only gave yields of **3** about 75%, whereas those with two free hydroxyls, **1m**, **1n** (Table 1, entries 13 and 14) gave yields of roughly 60%. Condensation of trihydroxy isofalvone genistein (4′,5,7-trihydroxy-isoflavone) with **2** failed to produce product **3**. The yields of **3** are directly dependant on the number of free hydroxyl group present on the engaged isoflavone. Because the hydroxyls of isoflavone **1** under basic condition would be oxygenions, which possess stronger electron donability than alkoxy and benzyoxyl groups of the isoflavone, it is not favorable to the condensation reaction.

To explain the mechanism for the formation of 2-amino-5-(4,5-diphenylpyrimidin-2-ylamino)pentanoic acid (**3**) by the cyclocondensation of isoflavones (**1**) with arginine (**2**) in the presence of NaOH, a postulated reaction course was illustrated in Scheme 1. As it was reported that isoflavone may undergo ring-opening reaction when refluxing in the presence of alkali to form a β-diketone intermediate **4** [29]. Subsequently, attack of the primary amine group from the arginine (**2**) on the aldehyde carbon in **4**, followed by ring closure reaction between secondary amine and the carbonyl carbon to produce **3**. Meanwhile, intermediate **4** at high concentration of base may eliminate HCOOH to generate byproduct **5** [29].

CONCLUSIONS

In summary, a convenient method for the synthesis of substituted pyrimidines bearing amino acid moiety in the 2 position was described. The protocol accepted a variety of isoflavones, arginine as starting materials and gave 2-amino-5-(4,5-diphenylpyrimidin-2-ylamino)pentanoic acid in good to high yield. Efforts to expand the scope of the method in combination with its application to the synthesis of pharmaceutical molecules are ongoing in our laboratory.

EXPERIMENTAL

All other commercially obtained reagents were used as received. The silica gel used for the column chromatography was purchased from Qingdao Haiyang Chemistry Plant. Thin Layer chromatography (TLC): silica gel 60 GF_{254} plate; the eluant of column chromatography was the mixture of chloroform and methanol at volume ratio of 5:1. Arginine, ipriflavone, daiazein, genistein, formonone, and 5-methyl-7-methoxy-isoflavone are without further purification. Substrates **1d** and **1l** are derived from ipriflavone. Substrates **1a**, **1h**, **1i**, **1j**, and **1n** are derived from daiazein. Substrate **1b** is derived from genistein. Substrate **1g** is derived from formonone. Substrate **1e** is derived from irisolidone (4′,6-dialkoxy-5,7-dihydroxy-isoflavone), which was separated from the flower of *Pueraria lobata* by one of the authors. Melting points were measured on X-5 micromelting point apparatus and were uncorrected. IR spectra were recorded on Fourier transform infrared spectrometer using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 Advance spectrometer at 300.00 MHz in DMSO-d_6 with TMS as internal standard (chemical shifts in

ppm). The elemental analyses were performed with an Elementar Analysensyteme GmbH Vario EL III.

General procedure for the preparation of 2-amino-5-(4,5-diphenylpyrimidin-2-ylamino)pentanoic acid (Table 1, entries 1–14). The corresponding isoflavones **1** (1 mmol), arginine **2** (3 mmol), and sodium hydroxide (3, 4, and 5 mmol were used for 0, 1, and 2 free hydroxyl of **1**, respectively) were refluxed in methanol (15 mL) for 5–12 h. All reactions were monitored by TLC, which showed the disappearance of **1** that was indicative of the reaction being complete. The reaction mixture was added into water (30 mL) and adjusted to neutrality with the solution of 5% HCl. A yellow precipitate appeared and was filtered. The yellow precipitate was dissolved in a solution of 10% HCl (15 mL) and filtered. The mother liquid was neutralized with sodium hydroxide until crude product was completely precipitated. The crude product was filtered and purified by column chromatography on silica gel using chloroform–methanol (5:1) to give the corresponding pure product.

2-Amino-5-[4-(2-hydroxy-4-methoxyphenyl)-5-(4-methoxyphenyl)pyrimidin-2-ylamino]pentanoic acid (3a). Yellow solid. mp 231.6–232.9°C. IR (KBr), ν (cm^{-1}): 3438, 2924, 2853, 1690, 1605, 1506, 1443, 1392, 1085, 1033, 686, 605. ^{1}H NMR (300 MHz, DMSO-d_6), δ 1.64–1.70 (m, 2H), 1.87 (d, 2H), 3.35 (s, 2H), 3.70 (s, 3H), 3.75 (s, 3H), 3.92 (s, 1H), 6.19 (d, J = 8.6 Hz, 1H), 6.37 (s, 1H), 6.90 (d, J = 8.4 Hz, 3H), 7.10 (d, J = 8.4 Hz, 2H), 7.62 (s, 1H), 8.21 (s, 1H), 8.35 (s, 3H), 11.98 (s, 1H); ^{1}H NMR (300 MHz, DMSO-d_6 + D_2O), δ 1.66–1.73 (m, 2H), 1.79–1.88 (m, 2H), 3.35 (s, 2H), 3.71 (s, 3H), 3.75 (s, 3H), 3.91–3.95 (m, 1H), 6.22 (d, J = 8.6 Hz, 1H), 6.37 (d, 1H), 6.90 (d, J = 8.3 Hz, 3H), 7.10 (d, J = 8.4 Hz, 2H), 8.21 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6 + D_2O), δ 24.5, 27.4, 51.7, 55.0, 55.1, 101.5, 104.9, 114.0, 114.4, 121.2, 129.7, 129.8, 131.6, 158.2, 158.7, 159.4, 159.7, 161.3, 161.9, 170.6. Anal. Calcd. for $C_{23}H_{26}N_4O_5$: C, 63.00; H, 5.98; N, 12.78. Found C, 63.26; H, 5.76; N, 12.96.

2-Amino-5-[4-(2-hydroxy-4,6-dimethoxyphenyl)-5-(4-methoxyphenyl)pyrimidin-2-ylamino]pentanoic acid (3b). Yellow solid. mp 218.3–219.6°C. IR (KBr), ν (cm^{-1}): 3416, 2927, 1643, 1612, 1507, 1458, 1337, 1250, 1157, 1030, 833. ^{1}H NMR (300 MHz, DMSO-d_6), δ 1.65–1.72 (m, 2H), 1.89 (d, 2H), 3.33 (s, 2H), 3.44 (s, 3H), 3.67 (s, 3H), 3.69 (s, 3H), 3.88 (s, 1H), 5.96 (s, 1H), 6.11 (s, 1H), 6.78 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 7.33–7.43 (m, 1H), 8.24 (s, 1H), 8.56 (s, 3H), 9.62–9.86 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 24.5, 27.3, 51.7, 54.9, 55.0, 55.3, 89.8, 93.5, 113.4, 124.6, 128.8, 128.9, 156.0, 157.3, 158.1, 159.3, 161.1, 170.5. Anal. Calcd. for $C_{24}H_{28}N_4O_6$: C, 61.53; H, 6.02; N, 11.96. Found C, 61.29; H, 5.85; N, 12.16.

2-Amino-5-[4-(2-hydroxy-4-isopropxyphenyl)-5-phenylpyrimidin-2-ylamino]pentanoic acid (3c). Yellow solid. mp 243.3–244.7°C. IR (KBr), ν (cm^{-1}): 3436, 2926, 1609, 1441, 1386, 700, 598, 544, 466. ^{1}H NMR (300 MHz, DMSO-d_6), δ 1.22 (d, J = 5.7 Hz, 6H), 1.71 (d, 2H), 1.89 (s, 2H), 3.36 (s, 2H), 3.93 (d, 1H), 4.53 (t, 1H), 6.15 (d, J = 8.3 Hz, 1H), 6.33 (s, 1H), 6.85 (d, J = 8.4 Hz, 1H), 7.17–7.32 (m, 5H), 7.50 (s, 1H), 8.24 (s, 1H), 8.60 (s, 3H); ^{1}H NMR (300 MHz, DMSO-d_6 + D_2O), δ 1.23 (d, J = 5.8 Hz, 6H), 1.71 (t, 2H), 1.89 (s, 2H), 3.36 (s, 2H), 3.94 (d, 1H), 4.54 (t, 1H), 6.15 (d, J = 8.3 Hz, 1H), 6.33 (s, 1H), 6.85 (d, J = 7.0 Hz, 1H), 7.18–7.33 (m, 5H), 8.24 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6 + D_2O), δ 21.7, 24.6, 27.5, 51.7, 69.3, 102.9, 106.1, 114.1, 121.4, 126.8, 128.5, 128.6, 131.8, 137.8, 158.8, 159.7, 159.8, 162.1, 170.6. Anal. Calcd. for $C_{24}H_{28}N_4O_4$: C, 66.04; H, 6.47; N, 12.84. Found C, 66.21; H, 6.55; N, 12.68.

2-Amino-5-[4-(2-hydroxy-4-methoxyphenyl)-5-phenylpyrimidin-2-ylamino]pentanoic acid (3d). Yellow solid. mp 223.6–224.9°C. IR (KBr), ν (cm^{-1}): 3435, 2925, 2828, 1624, 1529, 1430, 1375, 1072, 702. ^{1}H NMR (300 MHz, DMSO-d_6), δ 1.71 (s, 2H), 1.87 (s, 2H), 3.32 (s, 2H), 3.69 (s, 3H), 6.14 (d, J = 5.3 Hz, 1H), 6.40 (s, 1H), 6.83 (s, 1H), 7.20–7.30 (m, 5H), 7.66–7.78 (m, 3H), 8.23 (s, 1H), 11.95 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 25.2, 28.4, 53.6, 55.0, 101.6, 104.7, 114.3, 121.1, 126.7, 128.5, 128.7, 131.6, 137.9, 159.3, 159.8, 161.3, 171.3. Anal. Calcd. for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72. Found C, 64.42; H, 5.77; N, 13.98.

2-Amino-5-[4-(2-hydroxy-4,5,6-trimethoxyphenyl)-5-(4-methoxyphenyl)pyrimidin-2-ylamino]pentanoic acid (3e). Yellow solid. mp 230.8–232.1°C. IR (KBr), ν (cm^{-1}): 3397, 2938, 1643, 1607, 1458, 1247, 1103, 549. ^{1}H NMR (300 MHz, DMSO-d_6), δ 1.69 (d, J = 5.6 Hz, 2H), 1.89 (s, 2H), 3.31 (s, 2H), 3.45 (s, 3H), 3.58 (s, 3H), 3.69 (s, 3H), 3.70 (s, 3H), 6.30 (s, 1H), 6.77 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 8. 22 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 24.9, 27.9, 52.4, 54.9, 55.5, 60.4, 60.5, 95.8, 113.3, 124.0, 129.1, 129.5, 134.0, 150.8, 153.1, 157.1, 157.9, 161.0, 161.3, 171.1. Anal. Calcd. for $C_{25}H_{30}N_4O_7$: C, 60.23; H, 6.07; N, 11.24. Found C, 60.49; H, 6.26; N, 11.02.

2-Amino-5-[4-(2-hydroxy-4-methoxy-6-methylphenyl)-5-phenylpyrimidin-2-ylamino]pentanoic acid (3f). Yellow solid. mp 220.6–221.8°C. IR (KBr), ν (cm^{-1}): 3060, 2946, 1967, 1651, 1609, 1448, 1336, 1198, 1158, 1033, 832, 760, 703. ^{1}H NMR (300 MHz, DMSO-d_6), δ 1.68 (s, 2H), 1.83 (s, 3H), 1.89 (s, 2H), 3.36 (s, 2H), 3.65 (s, 3H), 3.89 (s, 1H), 6.16 (s, 1H), 6.30 (s, 1H), 7.16-7.19 (m, 5H), 7.40 (s, 1H), 8.30 (s, 1H), 8.56 (s, 2H), 9.55 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 20.1, 25.2, 28.1, 52.3, 55.2, 99.1, 106.2, 119.7, 124.7, 126.9, 128.3, 128.4, 137.1, 137.5, 156.1, 158.1, 159.8, 161.7, 164.2, 171.3. Anal. Calcd. for $C_{21}H_{21}N_5O_7$: C, 55.38; H, 4.65; N, 15.38. Found C, 55.10; H, 4.50; N, 15.64.

2-Amino-5-[4-(4-benzyl-2-hydroxyphenyl)-5-(4-methoxyphenyl)pyrimidin-2-ylamino]pentanoic acid (3g). Yellow solid. mp 254.5–255.8°C. IR (KBr), ν (cm^{-1}): 3425, 2927, 1620, 1599, 1521, 1423, 1402, 1055, 1021, 702, 630. ^{1}H NMR (300 MHz, DMSO-d_6), δ 1.69 (s, 2H), 1.86 (s, 2H), 3.30 (s, 2H), 3.73 (s, 3H), 5.02 (s, 2H), 6.23 (d, J = 8.0 Hz, 1H), 6.47 (s, 1H), 6.87 (d, J = 7.6 Hz, 3H), 7.09 (d, J = 7.5 Hz, 2H), 7.34–7.39 (m, 5H), 7.63 (s, 1H), 8.18 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 25.7, 29.2, 54.5, 55.5, 69.6, 103.0, 105.9, 114.5, 121.1, 128.2, 128.3, 128.9, 130.4, 130.5, 132.1, 137.2, 158.6, 160.0, 160.1, 160.4, 160.6, 160.9, 171.4. Anal. Calcd. for $C_{29}H_{30}N_4O_4$: C, 69.86; H, 6.06; N, 11.24. Found C, 69.63; H, 6.21; N, 11.49.

2-Amino-5-[4-(2-hydroxy-4-methoxyphenyl)-5-(3-nitro-4-methoxyphenyl)pyrimidin-2-ylamino]pentanoic acid (3h). Yellow solid. mp 219.7–221.0°C. IR (KBr), ν (cm^{-1}): 3420, 3047, 2925, 2711, 1650, 1614, 1574, 1332, 1276, 1211, 1025, 869, 750. ^{1}H NMR (300 MHz, DMSO-d_6), δ 1.69 (s, 2H), 1.89 (s, 2H), 3.34 (s, 2H), 3.70 (s, 3H), 3.84 (s, 1H), 3.90 (s, 3H), 6.34 (s, 1H), 6.38 (s, 1H), 7.00 (s, 1H), 7.28 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.66 (s, 2H), 8.28 (s, 1H), 8.52 (s, 2H), 10.91 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 24.5,

27.4, 51.9, 55.1, 56.6, 101.4, 105.2, 114.2, 115.7, 119.8, 124.4, 130.1, 131.4, 134.4, 138.8, 150.7, 157.2, 158.8, 160.3, 161.3, 162.7, 170.6. Anal. Calcd. for $C_{23}H_{25}N_5O_7$: C, 57.14; H, 5.21; N, 14.49. Found C, 57.01; H, 5.06; N, 14.76.

2-Amino-5-[4-(2-hydroxy-4-methoxyphenyl)-5-(3,5-diisopropyl-4-hydroxyphenyl)pyrimidin-2-ylamino]pentanoic acid (3i). Yellow solid. mp 248.2–249.5°C. IR (KBr), ν (cm^{-1}): 3329, 2961, 2868, 1594, 1536, 1439, 1379, 1292, 1205, 1151, 1030, 835, 790. ^{1}H NMR (300 MHz, DMSO-d_6), δ 1.04 (d, J = 5.0 Hz, 12H), 1.67 (s, 2H), 1.83 (s, 2H), 3.24–3.28 (t, 5H), 3.66 (s, 3H), 6.12 (s, 1H), 6.36 (s, 1H), 6.77–6.82 (d, 3H), 7.48 (s, 1H), 8.22 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 22.8, 25.3, 25.9, 28.7, 54.0, 55.1, 101.6, 104.6, 114.4, 121.7, 123.5, 128.6, 131.5, 135.3, 149.6, 159.4, 161.2, 170.4. Anal. Calcd. for $C_{28}H_{36}N_4O_5$: C, 66.12; H, 7.13; N, 11.02. Found C, 66.01; H, 7.35; N, 10.88.

2-Amino-5-[4-(2-hydroxy-4-methoxyphenyl)-5-(4-hydroxyphenyl)pyrimidin-2-ylamino]pentanoic acid (3j). Yellow solid. mp 254.5–255.8°C. IR (KBr), ν (cm^{-1}): 3415, 2924, 1610, 1448, 1385, 1294, 1162, 1019, 833, 630. ^{1}H NMR (300 MHz, DMSO-d_6), δ 1.68 (d, 2H), 1.86 (s, 2H), 3.33 (s, 2H), 3.81 (s, 3H), 3.88 (s, 1H), 6.20 (dd, J_1 = 1.6 Hz, J_2 = 8.7 Hz, 1H), 6.38 (s, 1H), 6.75 (d, J = 8.2 Hz, 2H), 6.91 (d, J = 8.7 Hz, 1H), 6.98 (d, J = 8.2 Hz, 2H), 8.19 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 24.6, 27.6, 52.4, 55.1, 101.5, 104.8, 114.2, 115.5, 121.3, 128.1, 129.8, 131.6, 156.1, 159.0, 159.3, 159.8, 161.3, 171.0. Anal. Calcd. for $C_{22}H_{24}N_4O_5$: C, 62.25; H, 5.70; N, 13.20. Found C, 62.43; H, 5.81; N, 13.01.

2-Amino-5-[4-(2,4-dihydroxyphenyl)-5-(4-methoxyphenyl)-pyrimidin-2-ylamino]pentanoic acid (3k). Yellow solid. mp 240.2–241.6°C. IR (KBr), ν (cm^{-1}): 3435, 2923, 2854, 1642, 1535, 1446, 1266, 1003, 597, 535, 458. ^{1}H NMR (300 MHz, DMSO-d_6), δ 1.70–1.82 (m, 2H), 1.89 (s, 2H), 3.45 (s, 2H), 3.74 (s, 3H), 3.94 (d, 1H), 6.15 (d, J = 8.1 Hz, 1H), 6.30 (s, 1H), 6.90 (d, J = 8.4 Hz, 3H), 7.10 (d, J = 8.4 Hz, 2H), 8.46 (s, 4H), 9.96–9.99 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 24.1, 27.1, 51.5, 55.1, 102.7, 107.1, 114.0, 122.2, 127.2, 129.6, 132.0, 154.1, 157.5, 158.6, 161.0, 170.4. Anal. Calcd. for $C_{22}H_{24}N_4O_5$: C, 62.25; H, 5.70; N, 13.20. Found C, 62.43, H, 5.31, N, 13.42.

2-Amino-5-[4-(2,4-dihydroxyphenyl)-5-phenylpyrimidin-2-ylamino]pentanoic acid (3l). Yellow solid. mp 257.1–258.6°C. IR (KBr), ν (cm^{-1}): 3408, 2958, 1610, 1574, 1536, 1392, 1327, 1196, 632. ^{1}H NMR (300 MHz, DMSO-d_6), δ 1.72 (s, 2H), 1.88 (s, 2H), 3.33 (s, 2H), 3.7 (s, 1H), 5.98 (d, J = 7.3 Hz, 1H), 6.27 (s, 1H), 6.71 (d, J = 8.5 Hz, 1H), 7.18–7.33 (m, 5H), 7.56 (s, 1H), 8.20 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 24.8, 27.9, 52.4, 103.3, 106.3, 112.1, 120.8, 126.5, 126.7, 128.5, 128.7, 131.7, 138.2, 159.6, 160.2, 161.9, 171.0. Anal. Calcd. for $C_{21}H_{22}N_4O_4$: C, 63.95; H, 5.62; N, 14.20. Found C, 64.20; H, 5.81; N, 14.43.

2-Amino-5-[4-(2,4-dihydroxyphenyl)-5-(4-hydroxyphenyl)-pyrimidin-2-ylamino]pentanoic acid (3m). Yellow solid. mp 275.2–276.7°C. IR (KBr), ν (cm^{-1}): 3409, 3111, 1666, 1612, 1507, 1447, 1403, 1249, 1216, 843. ^{1}H NMR (300 MHz, DMSO-d_6), δ 1.68 (d, 2H), 1.88 (s, 2H), 3.33 (s, 2H), 3.94 (s, 1H), 6.01 (d, J = 8.5 Hz, 1H), 6.23 (s, 1H), 6.73–6.80 (m, 3H), 6.97 (d, J = 8.2 Hz, 2H), 7.60 (s, 1H), 8.16 (s, 1H); ^{1}H NMR (300 MHz, DMSO-d_6 + D_2O), δ 1.69 (d, 2H), 1.88 (s, 2H), 3.34 (s, 2H), 3.94 (s, 1H), 6.01 (d, J = 8.2 Hz, 1H), 6.24 (s, 1H), 6.74–6.81 (m, 3H), 6.98 (d, J = 6.4 Hz, 2H), 8.16 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6 + D_2O), δ 24.5, 27.5, 51.7, 103.0, 106.2, 112.7, 115.5, 121.0, 128.4, 129.8, 131.8, 156.2, 159.2, 159.5, 159.8, 160.0, 161.9, 170.6. Anal. Calcd. for $C_{21}H_{22}N_4O_5$: C, 61.45; H, 5.40; N, 13.65. Found C, 61.20; H, 5.51; N, 13.46.

2-Amino-5-[4-(2,4-dihydroxyphenyl)-5-(3,5-diisopropyl-4-hydroxyphenyl)pyrimidin-2-ylamino]pentanoic acid (3n). Yellow solid. mp. 268.7–269.9°C. IR (KBr), ν (cm^{-1}): 3419, 2961, 2871, 1597, 1536, 1447, 1401, 1213, 592. ^{1}H NMR (300 MHz, DMSO-d_6), δ 1.06 (d, J = 5.0 Hz, 12H), 1.67 (s, 2H), 1.84 (s, 2H), 3.24–3.28 (t, 5H), 5.93 (d, J = 8.0 Hz, 1H), 6.23 (s, 1H), 6.74 (d, J = 8.3 Hz, 1H), 6.80 (s, 2H), 7.50 (s, 2H), 8.20 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 22.8, 25.2, 26.0, 28.6, 53.9, 103.2, 106.0, 112.0, 121.2, 123.6, 128.9, 131.6, 135.5, 149.6, 159.2, 160.0, 160.2, 170.7. Anal. Calcd. for $C_{27}H_{34}N_4O_5$: C, 65.57; H, 6.93; N, 11.33. Found C, 65.35; H, 6.75; N, 11.54.

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