Novel and Efficient Synthesis of DHPMs Catalyzed by di-DACH-Pyridylamide Ligands

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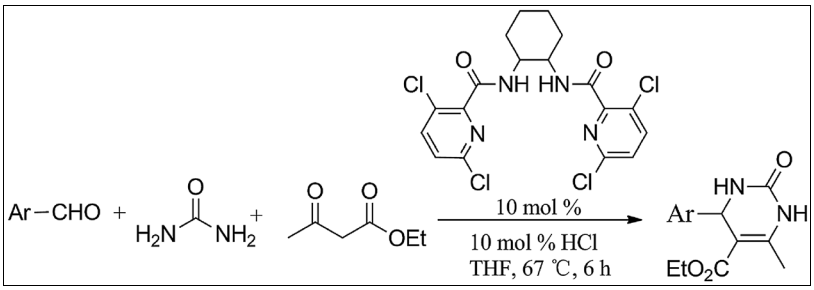

Di-DACH-pyridylamide ligands, symmetrical bridged bis-Schiff base, and spiro pyrrolizines as catalysts in the synthesis of dihydropyrimidinethiones (DHPMs) using the Biginelli reaction is first reported. This new protocol has the advantages of environmental friendliness, short reaction time, excellent yields, and simple post-treatment procedure. A series of DHPMs were obtained in high yields (up to 98%) in only 6 h. Moreover, based on the optimized condition, a novel Biginelli-like reaction was first developed.

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Multifunctionalized 3,4-dihydropyrimidin-2(1*H*)-one derivatives (DHPMs) are very important pharmacologically active molecules and have found applications as calcium channel modulators, α_{1a}-adrenoceptor selective antagonists, and inhibitors of the kinesin motor protein and HIV [1]. The Biginelli reaction [2], which is a three-component reaction of an aromatic aldehyde, urea, and acetoacetate, is the most efficient method for the assembly of these biologically significant heterocyclic compounds. In recent years, in order to improve and modify this reaction, several catalysts for the preparation of DHPMs have been explored. These include assistance from $FeCl_3$-supported nanopore silica [3], and ferric perchlorate [4], polyoxometalate [5], transition metals containing halides [6–8], L-AAIL/$ALCl_3$ [9], amino acids [10–13], and polymers [14–17] have been used, but most types of reaction suffer from several main drawbacks such as harsh conditions, strong acidic condition, huge amounts of organic solvents, expensive catalysts, low yields, low purity, long reaction time (from 2 days to a week), and cumbersome product isolation procedures. Thus, the primary task continues to attract the attention of researchers seeking a milder and more efficient reaction procedure as well as environment-friendly catalysts for the synthesis of DHPMs to optimize the reaction conditions and shorten the reaction time.

It is well known that di-DACH-pyridylamide ligands are multidentate nitrogen-donor ligands with amine and/or pyridine-type nitrogen atoms [18]. Conformational flexibility in these multidentate nitrogen-donor ligands often plays a crucial role in their catalytic capabilities in many reactions, such as the Ullmann reaction, the Henry reaction, and allylation reaction [19–27]. It also has not been documented that the diamide ligand was used to catalyze the Biginelli reaction. Moreover, Schiff base is a compound containing a C═N bond, and there are various kinds of Schiff base, such as single Schiff base, double Schiff base, macrocyclic Schiff base, and other types of Schiff base [28–31]. Symmetrical bis-Schiff base [32–38] plays an important role in coordination chemistry because of its special structure. Spiro pyrrolizines ring system represents an important class of naturally occurring substances characterized by highly pronounced biological properties. So far, no catalytic application of these compounds in Biginelli reaction has been reported.

Da and co-workers [39] used L-proline amides as catalyst in the Biginelli reaction; however, they obtained moderate yield and long reaction time in this case. Chen [40] reported bifunctional primary amine thiourea as catalyst, but it needs a cumbersome post-treatment. Not long after, double axially bis-phosphoryl imides were first applied in organocatalytic Biginelli reaction by Zhang [41] and co-workers with the complexity steps and high cost of crude material. In view of these few successful examples, it is still desirable to develop other new organocatalysts for the Biginelli reaction.

To the best of our knowledge of the open literatures, there is no report on the use of di-DACH-pyridylamide ligands, symmetrical bridged bis-Schiff base, and spiro pyrrolizines as catalysts in the synthesis of DHPMs during the progress of our current work. Herein, we wish to disclose our study on the use of these new types of ligands as catalysts in the synthesis of DHPMs using the Biginelli reaction. Good to excellent yields and short reaction time have been achieved without further purification.

RESULTS AND DISCUSSION

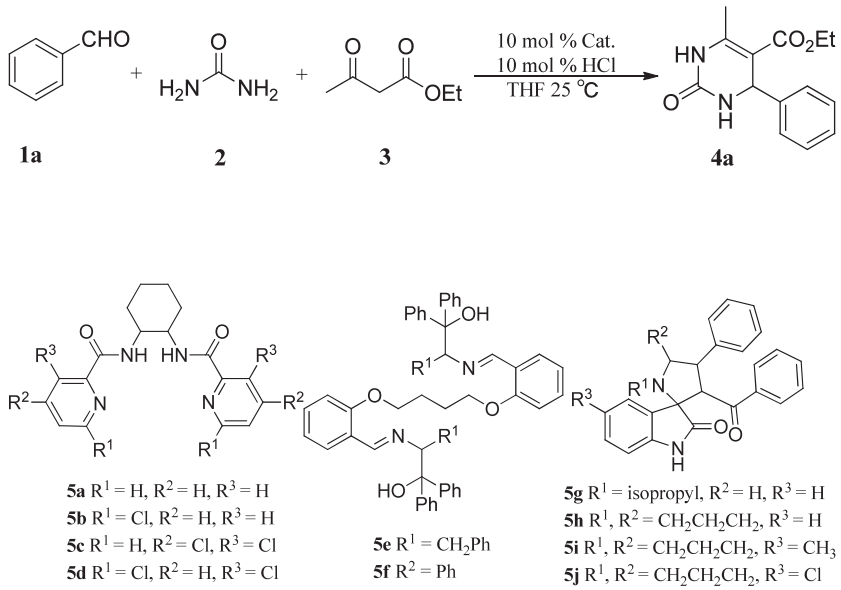
Initially, the catalytic Biginelli reaction was carried out in absence of any catalyst. It was found that no product was formed. This shows that the catalyst was necessary for this reaction (Table 1, entry 1).

Di-DACH-pyridylamide ligands, symmetrical bridged bis-Schiff base, and spiro pyrrolizines, to the best of our knowledge, had not been reported to be used in the Biginelli reaction, so we needed to investigate the eligibility of the catalysts for our purpose. The reaction mixture of benzaldehyde **1**, urea **2**, ethyl acetoacetate **3**, HCl, and each catalyst in THF was stirred at room temperature for 24 h to afford the mixture of DHPM **4a**. Screening results of catalysts are listed in Table 1. It was found that, when the reaction was carried out with spiro pyrrolizines such as **5g**, **5h**, **5i**, and **5j**, low yields (<30%) of products were observed (Table 1, entries 8–11). Symmetrical bridged bis-Schiff base **5e** and **5f** were superior to a series of spiro pyrrolizines, which promoted the Biginelli reaction with higher yields in 45% and 47% (Table 1, entries 6–7). Encouragingly, we found that di-DACH-pyridylamide ligands **5d** could effectively catalyze this reaction to provide the desired product DHPM **4a** in moderate yield of 73% in 24 h (Table 1, entry 5). Loading of **5d** of 5, 10, and 20 mol% was tested, and the results are summarized in Table 1 (entries 5, 12, and 13). It could be seen that 10 mol% loading of **5d** was optimal, while higher amounts of **5d** led to a slight decrease in yield. The yields indicated that overuse of the catalyst was needless and unfavorable for this reaction.

To optimize the reaction conditions further, the solvent effect was reinvestigated with the optimum catalyst **5d** at room temperature for 12 h, and the best result was obtained

Table 1

Screening catalysts for the Biginelli reaction.[a]



Entry	Cat.	Temp. (°C)	Time (h)	Yield[b] (%)	Entry	Cat.	Temp. (°C)	Time (h)	Yield[b] (%)
1	Nil	25	24	<5	8	**5g**	25	24	29
2	**5a**	25	24	52	9	**5h**	25	24	17
3	**5b**	25	24	46	10	**5i**	25	24	21
4	**5c**	25	24	68	11	**5j**	25	24	13
5	**5d**	25	24	73	12	**5d**[c]	25	24	51
6	**5e**	25	24	45	13	**5d**[d]	25	24	75
7	**5f**	25	24	47					

[a]The reaction was carried out on a 0.5 mmol scale, and the ratio of 1/2/3 is 1/1.5/3.
[b]Yield of isolated product.
[c]Catalyst **5d** (5 mol%) was used.
[d]Catalyst **5d** (20 mol%) was used.

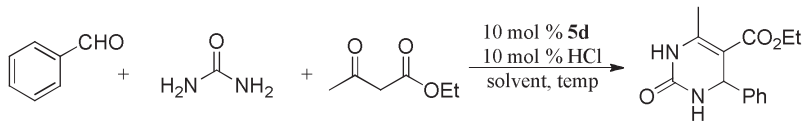
in THF (Table 2, entry 5). When toluene was used as the solvent, it is hard to separate the products without any improvement in terms of yield (Table 2, entry 6). When the reaction was performed in polar solvents, such as C_2H_5OH, DMSO, H_2O, and *i*-PrOH, the product DHPM was formed in lower yields (<15%) (Table 2, entries 1–4).

When the reaction was performed in DCM, $CHCl_3$, or 4-dioxane, low yields were obtained (Table 2, entries 7–9). Next, the effects of time and temperature on this reaction were evaluated. We attempted to relate yields to what will happen if we keep the temperature constant at room temperature. It was observed that the formation of the product increases with time duration (Table 2, entry 5 and entries 10–12). It was found that there was not much appreciable change in yield even when the reaction was carried out from 12 to 24 h (Table 2, entry 5, and Table 1, entry 7). Subsequently, the effect of temperature on the rate of reaction was studied. The temperature of the reaction was gradually increased from room temperature to 67°C (the boiling point of THF). The effect of temperature was clearly distinct on the rate of reaction enhancing it with temperature (Table 2, entry 5 and entries 13–16). It can be noticed that there was not much appreciable change in yield even when the reaction was changed from 6 to 8 h. To further decrease the reaction time, we concluded that the DHPM formation was most desirable at 67°C for 6 h (Table 2, entries 16–21).

Several Brønsted acids and Lewis acids were reported to catalyze the Biginelli reaction such as HCl, H_2SO_4, TsOH, LiBr, $InBr_3$, $FeCl_3$, and so on [42]. Next, in order to improve the efficiency, different acid cocatalysts combined with **5d** were employed to catalyze this reaction. In our investigation, Lewis acids such as $FeCl_3$, $ZnCl_2$, and $MgCl_2$ were not effective in promoting the reactivity of this reaction at all (Table 3, entries 9–11). Moderate yields of the product were obtained with HCOOH and *p*-TSA (Table 3, entries 3 and 7). We also screened organic acids. When benzoic acid, 2,4,5-trifluorophenylacetic acid, *p*-fluoroboric acid, and HOAc were used in the reaction, low yields were obtained (Table 3, entries 1, 2, and 6). Inorganic acids, such as H_3PO_4 and HCl, could

Table 2

Optimization of solvent, temperature, and time for the Biginelli reaction.[a]



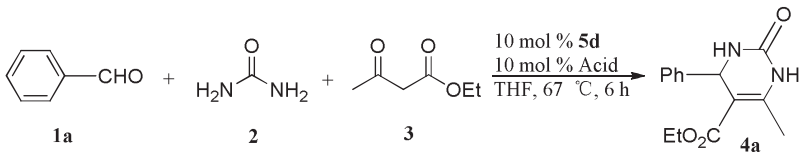
1a **2** **3** **4a**

Entry	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1	C_2H_5OH	25	12	15
2	DMSO	25	12	6
3	H_2O	25	12	10
4	*i*-PrOH	25	12	9
5	THF	25	12	69
6	Toluene	25	12	56
7	DCM	25	12	42
8	CH_3Cl	25	12	39
9	1, 4-Dioxane	25	12	30
10	THF	25	8	62
11	THF	25	6	55
12	THF	25	4	53
13	THF	40	12	73
14	THF	50	12	80
15	THF	60	12	89
16	THF	Reflux 67	12	90
17	THF	67	8	92
18	THF	67	6	91
19	THF	67	5	86
20	THF	67	4	80
21	THF	67	2	77

[a]Reagents and conditions: after stirring a solution of HCl (10 mol%), benzaldehyde (0.5 mmol), and urea (0.75 mmol), in 2 mL of solvent at specified temperature for 1 h, catalyst **5d** (10 mol%) and ethyl acetoacetate (1.5 mmol) were added sequentially.
[b]Yield of isolated product.

Table 3

Optimization of acid for the Biginelli reaction.[a]



1a 2 3 4a

Entry	Acid	Yield[b] (%)
1	TFPA[c]	Trace
2	HOAc	45
3	HCOOH	63
4	HCl	89
5	H_3PO_4	59
6	Benzoic acid	27
7	*p*-TSA	56
8	*p*-Fluoroboric acid	31
9	$FeCl_3$	Trace
10	$ZnCl_2$	Trace
11	$MgCl_2$	22

[a]After stirring a solution of specified acid (10 mol%), benzaldehyde (0.5 mmol), and urea (0.75 mmol), in 2 mL of THF at 67°C for 1 h, catalyst **5d** (10 mol%) and ethyl acetoacetate (1.5 mmol) were added sequentially.
[b]Yield of isolated product.
[c]TFPA: 2,4,5-trifluorophenylacetic acid.

promote the reaction effectively in the yield from 59 to 89% (Table 2, entries 4 and 5).

With the optimal conditions in hand, the Biginelli reactions of a variety of aldehydes with urea and ethyl acetoacetate were then investigated. As shown in Table 4, a variety of substituted benzaldehydes **4a–4j** could undergo the reactions to afford DHPMs in high yields ranging from 73 to 98%. Obviously, the electronic effect of the substituent of aromatic aldehydes had much influence on this reaction. Aldehydes with electron withdrawing substituents such as $–NO_2$, –F, –Cl, and –Br (Table 4, entries 2–7) gave similar high yields. However, aldehydes with electron donating substituents such as –Me and –OMe led to a significant decrease in yields (Table 4, entries 8 and 9). Benzaldehyde as the simplest aromatic aldehyde can obtain 92% yield (Table 4, entry 1). And high yield (95%) was obtained when sterically hindered 1-naphthyl aldehyde **4j** was employed (Table 4, entry 10).

Under the optimized condition, it also encouraged us to explore Biginelli-like reaction. In my experience, a straight substitution of bridged dialdehyde [43] **b** for aldehyde was reacted with urea and ethyl acetoacetate under reflux to successfully afford bis-DHPM **c** as white powder solid in 78% yield (Scheme 1).

In conclusion, we have reported a novel, efficient, and practical synthesis protocol of DHPMs via the Biginelli reaction of an aromatic aldehyde, urea, and ethyl acetoacetate catalyzed by DACH-pyridyl diamide ligands **5d** and HCl in THF at 67°C. Good to excellent yields (>90%) have been achieved without further purification. This new protocol has the advantages of environmental friendliness, short reaction time, excellent yields, and simple post-treatment procedure, which make it a useful and attractive protocol for scale-up synthesis of 3,4-dihydropyrimidin-2(1*H*)-one derivatives. Moreover, based on the optimized condition, a novel Biginelli-like reaction was first successfully reported.

EXPERIMENTAL

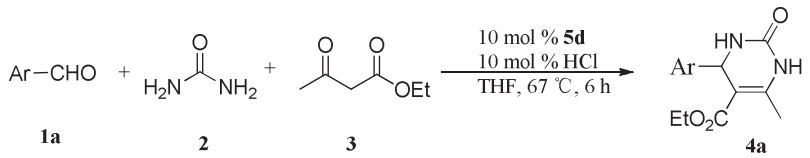
All the chemicals were analytical grade reagents and were used without further purification. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker Avance III 500 MHz spectrometer (Bruker, Switzerland) and using DMSO-d_6 (500 MHz for ^{1}H or 125 MHz for ^{13}C, respectively) as solvent. IR spectra were recorded on a Bruker TENSOR 27 spectrometer (Bruker Optics, Germany). Melting points were taken on a SGW X-4 digital display microscopic melting point apparatus (Shanghai Wuguang Company, China). Mass spectra were carried out on Varian 1200 (Thermo Fisher Scientific, America). Microanalyses were taken on a Costech ECS 4010 CHNSO elemental analyzer (Costech, Italy). The reaction mixture was monitored by silica gel plates (60F-254; Qingdao Jiyida Silica Reagent Factory, China).

General procedure for synthesis of diamide ligands 5a–5d. Following closely a literature procedure [44], we can obtain that the title compounds **5a–5d** was isolated as a white powder solid. And **5a** is a known compound.

N,N′-(Cyclohexane-1,2-diyl)dipicolinamide (5a). White powder, mp 170–173°C [44].

Table 4

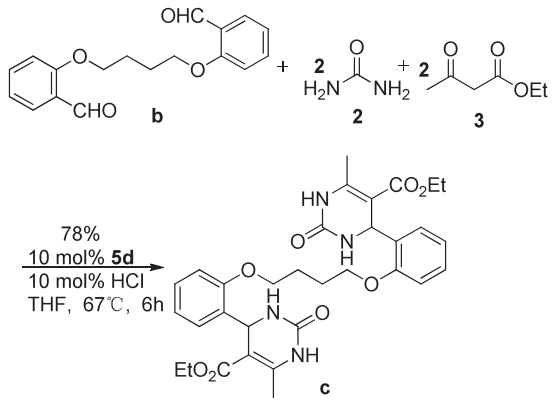
Scope of the Biginelli reaction[a] catalyzed by **5d**.



Entry	Product	Ar	Yield[b] (%)
1	**4a**	C_6H_5	92
2	**4b**	2-$NO_2C_6H_4$	96
3	**4c**	3-$NO_2C_6H_4$	95
4	**4d**	4-$NO_2C_6H_4$	98
5	**4e**	4-FC_6H_4	97
6	**4f**	4-ClC_6H_4	98
7	**4g**	4-BrC_6H_4	97
8	**4h**	4-MeC_6H_4	78
9	**4i**	4-$MeOC_6H_4$	73
10	**4j**	1-Naphthyl	95

[a]After stirring a solution of HCl (10 mol%), **1a** (0.5 mmol), and urea (0.75 mmol), in 2 mL of THF at 67°C for 1 h, catalyst **5d** (10 mol%) and ethyl acetoacetate (1.5 mmol) were added sequentially.
[b]Yield of isolated product.

Scheme 1. Biginelli-like reaction.



N,N′-(Cyclohexane-1,2-diyl)bis(6-chloropicolinamide) (5b). White powder; yield 72%; mp 201–205°C; IR (KBr, cm^{-1}): 3439, 2931, 2557, 2198, 1637, 1572, 1443, 1382, 1364, 1246, 1364, 1246, 1161, 1067, 960, 844; ^{1}H NMR (500 MHz, DMSO) δ 8.48 (s, 1H), 8.30 (dd, *J* = 4.7, 1.9 Hz, 1H), 7.88 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.36 (dd, *J* = 7.5, 4.8 Hz, 1H), 3.03 (dd, *J* = 11.7, 7.6 Hz, 1H), 2.03 (d, *J* = 12.9 Hz, 1H), 1.69 (d, *J* = 8.2 Hz, 1H), 1.36 (d, *J* = 9.3 Hz, 1H), 1.28–1.14 (m, 1H); ^{13}C NMR (126 MHz, DMSO) δ 168.42, 148.42, 146.64, 137.89, 135.73, 122.73, 52.57, 30.50, 23.52; MS *m/z* 392 (M^+). *Anal*. Calcd. for $C_{18}H_{18}Cl_2N_4O_2$: C, 54.97; H, 4.61; N, 14.25. Found: C, 54.96; H, 4.58; N, 14.23%.

N,N′-(Cyclohexane-1,2-diyl)bis(3,4-dichloropicolinamide) (5c). White powder; yield 77%; mp 197–199°C; IR (KBr, cm^{-1}): 3426, 2943, 2492, 2134, 1608, 1530, 1371, 1225, 1192, 1152, 1046, 934, 895, 843; ^{1}H NMR (500 MHz, DMSO) δ 8.72 (d, *J* = 1.9 Hz, 1H), 8.50 (d, *J* = 38.7 Hz, 1H), 8.29 (d, *J* = 1.9 Hz, 1H), 3.11 (dd, *J* = 5.7, 3.9 Hz, 1H), 2.06 (d, *J* = 13.2 Hz, 1H), 1.69 (d, *J* = 8.2 Hz, 1H), 1.39 (d, *J* = 9.2 Hz, 1H), 1.30–1.16 (m, 1H); ^{13}C NMR (126 MHz, DMSO) δ 166.05, 148.40, 145.64, 139.33, 133.91, 128.55, 52.29, 30.27, 23.42; MS *m/z* 462 (M^+). *Anal*. Calcd. for $C_{18}H_{16}Cl_4N_4O_2$: C, 46.78; H, 3.49; N, 12.12. Found: C, 46.76; H, 3.47; N, 12.13%.

N,N′-(Cyclohexane-1,2-diyl)bis(3,6-dichloropicolinamide) (5d). White powder; yield 71%; mp 209–211°C; IR (KBr, cm^{-1}): 3441, 2940, 2655, 2352, 2081, 1624, 1570, 1429, 1397, 1332, 1245, 1181, 1095, 882; ^{1}H NMR (500 MHz, DMSO) δ 8.25 (dd, *J* = 106.0, 64.7 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.41–7.37 (m, 1H), 2.05 (d, *J* = 13.3 Hz, 1H), 1.70 (d, *J* = 8.4 Hz, 1H), 1.39 (d, *J* = 9.2 Hz, 1H), 1.28–1.18 (m, 1H); ^{13}C NMR (126 MHz, DMSO) δ 167.64, 157.96, 147.35, 140.34, 124.60, 123.36, 52.13, 29.90, 23.28; MS *m/z* 462 (M^+). *Anal*. Calcd. for $C_{18}H_{16}Cl_4N_4O_2$: C, 46.78; H, 3.49; N, 12.12. Found: C, 46.76; H, 3.47; N, 12.13%.

General procedure for synthesis of symmetrical bridged bis-Schiff base 5e and **5f**. Following closely a literature procedure [45], first, we can obtain the yellow crystalline solid **b**. Then, to a solution of 4-(2-amino-3-hydroxy-3,3-diphenyl-propyl)-phenol (2 mmol) in 10 mL 95% EtOH was added substituted 2,2′-(butane-1,4-diylbis(oxy)) dibenzaldehyde (4 mmol) **b**. The resulting solution was vigorously stirred for 24 h at room temperature, and then the reaction was vacuum filtered to remove the solvent. The crude product was purified by silica gel flash column chromatography or recrystallized to give the resulting symmetrical bridged bis-Schiff base as a white solid, in high yield (>81%).

2,2′-((1E,1′E)-(((Butane-1,4-diylbis(oxy))bis(2,1-phenylene)) bis(methanylylidene))bis(azanylylidene))bis(1,1,3-triphenylpropan-1-ol) (5e). White powder; yield 81%; mp 177–181°C; IR (KBr, cm^{-1}): 3251, 2949, 1651, 1602, 1492, 1450, 1384, 1253, 1167, 752, 701; ^{1}H NMR (500 MHz, DMSO) δ 8.75 (s, 1H), 7.72 (d, *J* = 7.5 Hz, 4H), 7.65 (d, *J* = 7.5 Hz, 2H), 7.38 (d, *J* = 5.5 Hz, 2H), 7.35 (d, *J* = 2.4 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 4.3 Hz, 4H), 7.27 (d, *J* = 7.3 Hz, 2H), 7.06 (t, *J* = 7.2 Hz, 2H), 4.68 (d, *J* = 5.2 Hz, 1H),

4.09 (d, *J* = 32.2 Hz, 2H), 2.96 (d, *J* = 13.7 Hz, 1H), 2.83 (d, *J* = 6.3 Hz, 2H), 1.79 (s, 2H); MS *m/z* 869 (M^+). *Anal*. Calcd. for $C_{60}H_{56}N_2O_4$: C, 82.92; H, 6.49; N, 3.22. Found: C, 82.90; H, 6.45; N, 3.24%.

2,2′-((1E,1′E)-(((Butane-1,4-diylbis(oxy))bis(2,1-phenylene))bis(methanylylidene))bis(azanylylidene))bis(1,1,2-triphenylethanol) (5f). White powder; yield 75%; mp 217–221°C; IR (KBr, cm^{-1}): 3278, 3059, 2968, 2869, 1591, 1547, 1491, 1447, 1177, 1029, 971, 771, 740, 698, 538; ^{1}H NMR (500 MHz, DMSO) δ 8.27 (s, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.46–7.42 (m, 2H), 7.33 (dd, *J* = 10.5, 3.1 Hz, 2H), 7.21 (d, *J* = 2.3 Hz, 1H), 7.10 (dd, *J* = 14.6, 7.2 Hz, 2H), 7.02 (t, *J* = 7.3 Hz, 1H), 6.76 (s, 1H), 5.58 (d, *J* = 5.2 Hz, 1H), 4.26–4.18 (m, 1H), 4.13 (s, 1H), 4.07–3.99 (m, 1H), 1.99 (s, 1H), 0.91–0.76 (m, 1H); MS *m/z* 841 (M^+). *Anal*. Calcd. for $C_{58}H_{52}N_2O_4$: C, 82.83; H, 6.23; N, 3.33. Found: C, 82.81; H, 6.25; N, 3.35%.

General procedure for synthesis of spiro pyrrolizines 5g–5j. A mixture of isatin (1.0 mmol), L-proline (1.2 mmol), and chalcone (1.1 mmol) in methanol was refluxed for 6 h and then cooled to room temperature. The solvent was removed under reduced pressure, and the crude product obtained was purified by column chromatography using petroleum ether/ethyl acetate (4:1) as eluent.

(3′S,4′R)-3′-Benzoyl-1′-isopropyl-4′-phenylspiro[indoline-3,2′-pyrrolidin]-2-one (5g). White crystal; yield 89%; IR (KBr, cm^{-1}): 3188, 3060, 2963, 2870, 1734, 1677, 1616, 1470, 1448, 1385, 1329; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.55 (d, *J* = 7.3 Hz, 2H), 7.40–7.35 (m, 2H), 7.32 (dd, *J* = 12.4, 4.6 Hz, 3H), 7.20 (dd, *J* = 7.2, 5.9 Hz, 2H), 7.16 (t, *J* = 7.8 Hz, 2H), 7.02 (td, *J* = 7.6, 1.2 Hz, 1H), 6.98 (dd, *J* = 11.0, 4.0 Hz, 1H), 6.47 (d, *J* = 7.5 Hz, 1H), 4.64 (d, *J* = 10.6 Hz, 1H), 4.04 (t, *J* = 10.7 Hz, 1H), 3.94 (dd, *J* = 10.7, 4.4 Hz, 1H), 2.16 (s, 1H), 1.83 (qd, *J* = 11.3, 6.8 Hz, 1H), 0.99 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.36, 181.96, 140.63, 139.87, 137.23, 132.71, 129.93, 129.11, 128.66, 128.49, 128.09, 127.62, 126.81, 125.73, 123.07, 109.38, 77.29, 77.03, 76.78, 69.62, 68.64, 64.14, 51.18, 30.26, 20.52, 17.42; MS *m/z* 410 (M^+). *Anal*. Calcd. for $C_{27}H_{24}N_2O_2$: C, 79.00; H, 6.38; N, 6.82. Found: C, 78.97; H, 6.34; N, 6.78%.

(1′R,2′S)-2′-Benzoyl-1′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (5h). White crystal; yield 84%; IR (KBr, cm^{-1}):3363, 3184, 3030, 2959, 2114, 1896, 1618, 1352, 1067; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.53 (d, *J* = 7.3 Hz, 2H), 7.42–7.38 (m, 2H), 7.37–7.30 (m, 3H), 7.27 (d, *J* = 7.6 Hz, 4H), 7.23 (d, *J* = 7.3 Hz, 1H), 7.19 (dd, *J* = 13.4, 5.7 Hz, 2H), 7.13 (td, *J* = 7.7, 0.9 Hz, 1H), 7.03 (dd, *J* = 7.7, 7.1 Hz, 1H), 6.56 (d, *J* = 7.7 Hz, 1H), 4.96 (d, *J* = 11.4 Hz, 1H), 4.28 (dt, *J* = 9.8, 6.3 Hz, 1H), 3.96–3.89 (m, 1H), 2.76–2.60 (m, 2H), 2.05 (td, *J* = 12.2, 7.0 Hz, 1H), 1.99–1.87 (m, 2H), 1.77 (dt, *J* = 13.2, 7.6 Hz, 3H); MS *m/z* 408 (M^+). *Anal*. Calcd. for $C_{27}H_{24}N_2O_2$: C, 79.39; H, 5.92; N, 6.86. Found: C, 79.36; H, 5.93; N, 6.87%.

(1′R,2′S)-2′-Benzoyl-5-methyl-1′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (5i). White powder; yield 80%; IR (KBr, cm^{-1}): 3665, 3359, 3071, 3025, 2969, 2874, 1715, 1682, 1616, 1475, 1446, 1283, 998; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.54 (d, *J* = 7.3 Hz, 2H), 7.43–7.38 (m, 2H), 7.34 (dt, *J* = 13.1, 6.5 Hz, 3H), 7.20 (dt, *J* = 22.3, 7.6 Hz, 3H), 7.05 (s, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 7.9 Hz, 1H), 4.94 (d, *J* = 11.4 Hz, 1H), 4.28 (dt, *J* = 9.8, 6.3 Hz, 1H), 3.97–3.89 (m, 1H), 2.74 (dt, *J* = 14.5, 7.2 Hz, 1H), 2.69–2.62 (m, 1H), 2.36 (s, 3H), 2.06 (td, *J* = 12.2, 7.0 Hz, 1H), 1.99–1.88 (m, 2H), 1.78 (dt, *J* = 13.2, 7.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.11, 180.65, 139.83, 138.23, 137.19, 132.78, 131.70, 129.81, 128.67, 128.15, 128.08, 127.89, 126.96, 124.97, 109.72, 77.29, 77.03, 76.78, 73.59, 72.04, 64.42, 52.85, 48.29, 30.60, 27.17, 21.23; MS *m/z* 422 (M^+). *Anal*. Calcd. For $C_{28}H_{26}N_2O_2$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.55; H, 6.29; N, 6.67%.

(1′R,2′S)-2′-Benzoyl-5-chloro-1′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (5j). White powder; yield 82%; IR (KBr, cm^{-1}): 3414, 3027, 2955, 2936, 2873, 1730, 1676, 1365, 1305, 1164, 982, 861; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.52 (d, *J* = 7.3 Hz, 2H), 7.44 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.38–7.30 (m, 3H), 7.25–7.17 (m, 4H), 7.12 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.95 (d, *J* = 11.4 Hz, 1H), 4.26 (dt, *J* = 9.8, 6.3 Hz, 1H), 3.89 (dd, *J* = 11.0, 10.3 Hz, 1H), 3.49 (s, 1H), 2.73–2.62 (m, 2H), 2.10–2.01 (m, 1H), 2.01–1.89 (m, 2H), 1.80–1.72 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.65, 180.32, 139.37, 139.11, 136.99, 133.04, 129.50, 128.73, 128.24, 128.08, 127.92, 127.84, 127.77, 127.09, 126.89, 110.90, 77.27, 77.01, 76.76, 73.47, 72.00, 64.45, 52.87, 48.18, 30.54, 27.31; MS *m/z* 442 (M^+). *Anal*. Calcd. For $C_{27}H_{23}ClN_2O_2$: C, 73.21; H, 5.23; N, 6.32. Found: C, 73.25; H, 5.29; N, 6.27%.

General procedure for synthesis of DHPMs (4a–4j). After stirring a solution of HCl (10 mol%), **1a** (0.5 mmol), and urea (0.75 mmol), in 2 mL of THF at 67°C for 1 h, catalyst **5d** (10 mol %) and ethyl acetoacetate (1.5 mmol) were added sequentially. Then, the crude product was purified by recrystallization with ethanol to afford **4a–4j**.

Ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a). White solid; yield 92%; mp 199–203°C; ^{1}H NMR (500 MHz, DMSO): δ (ppm) 1.09 (t, *J* = 7.2 Hz, 3H), 2.25 (s, 3H), 3.98 (dd, *J* = 7.2 Hz, 14.4 Hz, 2H), 5.15 (d, *J* = 2.8 Hz, 1H), 7.23–7.34 (m, 5H), 7.74 (s, 1H), 9.19 (s, 1H).

Ethyl-6-methyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b). White solid; yield 96%; mp 218–221°C; ^{1}H NMR (500 MHz, DMSO): δ (ppm) 1.21 (t, *J* = 7.4 Hz, 3H), 2.26 (s, 3H), 4.20 (dd, *J* = 7.0 Hz, 14.2 Hz, 2H), 5.13 (d, *J* = 2.8 Hz, 1H), 7.47 (s, 1H), 7.52 (s, 1H), 7.70 (s, 1H), 7.96 (s, 1H), 8.31 (d, *J* = 8.8 Hz, 2H).

Ethyl-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c). White solid; yield 95%; mp 227–231°C; ^{1}H NMR (500 MHz, DMSO): δ (ppm) 1.29 (t, *J* = 7.2 Hz, 3H), 2.23 (s, 3H), 4.18 (dd, *J* = 7.2 Hz, 14.2 Hz, 2H), 5.12 (d, *J* = 2.8 Hz, 1H), 7.59 (s, 1H), 7.62 (s, 1H), 8.07 (s, 1H), 8.12 (s, 1H), 8.48 (d, *J* = 8.8 Hz, 2H).

Ethyl-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d). White solid; yield 98%; mp 205–208°C; ^{1}H NMR (500 MHz, DMSO): δ (ppm) 1.11 (t, *J* = 7.2 Hz, 3H), 2.29 (s, 3H), 4.00 (dd, *J* = 7.2 Hz, 14.4 Hz, 2H), 5.29 (d, *J* = 2.8 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.90 (s, 1H), 8.23 (d, *J* = 8.8 Hz, 2H), 9.37 (s, 1H).

Ethyl-4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e). White solid; yield 97%; mp 182–186°C; ^{1}H NMR (500 MHz, DMSO): δ (ppm) 1.09 (t, *J* = 6.8 Hz, 3H), 2.25 (s, 3H), 3.98 (dd, *J* = 6.8 Hz, 13.6 Hz, 2H), 5.15 (d, *J* = 2.8 Hz, 1H), 7.13–7.17 (m, 2H), 7.25–7.29 (m, 2H), 7.76 (s, 1H), 9.24 (s, 1H).

Ethyl-4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f). White solid; yield 98%; mp 211–215°C; ^{1}H NMR (500 MHz, DMSO): δ (ppm) 1.09 (t, *J* = 7.2 Hz, 3H), 2.25 (s, 3H), 2.26 (s, 3H), 3.98 (dd, *J* = 6.6 Hz, 13.8 Hz, 2H), 5.15 (d, *J* = 2.4 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.78 (s, 1H), 9.26 (s, 1H).

Ethyl-4-(4-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g). White solid; yield 97%; mp 206–209°C; ^{1}H NMR (500 MHz, DMSO): δ (ppm) 1.09 (t, *J* = 6.6 Hz, 3H), 2.26 (s, 3H), 3.99 (dd, *J* = 6.3 Hz, 13.2 Hz, 2H), 5.14 (d, *J* = 2.8 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.77 (s, 1H), 9.25 (s, 1H).

Ethyl-6-methyl-2-oxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h). White solid; yield 78%; mp 233–236°C; ^{1}H NMR (500 MHz, DMSO): δ (ppm) 1.10 (t, *J* = 7.0 Hz, 3H), 2.25 (s,

3H), 2.26 (s, 3H), 3.99 (dd, $J = 7.2$ Hz, 14.4 Hz, 2H), 5.11 (d, $J = 2.8$ Hz, 1H), 7.12 (d, $J = 8.4$ Hz, 2H), 7.14 (d, $J = 8.4$ Hz, 2H), 7.70 (s, 1H), 9.17 (s, 1H).

Ethyl-4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i). White solid; yield 73%; mp 201–205°C; ^{1}H NMR (500 MHz, DMSO): δ (ppm) 1.10 (t, $J = 7.0$ Hz, 3H), 2.24 (s, 3H), 3.71 (s, 3H), 3.98 (dd, $J = 6.4$ Hz, 13.2 Hz, 2H), 5.10 (d, $J = 2.8$ Hz, 1H), 6.87 (d, $J = 8.0$ Hz, 2H), 7.15 (d, $J = 8.0$ Hz, 2H), 7.68 (s, 1H), 9.17 (s, 1H).

Ethyl-6-methyl-4-(4-(naphthalen-1-yl)phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j). White solid; yield 95%; mp 232–236°C; ^{1}H NMR (500 MHz, DMSO): δ (ppm) 0.81 (t, $J = 6.9$ Hz, 3H), 2.36 (s, 3H), 3.79 (dd, $J = 7.5$ Hz, 15 Hz, 2H), 6.05 (d, $J = 2.4$ Hz, 1H), 7.39–7.59 (m, 4H), 7.46 (s, 1H), 7.84 (d, $J = 7.8$ Hz, 1H), 7.94 (d, $J = 7.5$ Hz, 1H), 8.30 (d, $J = 7.8$ Hz, 1H), 9.25 (s, 1H).

General procedure for synthesis of bis-DHPM (c). After stirring a solution of HCl (10 mol%), **b** (0.25 mmol), and urea (0.75 mmol), in 2 mL of THF at 67°C for 1 h, catalyst **5d** (10 mol%) and ethyl acetoacetate (1.5 mmol) were added sequentially. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, and the precipitated product was filtered and washed with cooled ethanol (1 mL × 2) to afford the pure product as a solid powder in good to excellent yield without further purification.

Diethyl4,4′-((butane-1,4-diylbis(oxy)) bis(2,1-phenylene))bis(6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate) (c). White powder; yield 78%; IR (KBr, cm^{-1}): 3409, 3222, 31,112, 2956, 1689, 1647, 1598, 1489, 1234, 1082, 1045, 756; ^{1}H NMR (500 MHz, DMSO) δ 9.22–9.09 (m, 1H), 7.24–7.17 (m, 2H), 7.08 (ddd, $J = 7.4$, 4.3, 1.6 Hz, 1H), 7.00 (t, $J = 9.1$ Hz, 1H), 6.87 (t, $J = 7.4$ Hz, 1H), 5.54–5.49 (m, 1H), 4.08 (ddd, $J = 13.1$, 9.2, 4.3 Hz, 2H), 3.93–3.86 (m, 2H), 2.29–2.26 (m, 3H), 1.97 (s, 2H), 1.03–0.98 (m, 3H); ^{13}C NMR (126 MHz, DMSO) δ 189.15, 165.32, 156.22, 156.09, 152.03, 148.52, 131.67, 128.60, 128.00, 127.80, 119.92, 111.97, 97.40, 91.03, 67.72, 67.53, 60.72, 58.87, 54.28, 50.29, 49.98, 45.20, 25.61, 25.48, 17.71, 13.92; MS *m/z* 606 (M^+). *Anal*. Calcd. for $C_{32}H_{38}N_4O_8$: C, 63.35; H, 6.31; N, 9.24. Found: C, 63.32; H, 6.29; N, 9.25%.

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