Synthesis of Novel 8,9-Dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-ones

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Practical and efficient methods have been developed for the synthesis of 4,6,8,9-tetrasubstituted 8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-ones from 4,6-dicholoropyrimidine aldehyde, N-substituted amino acid esters, and amines in five steps. This synthetic strategy is based on suitably substituted pyrimidines as bis-electrophilic species reacting with various amines to construct the pyrimido[4,5-*e*][1,4]diazepine core with a strategically anchored functional group for further derivatization. The utility of this methodology was demonstrated through the preparation of a 33-membered library of representative 8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-ones in good to excellent yields.

Introduction

The search for novel compound libraries with potential biological activities is a major focus for chemical biology and medicinal chemistry. Libraries based on small molecules of privileged structures are of special interest.[1] The pyrimidine moiety was widely incorporated in the design of privileged structures in medicinal chemistry.[1b] Bicyclic pyrimido[4,5-*e*][1,4]diazepines have been reported to exhibit a variety of biological activities. For example, their analogs are known as tachykinin receptor antagonists,[2] anticonvulsant agents,[3] raf kinase inhibitors,[4] and cysteine protease inhibitors.[5] Despite interesting biological activities and a few reported syntheses of pyrimido[4,5-*e*][1,4]diazepines,[6] we were only able to find one method for the synthesis of pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one derivatives which were prepared by condensation of 2-cyano-5-((4-methoxyphenylamino)methyl)-4-(neopentylamino) pyrimidine with chloroacetyl chloride.[5] An efficient synthetic method to access pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-ones with diverse structural features should be useful for the exploration of biological activities of this class of compounds.

As part of our ongoing efforts to prepare libraries of novel heterocycles,[7] we reported a series of methodologies to rapidly access various tricyclic or tetracyclic heterocyclic scaffolds with pyrimidodiazepine as the core.[8] As a continuing endeavor, we envisioned that 8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-ones **3** could be readily prepared by the reaction of key precursors **2**, prepared from simple pyrimidine **1** and derivatives of amino acids, with different amines (Scheme 1). Moreover, compounds **3** could be further modified by taking advantage of the reactive chloro functionality as shown in Scheme 1. Herein, the details of these studies are presented.

Results and Discussion

The key precursors **2** were synthesized in a three-step sequence as depicted in Scheme 2. The treatment of 4,6-dichloro-5-formylpyrimidine[9] **1** with racemic amino acid esters in $CHCl_3$ in the presence of Et_3N gave corresponding substituted 5-formylpyrimidines **5** in good yields. Reduction of the formyl group in **5** with $NaBH_3CN$ in the presence of AcOH in EtOH furnished the corresponding alcohol derivatives **6**. Intermediates **6** were treated with $SOCl_2$ to afford the desired chloromethylpyrimidine precursors **2** in high overall yields from **5**.

Initially, precursor **2a** was selected to test the reaction conditions required to generate pyrimidodiazepine **3a**. When **2a** and 1.2 equiv of *n*-$BuNH_2$ were treated with Et_3N in CH_3CN for 25 h at room temperature, cyclization product **3.1a** was successfully obtained in 87% yield (entry 1, Table 1). However, under the above conditions, treatment of precursor **2a** with aniline did not give the desired product **3.14a** (entry 2, Table 1). When the reaction temperature was increased to refluxing CH_3CN, intermediate **7a** was isolated as the sole product in 91% yield after 7.5 h (entry 3, Table 1). Changing the solvent to toluene led to the desired product **3.14a** in 40% yield (entry 4, Table 1), while the use of AcOH−toluene conditions only produced 38% yield of the desired product **3.14a** after 72 h (entry 5, Table 1). Inspired by the publication of Prasad and co-workers,[10] the conditions of Et_3N/CH_3CN under reflux for 11 h and then reflux in 10% acetic acid in toluene for 1 h were investigated, which produced the desired product in 86% yield (entry 6, Table 1). To test whether acetic acid is required or not, the conditions of Et_3N/DMF/120 °C were tested (entry 7, Table 1). Although the desired product was isolated in 49% yield, the

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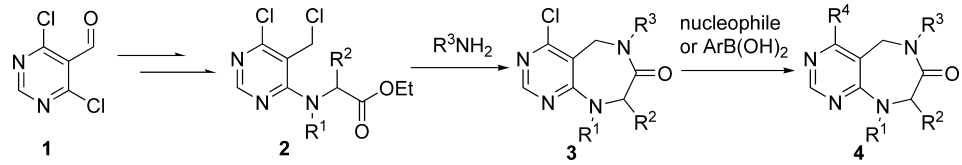
Scheme 1. Strategy for Preparation of Pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-ones



Scheme 2. Synthesis of the Key Precursors **2**

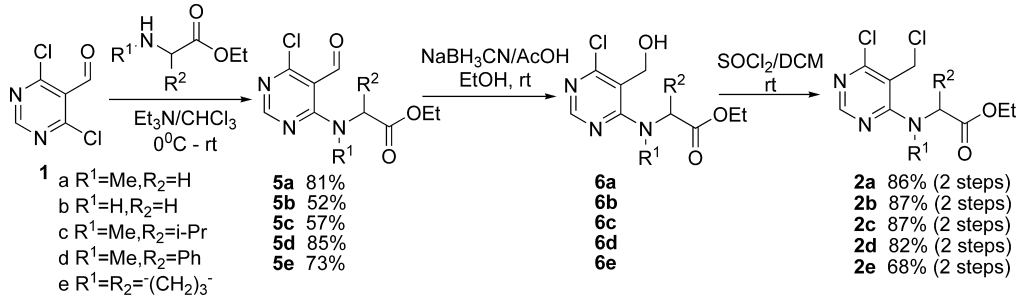
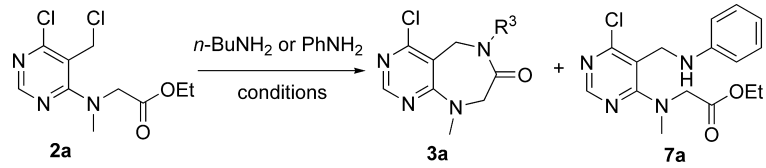


Table 1. Optimization of the Cyclization Conditions



entry	R^3NH_2	conditions	time (h)	product	yield (%)[a]	yield **7a** (%)[a]
1	*n*-$BuNH_2$	Et_3N/CH_3CN, rt	25	**3.1a**	87	
2	$PhNH_2$	Et_3N/CH_3CN, rt	24	**3.14a**	NR[b]	
3	$PhNH_2$	Et_3N/CH_3CN, reflux	7.5	**3.14a**		91
4	$PhNH_2$	Et_3N/toluene, reflux	72	**3.14a**	40	
5	$PhNH_2$	AcOH/toluene, reflux	72	**3.14a**	38	
6	$PhNH_2$	1) Et_3N/CH_3CN, reflux, 2) AcOH/toluene, reflux	11 + 1	**3.14a**	86	
7	$PhNH_2$	Et_3N/DMF, 120 °C	12	**3.14a**	49	37

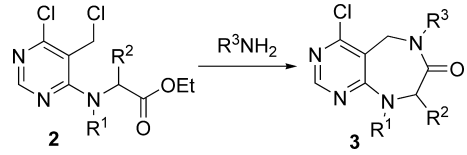
[a] Isolated yield. [b] NR denotes no reaction.

precyclized product **7a** was also isolated, suggesting that acetic acid is required for the efficient cyclization of the current reaction. Therefore, the conditions of Et_3N/CH_3CN were used in the current cyclization reactions with aliphatic amines, while Et_3N/CH_3CN and follow-up treatment with AcOH−toluene was used in the case of aromatic amines. The results are summarized in Table 2.

As disclosed in Table 2, various amines ranging from ammonia, aliphatic amines, and aromatic amines to amino acid esters and amino alcohol are compatible for the current reactions to produce the expected pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-ones **3** in good to excellent yields. The reaction rate appeared to be sensitive to both steric and electronic effects. For aliphatic amines, the reaction temperature was increased with increasing size of the aliphatic group (entries 1, 2, and 4 vs entries 5−9, Table 2). For aromatic amines, the reaction proceeded faster for aromatic amines with an electron-donating group compared to those with an electron-withdrawing group (entries 10−14 vs entries 15−17, Table 2). When an *ortho* substituent is present in the aromatic amine, the reaction was slower than the corresponding *meta* and *para* substituted analogs (entry 13 vs entries 12 and 11, Table 2). For amino acid esters, the cyclization reactions involving phenylalanine ethyl ester required higher temperature for completion compared to phenylglycine ethyl ester and glycine ethyl ester (entry 19 vs entries 18 and 17, Table 2). Similarly, reactions with larger R^1 and R^2 groups also required higher temperature for completion (entry 25 vs entry 24 vs entry 23, Table 2).

Two compounds (**3.1a** and **3.14a**) were selected as representative examples to examine the reactivity of the 4-Cl group toward various nucleophiles and coupling reagents. As depicted in Table 3, compounds **3.1a** or **3.14a** reacted readily with an amine under either basic conditions of Et_3N (for *n*-$BuNH_2$, piperazine, pyrrolidine) or acidic conditions of concentrated aqueous HCl (for aniline) to give the desired N-substituted products in good to excellent yields (entries 1−4, 8, Table 3). Other nucleophiles with heteroatoms, such as alcohols and thiols, were also tested. Compounds **3.1a** reacted with thiophenol under Et_3N/EtOH conditions to give the corresponding substituted product **4.1.5a** in 91% yield (entry 5, Table 3), while compounds **3.1a** reacted with *n*-butanol smoothly under NaH/THF conditions to give the *n*-butyloxy-substituted product **4.1.6a** in 94% yields (entry 6, Table 3). Under Suzuki-Miyaura cross-coupling conditions, compound **3.1a** reacted with phenylboronic acid to yield aryl-substituted product **4.1.7a** in 99% yields (entry 7, Table 3). These results clearly indicate that the chloro group

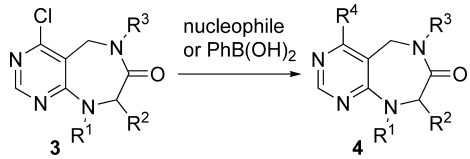
Table 2. Preparation of Pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-ones



entry	R^1	R^2	R^3	conditions	time (h)	product	yield (%)[a]
1	Me	H	*n*-Bu	Et_3N/CH_3CN, rt	25	**3.1a**	86
2	Me	H	Me	Et_3N/CH_3CN, rt	35	**3.2a**	74[b]
3	Me	H	H	Et_3N/CH_3CN, 85 °C	9	**3.3a**	70[c]
4	Me	H	Bn	Et_3N/CH_3CN, rt	45	**3.4a**	99
5	Me	H	cyclobutyl	Et_3N/CH_3CN, reflux	3.5	**3.5a**	86
6	Me	H	cyclopentyl	Et_3N/CH_3CN, reflux	17	**3.6a**	86
7	Me	H	cyclohexyl	Et_3N/CH_3CN, reflux	23	**3.7a**	70
8	Me	H	*i*-Pr	Et_3N/CH_3CN, reflux	8	**3.8a**	79
9	Me	H	1-phenylethyl	Et_3N/CH_3CN, reflux	36	**3.9a**	98
10	Me	H	*p*-MeOPh	(1) Et_3N/CH_3CN, reflux, (2) AcOH/toluene, reflux	3 + 0.5	**3.10a**	87
11	Me	H	*p*-MePh	(1) Et_3N/CH_3CN, reflux, (2) AcOH/toluene, reflux	3.5 + 0.7	**3.11a**	86
12	Me	H	*m*-MePh	(1) Et_3N/CH_3CN, reflux, (2) AcOH/toluene, reflux	4.5 + 1	**3.12a**	78
13	Me	H	*o*-MePh	(1) Et_3N/CH_3CN, reflux, (2) AcOH/toluene, reflux	6 + 4	**3.13a**	81
14	Me	H	Ph	(1) Et_3N/CH_3CN, reflux, (2) AcOH/toluene, reflux	11 + 1	**3.14a**	83
15	Me	H	*p*-ClPh	(1) Et_3N/CH_3CN, reflux, (2) AcOH/toluene, reflux	24 + 4.5	**3.15a**	84
16	Me	H	*p*-CH_3COPh	(1) Et_3N/CH_3CN, reflux, (2) AcOH/toluene, reflux	20 + 4	**3.16a**	88
17	Me	H	*p*-NO_2Ph	(1) Et_3N/CH_3CN, reflux, (2) AcOH/toluene, reflux	42 + 4.5	**3.17a**	60
18	Me	H	$CH_2CO_2C_2H_5$	Et_3N/CH_3CN, reflux	7	**3.18a**	90
19	Me	H	$CH(Ph)CO_2C_2H_5$	Et_3N/CH_3CN, reflux	28	**3.19a**	73
20	Me	H	$CH(Bn)CO_2C_2H_5$	(1) Et_3N/CH_3CN, reflux, (2) AcOH/toluene, reflux	11 + 2	**3.20a**	57
21	Me	H	CH_2CH_2OH	Et_3N/CH_3CN, rt	12	**3.21a**	84
22	H	H	*n*-Bu	(1) K_2CO_3/CH_3CN, reflux, (2) AcOH/toluene, reflux	1.5 + 6	**3.1b**	67
23	Me	*i*-Pr	*n*-Bu	(1) Et_3N/CH_3CN, reflux, (2) AcOH/toluene, reflux	4 + 3	**3.1c**	73
24	Me	Ph	*n*-Bu	Et_3N/CH_3CN, reflux	20	**3.1d**	50
25	$-(CH_2)_3-$		*n*-Bu	Et_3N/CH_3CN, rt	17	**3.1e**	86

[a] Isolated yield. [b] Methylamine alcohol solution (27−32%) was utilized. [c] Ammonia saturated methanol was utilized, and the reaction was conducted in a sealed tube.

Table 3. Results of 4-Cl Replacements in Compounds **3**



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entry	R^1	R^2	R^3	R^4	conditions	time (h)	product	yield (%)[a]
1	Me	H	*n*-Bu	*n*-BuNH	Et_3N/*n*-BuOH, reflux	72	**4.1.1a**	78
2	Me	H	*n*-Bu	piperazin-1-yl	Et_3N/*n*-BuOH, reflux	24	**4.1.2a**	91
3	Me	H	*n*-Bu	pyrrolidin-1-yl	Et_3N/*n*-BuOH, reflux	25	**4.1.3a**	99
4	Me	H	*n*-Bu	PhNH	conc. HCl/*n*-BuOH, reflux	12	**4.1.4a**	83
5	Me	H	*n*-Bu	PhS	Et_3N/EtOH, reflux	5	**4.1.5a**	91
6	Me	H	*n*-Bu	*n*-BuO	NaH/THF, rt	72	**4.1.6a**	94
7	Me	H	*n*-Bu	Ph[b]	$Pd(OAc)_2$, K_2CO_3, Ph_3P/DME-H_2O, reflux	2	**4.1.7a**	99
8	Me	H	Ph	PhNH	conc. HCl/*n*-BuOH, reflux	18	**4.14.4a**	64

[a] Isolated yield. [b] $PhB(OH)_2$ was used.

in compounds **3** is highly reactive toward further modifications to increase the molecular diversity.

Conclusion

In summary, a representative library of pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-ones was readily prepared by the reaction of suitably substituted pyrimidines **2** with different amines. The synthetic strategy combines three structural motifs, namely a pyrimidine, an amino acid ester, and an amine, to form a pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one scaffold. The resulting heterocycles possess a reactive chloro group on the pyrimidine moiety which allows further introduction of a new element via nucleophilic substitution or transition-metal-catalyzed cross coupling reactions. These novel heterocycles based on privileged structures could be of interest in studies of chemical biology and drug discovery.

Experimental Section

General Consideration. Acetonitrile (CH_3CN) was dried with CaH_2 and distilled. Dichloromethane (CH_2Cl_2) was dried with P_2O_5 and distilled. Ethanol (EtOH) was dried with Na and distilled. All other commercial reagents were used as received without additional purification. The melting point was uncorrected. Mass spectra and HPLC data were recorded on a LC/MS system with an evaporative light scattering detector (ELSD). The ^1H and ^{13}C NMR data were obtained

on a 300 MHz NMR spectrometer with tetramethylsilane (TMS) as the internal standard and $CDCl_3$ as solvent unless otherwise stated. Multiplicities are indicated as the following: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doubled doublet; br, broad. Coupling constants (*J* values) where noted are quoted in hertz.

General Procedure for the Synthesis of Amino Acid Ester Substituted 6-Chloro-5-formylpyrimidine 5. Et_3N (7 mmol) in CH_2Cl_2 (3 mL) was added dropwise to a stirred solution of 4,6-dichloro-5-formylpyrimidine **1** (2.8 mmol) and amino acid ester hydrochloride (3.08 mmol) in $CHCl_3$ (3 mL) at 0 °C. After an additional 10 min, the reaction mixture was allowed to warm to room temperature. After complete consumption of the starting material **1**, as indicated by thin-layer chromatography (TLC), the solvent was removed in vacuo and water (50 mL) was added, it was then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water (30 mL) and brine (50 mL), dried over Na_2SO_4, concentrated in vacuo, and purified by flash chromatography (petroleum ether/EtOAc, 4:1, v/v) to afford the desired product **5**.

Ethyl 2-((6-Chloro-5-formylpyrimidin-4-yl)(methyl) amino)acetate 5a. 81%. mp: 75−77 °C. ^{1}H NMR δ 10.43 (s, 1H), 8.35 (s, 1H), 4.33 (s, 2H), 4.25 (q, 2H, J = 7.2), 3.01 (s, 3H), 1.29 (t, 3H, J = 7.5). MS (ESI): *m*/*z* 258.0 [M + H$^+$].

Ethyl 2-(6-Chloro-5-formylpyrimidin-4-ylamino)acetate 5b. 52%. mp: 120−122 °C. ^{1}H NMR δ 10.41 (s, 1H), 9.50 (br, 1H), 8.44 (s, 1H), 4.34 (d, 2H, J = 5.4), 4.26 (q, 2H, J = 7.2), 1.31 (t, 3H, J = 7.2). MS (ESI): *m*/*z* 244.2 [M + H$^+$].

Ethyl 2-((6-Chloro-5-formylpyrimidin-4-yl)(methyl) amino)-3-methylbutanoate 5c. 57%. oil ^{1}H NMR δ 10.40 (s, 1H), 8.37 (s, 1H), 4.99 (d, 1H, J = 10.2), 4.21 (q, 2H, J = 7.2), 2.91 (s, 3H), 2.41−2.33 (m, 1H), 1.28 (t, 3H, J = 7.5), 1.09 (d, 3H, J = 6.3), 0.99 (d, 3H, J = 6.6). MS (ESI): *m*/*z* 300.1 [M + H$^+$].

Ethyl 2-((6-Chloro-5-formylpyrimidin-4-yl) (methyl)amino)-2-phenylacetate 5d. 85%. oil. ^{1}H NMR δ 10.42 (s, 1H), 8.43 (s, 1H), 7.44−7.37 (m, 3H), 7.29−7.26 (m, 2H), 6.38 (s, 1H), 4.39−4.28 (m, 2H), 2.67 (s, 3H), 1.32 (t, 3H, J = 7.5). MS (ESI): *m*/*z* 334.0 [M + H$^+$].

Ethyl 1-(6-Chloro-5-formylpyrimidin-4-yl)pyrrolidine-2-carboxylate 5e. 73%. oil. ^{1}H NMR δ 10.43 (s, 1H), 8.34 (s, 1H), 4.75 (t, 1H, J = 4.2), 4.19 (q, 2H, J = 6.9), 3.33 (m, 1H), 3.16 (m,1H), 2.34 (m, 1H), 2.15−2.00 (m, 3H), 1.26 (t, 3H, J = 7.2). MS (ESI): *m*/*z* 284.0 [M + H$^+$].

General Procedure for the Synthesis of Amino Acid Ester Substituted 6-Chloro-5-chloromethylpyrimidine 2. To a stirred solution of compound **5** (1.2 mmol) in EtOH (4 mL) was added $NaBH_3CN$ (3.1 mmol) followed by AcOH (12.5 mmol). After complete consumption of the starting material **5**, as indicated by TLC, water (0.2 mL) was added to quench the reaction. The volatiles were removed in vacuo, and water (10 mL) was added; it was then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL) and water (5 mL), dried ($MgSO_4$), and concentrated in vacuo to afford product **6**. Compound **6** was used at the next step without further purification. The crude **6** was dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C before $SOCl_2$ (4.8 mmol) was added. The mixture was allowed to warm to room temperature. After complete consumption of compound **6**, as indicated by TLC, cold water (5 mL) was added. The water layer was treated with saturated aqueous $NaHCO_3$ (1 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by flash chromatography (petroleum ether/EtOAc, 4:1, v/v) to afford the desired product **2**.

Ethyl 2-((6-Chloro-5-(chloromethyl)pyrimidin-4-yl) (methyl)amino)acetate 2a. 86%. mp: 78−80 °C. ^{1}H NMR δ 8.31 (s, 1H), 4.72 (s, 2H), 4.28−4.21 (m, 4H), 3.42 (s, 3H), 1.30 (t, 3H, J = 7.5). ^{13}C NMR δ 169.5, 164.0, 163.2, 155.9, 61.2, 54.2, 40.7, 40.3, 14.1. MS (ESI): *m*/*z* 278.0 [M + H$^+$].

Ethyl 2-(6-Chloro-5-(chloromethyl)pyrimidin-4-ylamino)acetate 2b. 89%. mp: 86−88 °C. ^{1}H NMR δ 8.37 (s, 1H), 5.86 (s, 1H), 4.73 (s, 2H), 4.31−4.24 (m, 4H), 1.30 (t, 3H, J = 7.2). MS (ESI): *m*/*z* 263.9 [M + H$^+$].

Ethyl 2-((6-Chloro-5-(chloromethyl)pyrimidin-4-yl) (methyl)amino)-3-methylbutanoate 2c. 92%. oil. ^{1}H NMR δ 8.35 (s, 1H), 4.77 (s, 2H), 4.58 (d, 1H, J = 11.1), 4.24 (q, 2H, J = 7.5), 3.30, (s, 3H), 2.42−2.33 (m, 1H), 1.29 (t, 3H, J = 7.2), 1.06 (d, 3H, J = 6.6). 0.92 (d, 3H, J = 7.2). MS (ESI): *m*/*z* 320.0 [M + H$^+$].

Ethyl 2-((6-Chloro-5-(chloromethyl)pyrimidin-4-yl) (methyl)amino)-2-phenylacetate 2d. 90%. oil. ^{1}H NMR δ 8.39 (s, 1H), 7.41−7.39 (m, 3H), 7.34−7.26 (m, 2H), 6.04 (s, 1H), 4.69 (q, 2H, J = 12.4), 4.29−4.23 (m, 2H), 3.08 (s, 3H), 1.27 (t, 3H, J = 7.2). MS (ESI): *m*/*z* 354.0 [M + H$^+$].

Ethyl 1-(6-Chloro-5-(chloromethyl)pyrimidin-4-yl)pyrrolidine-2-carboxylate 2e. 71%. oil. ^{1}H NMR δ 8.24 (s, 1H), 4.85 (d, 2H, J = 4.6), 4.72 (dd, 1H, J = 7.7, 5.7), 4.29−3.99 (m, 4H), 2.41−2.14 (m, 2H), 2.14−1.93 (m, 2H), 1.26 (t, 3H, J = 7.1). MS (ESI): *m*/*z* 304.0 [M + H$^+$].

Synthesis of 8,9-Dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-ones 3 (for Aliphatic Amines). To a stirred solution of compound **2** (1 mmol) in CH_3CN (4 mL) was added amine (1.2 mmol) followed by Et_3N (1.5 mmol). The resulting solution was stirred for the corresponding time at room temperature or reflux. After complete consumption of the starting material **2**, as indicated by TLC, the volatiles were removed in vacuo before water (5 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL) followed by drying (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (petroleum ether/DCM 2:1−1:2 or DCM/MeOH 40:1−10:1, v/v) afforded the desired products **3**.

Aternative Procedure (For Aromatic Amines). To a stirred solution of compound **2** (1 mmol) in CH_3CN (4 mL) was added amine (1.2 mmol) followed by Et_3N or K_2CO_3 (1.5 mmol). The resulting solution was stirred for the corresponding time at reflux. The volatiles were removed in vacuo to dryness. The crude residue was dissolved in toluene (4 mL) and AcOH (0.4 mL). The mixture was stirred for the corresponding time at reflux. The volatiles were removed

in vacuo before water (10 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (petroleum ether/DCM 2:1−1:2, v/v) afforded the desired products **3**.

6-Butyl-4-chloro-9-methyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.1a. 86%. mp: 81−83 °C. ^{1}H NMR δ 8.27 (s, 1H), 4.73 (s, 2H), 4.34 (s, 2H), 3.49 (t, 2H, J = 7.2), 3.33 (s, 3H), 1.55−1.48 (m, 2H), 1.32−1.24 (m, 2H), 0.90 (t, 3H, J = 7.2). MS (ESI): m/z 269.2 [M + H$^+$].

4-Chloro-6,9-dimethyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.2a. 74%. mp: 116−118 °C. ^{1}H NMR δ 8.27 (s, 1H), 4.74 (s, 2H), 4.35 (s, 2H), 3.33 (s, 3H), 3.10 (s, 3H). MS (ESI): m/z 227.1 [M + H$^+$].

4-Chloro-9-methyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.3a. 70%. mp: 220−222 °C. ^{1}H NMR δ 8.29 (s, 1H), 6.47 (br, 1H), 4.63 (d, 2H, J = 6.0), 4.27 (s, 2H), 3.34 (s, 3H). MS (ESI): m/z 213.0 [M + H$^+$].

6-Benzyl-4-chloro-9-methyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.4a. 99%. mp: 155−156 °C. ^{1}H NMR δ 8.22 (s, 1H), 7.31−7.23 (m, 5H), 4.65 (s, 2H), 4.62 (s, 2H), 4.39 (s, 2H), 3.35 (s, 3H). MS (ESI): m/z 303.1 [M + H$^+$].

4-Chloro-6-cyclobutyl-9-methyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.5a. 86%. mp: 161−163 °C. ^{1}H NMR δ 8.26 (s, 1H), 4.98−4.89 (m, 1H), 4.79 (s, 2H), 4.33 (s, 2H), 3.32 (s, 3H), 2.23−2.03 (m, 4H), 1.78−1.59 (m, 2H). ^{13}C NMR δ 167.1, 161.8, 157.1, 156.5, 156.4, 110.4, 90.4, 56.1, 48.3, 41.5, 40.3, 28.7, 28.5, 28.4, 14.8. MS (ESI): m/z 267.0 [M + H$^+$].

4-Chloro-6-cyclopentyl-9-methyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.6a. 86%. mp: 143−144 °C. ^{1}H NMR δ 8.26 (s, 1H), 4.93 (m, 1H), 4.67 (s, 2H), 4.33 (s, 2H), 3.33 (s, 3H), 1.91−1.89 (m, 2H), 1.83−1.77 (m, 2H), 1.63−1.59 (m, 2H), 1.49−1.40 (m, 2H). ^{13}C NMR δ 167.8, 161.9, 157.1, 156.5, 110.7, 55.9, 54.4, 41.6, 40.3, 29.6, 24.4. MS (ESI): m/z 281.1 [M + H$^+$].

4-Chloro-6-cyclohexyl-9-methyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.7a. 70%. mp: 193−195 °C. ^{1}H NMR δ 8.25 (s, 1H), 4.68 (s, 2H), 4.39−4.38 (m, 1H), 4.35 (s, 2H), 3.33 (s, 3H), 1.80−1.79 (m, 2H), 1.65−1.62 (m, 4H), 1.46−1.35 (m, 4H). ^{13}C NMR δ 167.1, 161.8, 156.9, 156.4, 110.8, 55.9, 53.0, 41.0, 40.2, 30.6, 25.4, 25.2. MS (ESI): m/z 295.2 [M + H$^+$].

4-Chloro-6-isopropyl-9-methyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.8a. 79%. mp: 131−134 °C. ^{1}H NMR δ 8.25 (s, 1H), 4.84−4.77 (m, 1H), 4.66 (s, 2H), 4.33 (s, 2H), 3.33 (s, 3H), 1.17 (s, 3H), 1.44 (s, 3H). MS (ESI): m/z 255.0 [M + H$^+$].

4-Chloro-9-methyl-6-(1-phenylethyl)-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.9a. 98%. mp: 135−136 °C. ^{1}H NMR δ 8.21 (s, 1H), 7.33−7.26 (m, 5H), 5.6 (q, 1H, J = 6.9), 4.52(d, 1H, J = 15.0), 4.54−4.45 (m, 2H), 4.22 (d, 1H, J = 15.0), 3.37 (s, 3H), 1.52 (d, 3H, J = 7.2). ^{13}C NMR δ 167.7, 162.0, 157.4, 156.4, 139.5, 128.7, 128.1, 127.4, 110.8, 55.8, 51.3, 41.7, 40.4, 16.5. MS (ESI): m/z 316.8 [M + H$^+$].

4-Chloro-6-(4-methoxyphenyl)-9-methyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.10a. 87%. mp: 192−193 °C. ^{1}H NMR δ 8.32 (s, 1H), 7.14 (d, 2H, J = 8.7), 6.90 (d, 2H, J = 9.0), 5.13 (s, 2H), 4.51 (s, 2H), 3.81 (s, 3H), 3.39 (s, 3H). ^{13}C NMR δ 166.9, 161.9, 158.5, 157.6, 156.8, 134.6, 126.9, 114.6, 110.3, 56.2, 55.6, 50.5, 40.5. MS (ESI): m/z 319.1 [M + H$^+$].

4-Chloro-9-methyl-6-*p*-tolyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.11a. 86%. mp: 232−234 °C. ^{1}H NMR δ 8.32 (s, 1H), 7.19 (d, 2H, J = 7.8), 7.11 (d, 2H, J = 8.4), 5.14 (s, 2H), 4.5 (s, 2H), 3.39 (s, 3H), 2.35 (m, 3H). MS (ESI): m/z 303.1 [M + H$^+$].

4-Chloro-9-methyl-6-*m*-tolyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.12a. 78%. mp: 229−230 °C. ^{1}H NMR δ 8.33 (s, 1H), 7.30−7.25(m, 1H), 7.11−7.02 (m, 3H), 5.15 (s, 2H), 4.51 (s, 2H), 3.39(s, 3H), 2.35 (s, 3H). MS (ESI): m/z 303.1 [M + H$^+$].

4-Chloro-9-methyl-6-*o*-tolyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.13a. 81%. mp: 200−201 °C. ^{1}H NMR δ 8.33 (s, 1H), 7.26−7.22 (m, 3H), 7.07−7.04 (m, 1H), 5.04 (s, 2H), 4.54 (d, 1H, J = 14.4), 4.47 (d, 1H, J = 15), 3.42 (s, 3H), 2.13 (s, 3H). MS (ESI): m/z 303.1 [M + H$^+$].

4-Chloro-9-methyl-6-phenyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.14a. 83%. mp: 263−265 °C. ^{1}H NMR δ 8.33 (s, 1H), 7.42−7.38 (m, 2H), 7.31−7.24 (m, 3H), 5.12 (s,2H), 4.52 (s, 2H), 3.40 (s, 3H). MS (ESI): m/z 289.0 [M + H$^+$].

4-Chloro-6-(4-chlorophenyl)-9-methyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.15a. 84%. mp: 221−222 °C. ^{1}H NMR δ 8.33 (s, 1H), 7.36 (d, 2H, J = 9.0), 7.2 (d, 2H, J = 8.4), 5.16 (s, 2H), 4.51 (s, 2H), 3.39 (s, 3H). MS (ESI): m/z 323.0 [M + H$^+$].

6-(4-Acetylphenyl)-4-chloro-9-methyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.16a. 88%. mp: 196−197 °C. ^{1}H NMR δ 8.34 (s, 1H), 7.99 (d, 2H, J = 9.0), 7.40 (d, 2H, J = 9.0), 5.23 (s, 2H), 4.53 (s, 2H), 3.40 (s, 3H), 2.59 (s, 3H). MS (ESI): m/z 331.0 [M + H$^+$].

4-Chloro-9-methyl-6-(4-nitrophenyl)-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.17a. 60%. mp: 232−233 °C. ^{1}H NMR δ 8.35 (s, 1H), 8.26 (d, 2H, J = 9.6), 7.5 (d, 2H, J = 9.0), 5.27 (s, 2H), 4.55 (s, 2H), 3.40 (s, 3H). ^{13}C NMR δ 166.6, 161.9, 157.7, 157.2, 147.0, 145.6, 125.7, 124.8, 109.5, 56.2, 49.8, 40.6. MS (ESI): m/z 334.0 [M + H$^+$].

4-Chloro-6-(2-ethoxy-2-oxoethyl)-9-methyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.18a. 90%. mp: 120−121 °C. ^{1}H NMR δ 8.29 (s, 1H), 4.81 (s, 2H), 4.38 (s, 2H), 4.25 (s, 2H), 4.16 (q, 2H, J = 6.9), 3.34 (s, 3H), 1.23 (t, 3H, J = 7.2). MS (ESI): m/z 299.1 [M + H$^+$].

4-Chloro-6-(2-ethoxy-2-oxo-1-phenylethyl)-9-methyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.19a. 73%. mp: 98−100 °C. ^{1}H NMR δ 8.18 (s, 1H), 7.34−7.33(m, 3H), 7.20−7.19 (m, 2H), 6.38 (s, 1H), 4.80 (d, 1H, J = 18.0), 4.63−4.53 (m, 2H), 4.27 (q, 2H, J = 6.9), 4.15 (d, 1H, J = 15.0), 3.35 (s, 3H), 1.25 (t, 3H, J = 6.9). ^{13}C NMR δ 170.0, 168.8, 161.9, 157.8, 156.1, 133.7, 129.2, 129.1, 128.8, 110.5, 61.9, 60.4, 55.2, 43.6, 40.2, 14.1. MS (ESI): m/z 375.1 [M + H$^+$].

4-Chloro-6-(1-ethoxy-1-oxo-3-phenylpropan-2-yl)-9-methyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6H)-one 3.20a. 57%. mp: 108−109 °C. ^{1}H NMR δ 8.13 (s, 1H), 7.10−7.08 (m, 3H), 6.96−6.94 (m, 2H), 5.50 (dd, 1H, J = 12.6, 5.1), 4.76−4.49 (m, 2H), 4.47 (d, 1H, J = 14.7), 4.22 (q, 2H, J = 7.2), 3.85 (d, 1H, J = 14.7), 3.48 (dd, 1H, J = 15.3, 5.1), 3.07 (s, 3H), 3.01−2.95 (m, 1H). 1.27 (t, 3H, J = 7.2).^{13}C NMR δ 170.8, 168.9, 162.0, 157.8, 156.4, 136.2, 128.6, 128.4, 127.2, 110.4, 62.2, 58.1, 55.1, 45.2, 40.2, 35.8, 14.5. MS (ESI): m/z 389.1 [M + H$^+$].

4-Chloro-6-(2-hydroxyethyl)-9-methyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.21a. 84%. mp: 136−138 °C. ^{1}H NMR δ 8.27 (s, 1H), 4.85 (s, 2H), 4.38 (s, 2H), 3.81 (t, 2H, J = 5.1), 3.68 (t, 2H, J = 5.4), 3.36 (s, 3H). ^{13}C NMR δ 168.4, 161.9, 157.5, 156.5, 110.2, 60.9, 55.8, 50.2, 48.0, 40.4. MS (ESI): m/z 256.8 [M + H$^+$].

6-Butyl-4-chloro-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.1b. 67%. mp: 195−197 °C ^{1}H NMR δ 8.20 (s, 1H), 5.95 (br, 1H), 4.72 (s, 2H), 4.25 (d, 2H, J = 5.1), 3.52 (t, 2H, J = 7.2), 1.60−1.52(m, 2H), 1.35−1.23 (m, 2H), 0.90 (t, 3H, J = 7.2). MS (ESI): m/z 255.1 [M + H$^+$].

6-Butyl-4-chloro-8-isopropyl-9-methyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.1c. 73%. oil. ^{1}H NMR δ 8.33 (s, 1H), 4.72 (d, 1H, J = 17.7), 4.60 (d, 1H, J = 17.4), 3.85 (d, 1H, J = 5.1), 3.59−3.49 (m, 1H), 3.42−3.20 (m, 4H), 2.39−2.31 (m, 1H), 1.53−1.37 (m, 2H), 1.32−1.20 (m, 2H), 1.05−0.81 (m, 9H). MS (ESI): m/z 310.8 [M + H$^+$].

6-Butyl-4-chloro-9-methyl-8-phenyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 3.1d. 50%. mp: 90−92 °C. ^{1}H NMR δ 8.39 (s, 1H), 7.46−7.34 (m, 3H), 7.27−7.23 (m, 2H), 5.52 (s, 1H), 4.20 (d, 1H, J = 16.2), 4.08 (d, 1H, J = 16.8), 3.52−3.41 (m, 5H).1.55−1.45 (m,2H),1.28−1.21 (m,2H), 0.89 (t, 3H, J = 7.2). MS (ESI): m/z 345.1 [M + H$^+$].

6-Butyl-4-chloro-7a,8,9,10-tetrahydro-5*H*-pyrimido[5,4-f]pyrrolo[1,2-*a*][1,4]diazepin-7(6*H*)-one 3.1e. 86%. oil. ^{1}H NMR δ 8.24 (s, 1H), 5.07−4.97 (m, 2H), 4.51 (d, 1H, J = 17.4), 3.76−3.65 (m, 2H), 3.64−3.43 (m, 2H), 2.75−2.64 (m, 1H), 2.13−1.87 (m, 3H), 1.58−1.49 (m, 2H), 1.35−0.93 (m, 2H), 0.90 (t, 3H, J = 7.5). MS (ESI): m/z 295.2 [M + H$^+$].

Ethyl 2-((6-Chloro-5-((phenylamino)methyl)pyrimidin-4-yl)(methyl)amino)acetate 7a. 91%. mp: 107−109 °C. ^{1}H NMR δ 8.34 (s, 1H), 7.28−7.23 (m, 2H), 6.84 (t, 1H, J = 7.2), 6.73 (d, 2H, J = 7.8), 4.31 (s, 2H), 4.22−4.15 (m, 4H), 3.33 (s, 3H), 1.23 (t, 3H, J = 7.2). MS (ESI): m/z 335.0 [M + H$^+$].

General Procedure for Displacement of the Chloro Group in 3.1a with *n*-BuNH$_2$, Piperazine, and Pyrrolidine, Preparation of Compounds 4.1.1a, 4.1.2a, and 4.1.3a. To a solution of compound **3.1a** (0.5 mmol) in *n*-BuOH (4.0 mL) was added amine (1.5 mmol) followed by Et$_3$N (2 mmol). The resulting solution was stirred for the corresponding time at reflux. The volatiles were removed in vacuo, before water (10 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (petroleum ether/DCM 2:1−1:2, v/v) afforded the desired products.

6-Butyl-4-(butylamino)-9-methyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 4.1.1a. 78%. mp: 46−47 °C. ^{1}H NMR δ 8.17 (s, 1H), 4.26 (s, 2H), 4.13 (s, 2H), 4.06 (t, 1H, J = 5.1), 3.49−3.42 (m, 4H), 3.25 (s, 3H), 1.65−1.56 (m, 2H), 1.51−1.40 (m, 4H), 1.38−1.22 (m, 2H), 0.96 (t, 3H, J = 7.2), 0.88 (t, 3H, J = 7.2). ^{13}C NMR δ 168.9, 160.7, 159.4, 156.0, 92.4, 55.3, 47.5, 44.7, 41.7, 39.0, 32.1, 30.3, 20.2, 20.0, 13.9, 13.8. MS (ESI): m/z 306.0 [M + H$^+$].

6-Butyl-9-methyl-4-(piperazin-1-yl)-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 4.1.2a. 91%. mp: 67−68 °C. ^{1}H NMR δ 8.28 (s, 1H), 4.44 (s, 2H), 4.21 (s, 2H), 3.42 (t, 2H, J = 7.2), 3.30 (s, 3H), 3.17−3.14 (m, 4H), 3.04−3.01 (m, 4H), 2.46 (br, 1H), 1.44−1.39 (m, 2H), 1.23−1.16 (m, 2H), 0.84 (t, 3H, J = 7.2). ^{13}C NMR δ 168.5, 165.9, 162.0, 155.9, 100.1, 55.0, 51.1, 47.0, 46.7, 45.9, 45.7, 39.2, 30.3, 19.8, 13.8. MS (ESI): m/z 319.4 [M + H$^+$].

6-Butyl-9-methyl-4-(pyrrolidin-1-yl)-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 4.1.3a. 99%. mp: 76−77 °C. ^{1}H NMR δ 8.16 (s, 1H), 4.34 (s, 2H), 4.12 (s, 2H), 3.45−3.36 (m, 6H), 3.28 (s, 3H), 1.93 (s, 4H), 1.42−1.35 (m, 2H), 1.27−1.72 (m, 2H), 0.85 (t, 3H, J = 7.2). ^{13}C NMR δ 168.9, 163.5, 161.6, 154.7, 94.7, 54.7, 50.6, 48.3, 47.1, 38.5, 30.3, 25.6, 19.8, 13.7. MS (ESI): m/z 304.0 [M + H$^+$].

General Procedure for Displacement of the Chloro Group in 3.1a or 3.14a with Aniline, Preparation of Compounds 4.1.4a and 4.14.4a. To a solution of compound **3.1a** or **3.14a** (0.5 mmol) in *n*-BuOH (4.0 mL) was added aniline (5 mmol) followed by concentrated aqueous HCl (3 to 4 drops). The resulting solution was stirred for the corresponding time at reflux. The volatiles were removed in vacuo before water (10 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (petroleum ether/DCM 2:1−1:2, v/v) afforded the desired products.

6-Butyl-9-methyl-4-(phenylamino)-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 4.1.4a. 83%. mp: 131−133 °C. ^{1}H NMR δ 8.25 (s, 1H), 7.36−7.30 (m, 2H), 7.16−7.06 (m, 3H), 6.34 (br, 1H), 4.24 (s, 2H), 4.19 (m, 2H), 3.75 (t, 2H, J = 7.2), 3.32 (s, 3H), 1.44−1.34 (m, 2H), 1.25−1.13 (m, 2H), 0.83 (t, 3H, J = 7.2). ^{13}C NMR δ 168.3, 161.6, 157.6, 156.2, 140.7, 129.1, 123.3, 120.5, 96.5, 54.9, 47.0, 46.0, 39.1, 30.1, 19.7, 13.6. MS (ESI): m/z 326.0 [M + H$^+$].

9-Methyl-6-phenyl-4-(phenylamino)-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 4.14.4a. 64%. mp: 173−174 °C. ^{1}H NMR δ 8.29 (s, 1H), 7.37−7.05 (m, 10H), 6.22 (br, 1H), 4.70 (s, 2H), 4.38 (s, 2H), 3.37 (s, 3H). ^{13}C NMR δ 167.7, 161.8, 157.7, 156.6, 142.3, 140.6, 129.2, 126.9, 125.5, 123.5, 120.8, 96.3, 55.8, 49.5, 39.2. MS (ESI): m/z 346.0 [M + H$^+$].

Preparation of 6-Butyl-9-methyl-4-(phenylthio)-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 4.1.5a. To a solution of compound **3.1a** (0.5 mmol) in EtOH (3 mL) was

added PhSH (5 mmol) followed by Et_3N (5 mmol). The resulting solution was stirred for 5 h at room temperature. Saturated aqueous NH_4Cl was added to quench the reaction. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (DCM/MeOH 30:1, v/v) afforded 161 mg (94%) of **4.1.5a** as a white solid. mp: 86−87 °C. ^{1}H NMR δ 8.24 (s, 1H), 7.51−7.46 (m, 2H), 7.44−7.40 (m, 3H), 4.70 (s, 2H), 4.32 (s, 2H), 3.53 (t, 2H, J = 7.5), 3.30 (s, 3H), 1.61−1.54 (m, 2H), 1.34−1.27 (m, 2H), 0.92 (t, 3H, J = 7.5). ^{13}C NMR δ 167.6, 163.7, 160.0, 156.2, 134.4, 129.4, 129.1, 128.9, 109.6, 55.6, 46.9, 46.0, 39.8, 30.2, 19.8, 13.7. MS (ESI): m/z 342.7 [M + H$^+$].

Preparation of 4-Butoxy-6-butyl-9-methyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 4.1.6a. To a solution of compound **3.1a** (0.5 mmol) in THF (2 mL) was added EtOH (5 mmol) followed by NaH (2 mmol). The resulting solution was stirred for 72 h at room temperature. Saturated aqueous NH_4Cl was added to quench the reaction and water (10 mL). The reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (DCM/MeOH 10:1, v/v) afforded 139 mg (91%) of **4.1.6a** as a white solid. mp: 55−57 °C. ^{1}H NMR δ 8.21 (s, 1H), 4.54 (s, 2H), 4.32 (t, 2H, J = 6.3), 4.26 (s, 3H), 3.45 (t, 2H, J = 7.5), 3.29 (s, 3H), 1.79−1.69 (m, 2H), 1.49−1.42 (m, 4H), 1.30−1.22 (m, 2H), 0.98 (t, 3H, J = 7.5), 0.88 (t, 3H, J = 6.9). ^{13}C NMR δ 167.8, 165.2, 161.6, 155.7, 96.1, 66.2, 55.4, 46.6, 42.1, 39.2, 30.8, 29.9, 19.7, 19.0, 13.5, 13.4. MS (ESI): m/z 307.0 [M + H$^+$].

Preparation of 6-Butyl-9-methyl-4-phenyl-8,9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one 4.1.7a. Compound **3.1a** (0.5 mmol) and phenylboronic acid (0.6 mmol) were dissolved in DME (ethylene glycol dimethyl ether) (2 mL) under a nitrogen atmosphere. K_2CO_3 (138 mg, 1.0 mmol) in water (2 mL) was added, followed by palladium(II) acetate (0.005 mmol) and triphenylphosphine (0.02 mmol). The resulting mixture was refluxed with stirring for 2 h before water (10 mL) was added. The reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL) in sequence, dried with Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (DCM/MeOH 30:1, v/v) afforded 154 mg (99%) of **4.1.7a** as a white solid. mp: 100−102 °C. ^{1}H NMR δ 8.56 (s, 1H), 7.49−7.45 (m, 3H), 7.41−7.38 (m, 2H), 4.51 (s, 2H), 4.37 (s, 2H), 3.38 (s, 3H), 3.25 (t, 2H, J = 7.2), 1.20−1.17 (m, 2H), 1.11−1.06 (m, 2H), 0.74 (t, 3H, J = 7.2). ^{13}C NMR δ 167.7, 163.2, 161.3, 156.5, 138.1, 129.1, 128.7, 128.5, 110.5, 55.6, 47.2, 46.2, 39.9, 29.9, 19.6, 13.5. MS (ESI): m/z 311.2 [M + H$^+$]

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Supporting Information Available. Copies of LC-MS-ELSD and NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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