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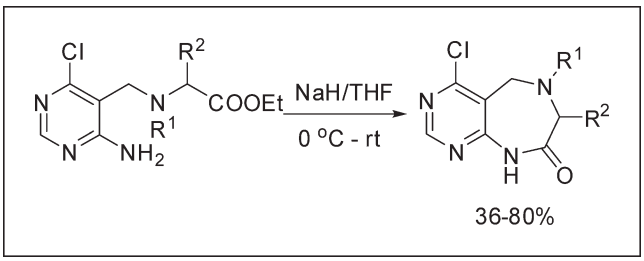

A new method was developed for the synthesis of 6,7-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-8(9*H*)-one derivatives. The key to construct the pyrimido[4,5-*e*][1,4]diazepine core is the intramolecular amidation of *N*-((4-amino-6-chloropyrimidin-5-yl)methyl)-substituted amino acid esters. This methodology was validated through the preparation of 13 representative 6,7-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-8(9*H*)-ones in moderate to good yields.

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INTRODUCTION

The bicyclic pyrimido[4,5-*e*][1,4]diazepine derivatives are known as tachykinin receptor antagonists [1], anticonvulsant agents [2], cysteine protease inhibitors [3], and raf kinase inhibitors [4]. However, the synthetic methodologies for pyrimido[4,5-*e*][1,4]diazepines are very limited in the literature. We only found the synthesis of one pyrimido[4,5-*e*][1,4]diazepin-8(9*H*)-one derivative by an intramolecular coupling reaction of 2-(((4-amino-6-(methoxycarbonyl)pyrimidin-5-yl)methyl)(methyl)amino)acetic acid as the key step shown in Scheme 1 and the scope of the synthesis was not reported [4].

In our efforts to prepare novel heterocyclic libraries [5], we have developed a series of methodologies to rapidly access various tricyclic and tetracyclic heterocyclic scaffolds with pyrimidodiazepine as the core [6]. As a continuing endeavor, we have studied the synthesis of 6,7-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-8(9*H*)-ones **5** *via* intramolecular amidation of ester precursors **4**, accessed by the reaction of chloromethylpyrimidine **3** and the ethyl ester of *N*-substituted amino acids (Scheme 2). The current procedure involving the direct amidation cyclization of the ester precursor by a simple base is complimentary to the literature one [4]. Subsequently, a sample library of the representative compounds has been prepared. Herein, the details of investigations are reported.

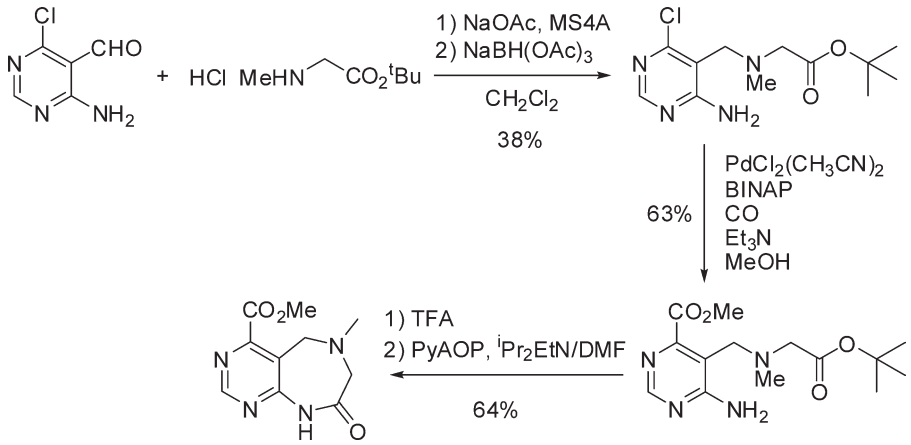
RESULTS AND DISCUSSION

The synthesis of bicyclic scaffold **5** is depicted in Scheme 2. Reduction of the formyl group in compound **1** [7] with $NaBH_4$ in MeOH furnished the corresponding alcohol derivatives **2** in 92% yields. Compound **2** was treated with $SOCl_2$ to lead to chloromethylpyrimidine **3**, which without further purification, reacted with various racemic amino acid esters [8] to provide precursors **4** in high overall yields (Table 1). Treatment of **4** with NaH in tetrahydrofuran (THF) resulted the ring closure product **5** in moderate to good yields.

As shown in Table 1, the ring closure reaction proceeded slower when the size of R^1 and R^2 increased (entries 1–5, entries 9–12). The amidation cyclization tolerated various side-chain groups in the amino acid esters, such as alkyl (entries 1–5, 9, 10, 12, and 13; Table 1), aryl (entries 6 and 11; Table 1), hydrogen (entry 8; Table 1), and hydroxyethyl groups (entry 7; Table 1).

In summary, we have prepared a representative library of pyrimido[4,5-*e*][1,4]diazepin-8(9*H*)-ones from a simple aminopyrimidinealdehyde precursor and amino acid esters. The key reaction in this synthetic protocol is the base-effected intramolecular aminolysis of amino acid esters. This new procedure complements existing method for the synthesis of pyrimido[4,5-*e*][1,4]diazepin-8(9*H*)-one derivatives.

Scheme 1. Synthesis of pyrimido[4,5-*e*][1,4]diazepin-8(9*H*)-one.



EXPERIMENTAL

General consideration. Dichloromethane (CH_2Cl_2) was dried with CaH_2 and distilled. Methanol (MeOH) was dried with Na and distilled. Acetonitrile (CH_3CN) was dried with CaH_2 and distilled. THF was dried with P_2O_5 and distilled from sodium before usage. All other commercial reagents were used as received without additional purification. Melting point was uncorrected. Mass spectra and HPLC data were recorded on an LC/MS system with ELSD. The ^{1}H-NMR data were obtained on a 300-MHz NMR spectrometer with 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; and br, broad. Coupling constants (*J* values) were noted are quoted in hertz.

Preparation of (4-amino-6-chloropyrimidin-5-yl)methanol 2. $NaBH_4$ (1.2 g, 30.08 mmol) was added to a stirred solution of compound **1** (3.235 g, 20.53 mmol) in MeOH (80 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 TLC, the volatiles were removed *in vacuo* and the residue was partitioned between water (8 mL) and EtOAc (6 × 8 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (5 mL) and brine (5 mL), dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (petroleum ether/EtOAc, 10:1–5:1, v/v) to afford 3.0 g (92%) of **2** as a white solid. mp: 179–180°C. ^{1}H-NMR (DMSO-d_6) δ 8.12 (s, 1H), 4.50 (s, 2H). MS (ESI): *m*/*z* 159.8 [M + H$^+$].

General procedure for the synthesis of 4-aminopyrimidine precursors 4. $SOCl_2$ (0.58 mL, 8 mmol) was added dropwise to a stirred solution of **2** (318 mg, 2 mmol) in CH_2Cl_2 (7 mL) at 0°C. After being stirred for an additional 10 min, the reaction mixture was allowed to warm to room temperature. After starting material **2** was completely consumed, as indicated by TLC, the volatiles were removed *in vacuo* to afford crude product **3**. MS (ESI): *m*/*z* 177.7 [M + H$^+$]. The crude **3** was dissolved in CH_3CN (8 mL), followed by addition of amino acid ester hydrochloride (2.4 mmol) and DIPEA (1.22 mL, 7 mmol) dropwise at 0°C. The reaction mixture was stirred for 10 min and allowed to warm to room temperature. After starting material **3** was consumed completely, as indicated by TLC, the volatiles were removed *in vacuo*. The residue was partitioned between water (5 mL) and EtOAc (3 × 5 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (6 mL) and brine (5 mL), dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (CH_2Cl_2/EtOAc, 30:1–5:1, v/v) to afford the desired product **4**.

Ethyl 2-(((4-amino-6-chloropyrimidin-5-yl)methyl)(methyl)amino)acetate 4.1. 486 mg (94%). mp: 102–104°C. ^{1}H-NMR δ 8.25 (s, 1H), 4.23 (q, 2H, *J* = 7.2), 3.67 (s, 2H), 3.31 (s, 2H), 2.29 (s, 3H), 1.30 (t, 3H, *J* = 7.2). MS (ESI): *m*/*z* 258.9 [M + H$^+$].

Ethyl 2-(((4-amino-6-chloropyrimidin-5-yl)methyl)(butyl)amino)acetate 4.2. 366 mg (61%). mp: 79–81°C. ^{1}H-NMR δ 8.23 (s, 1H), 4.21 (q, 2H, *J* = 7.2), 3.74 (s, 2H), 3.31 (s, 2H), 2.45 (t, 2H, *J* = 7.2), 1.46–1.36 (m, 2H), 1.32–1.18 (m, 5H), 0.83 (t, 3H, *J* = 7.2). MS (ESI): *m*/*z* 300.9 [M + H$^+$].

Ethyl 2-(((4-amino-6-chloropyrimidin-5-yl)methyl)(cyclohexyl)amino)acetate 4.3. 470 mg (72%). mp: 97–99°C. ^{1}H-NMR δ 8.23 (s, 1H), 4.20 (q, 2H, *J* = 7.2), 3.82 (s, 2H), 3.32 (s, 2H), 2.35–2.28 (m, 1H), 1.85–1.75 (m, 4H), 1.63–1.59 (m, 1H), 1.29 (t, 3H, *J* = 7.2), 1.19–1.00 (m, 5H). MS (ESI): *m*/*z* 326.9 [M + H$^+$].

Ethyl 2-(((4-amino-6-chloropyrimidin-5-yl)methyl)(phenethyl)amino)acetate 4.4. 586 mg (84%). mp: 74–75°C. ^{1}H-NMR δ 8.20 (s, 1H), 7.27–7.19 (m, 3H), 7.07 (d, 2H, *J* = 6.9), 4.22 (q, 2H, *J* = 7.2), 3.79 (s, 2H), 3.39 (s, 2H), 2.76 (s, 4H), 1.30 (d, 3H, *J* = 7.2). MS (ESI): *m*/*z* 348.8 [M + H$^+$].

Scheme 2. Synthesis of 6,7-disubstituted pyrimido[4,5-*e*][1,4]diazepin-8(9*H*)-ones.

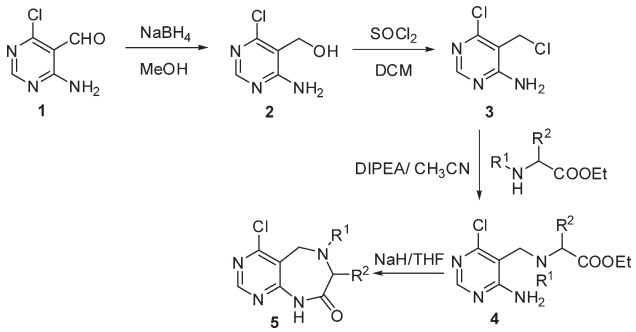


Table 1

Preparation of pyrimido[4,5-*e*][1,4]diazepin-8(9*H*)-ones.

			Intermediate **4**			Product **5**		
Entry	R^1	R^2		Time (h)	Yield (%)[a]		Time (h)	Yield (%)
1	Me	H	**4.1**	5	94	**5.1**	1.5	70
2	*n*-Bu	H	**4.2**	8	61	**5.2**	3	76
3	Cyclohexyl	H	**4.3**	11	72	**5.3**	3.5	80
4	$PhCH_2CH_2$	H	**4.4**	12	84	**5.4**	6	77
5	$PhCH_2$	H	**4.5**	9	80	**5.5**	6.5	64
6	Ph	H	**4.6**	13	53	**5.6**	11	45
7	Hydroxyethyl	H	**4.7**	18	70	**5.7**	20	44[b]
8	H	H	**4.8**	9	74	**5.8**	1.3	36[b]
9	Me	Me	**4.9**	9	64	**5.9**	5	67
10	Me	*i*-Pr	**4.10**	10	70	**5.10**	10	47
11	Me	Ph	**4.11**	12	86	**5.11**	12	49
12	Me	$PhCH_2$	**4.12**	8	84	**5.12**	4	72
13	$-(CH_2)_3-$		**4.13**	5	77	**5.13**	1	63

[a] Overall yield (two steps) from alcohol **2**.
[b] NaH of 2.2 equiv. was used.

Ethyl 2-(((4-amino-6-chloropyrimidin-5-yl)methyl)(benzyl)amino)acetate 4.5. 535 mg (80%). mp: 43–45°C. ^{1}H-NMR δ 8.24 (s, 1H), 7.33–7.22 (m, 5H), 4.17 (q, 2H, J = 6.9), 3.82 (s, 2H), 3.57 (s, 2H), 3.26 (s, 2H), 1.25 (t, 3H, J = 7.2). MS (ESI): m/z 334.9 [M + H^+].

Ethyl 2-(((4-amino-6-chloropyrimidin-5-yl)methyl)(phenyl)amino)acetate 4.6. 341 mg (53%). mp: 134–135°C. ^{1}H-NMR δ 8.20 (s, 1H), 7.28–7.22 (m, 2H), 6.98–6.92 (m, 3H), 4.51 (s, 2H), 4.23 (q, 2H, J = 7.2), 3.93 (s, 2H), 1.29 (t, 3H, J = 7.2). MS (ESI): m/z 320.8 [M + H^+].

Ethyl 2-(((4-amino-6-chloropyrimidin-5-yl)methyl)(2-hydroxyethyl)amino)acetate 4.7. 404 mg (70%). mp: 109–111°C. ^{1}H-NMR (DMSO-d_6) δ 8.12 (s, 1H), 4.11 (q, 2H, J = 7.2), 3.77 (s, 2H), 3.48–3.39 (m, 4H), 2.61 (t, 2H, J = 5.4), 1.20 (t, 3H, J = 7.2). MS (ESI): m/z 288.8 [M + H^+].

Ethyl 2-((4-amino-6-chloropyrimidin-5-yl)methylamino)acetate 4.8. 362 mg (74%). mp: 95–97°C. ^{1}H-NMR δ 8.25 (s, 1H), 4.24 (q, 2H, J = 7.2), 3.96 (s, 2H), 3.46 (s, 2H), 2.24 (br, 1H), 1.30 (t, 3H, J = 7.2). MS (ESI): m/z 244.8 [M + H^+].

Ethyl 2-(((4-amino-6-chloropyrimidin-5-yl)methyl)(methyl)amino)propanoate 4.9. 349 mg (64%). mp: 75–76°C. ^{1}H-NMR δ 8.24 (s, 1H), 4.22 (q, 2H, J = 7.2), 3.75 (s, 2H), 3.41 (q, 1H, J = 7.2), 2.25 (s, 3H), 1.38–1.29 (m, 6H). MS (ESI): m/z 272.9 [M + H^+].

Ethyl 2-(((4-amino-6-chloropyrimidin-5-yl)methyl)(methyl)amino)-3-methylbutanoate 4.10. 421 mg (70%). Oil. ^{1}H-NMR δ 8.25 (s, 1H), 4.29–4.21 (m, 2H), 3.79 (d, 2H, J = 2.4), 2.84 (d, 1H, J = 9.6), 2.25 (s, 3H), 2.22–2.14 (m, 1H), 1.33 (t, 3H, J = 7.2), 1.00 (d, 3H, J = 6.6), 0.92 (d, 3H, J = 6.6). MS (ESI): m/z 300.9 [M + H^+].

Ethyl 2-(((4-amino-6-chloropyrimidin-5-yl)methyl)(methyl)amino)-2-phenylacetate 4.11. 575 mg (86%). mp: 97–99°C. ^{1}H-NMR δ 8.23 (s, 1H), 7.41–7.35 (m, 5H), 4.27–4.08 (m, 3H), 3.78–3.61 (m ,2H), 2.03 (s, 3H), 1.20 (t, 3H, J = 7.2). MS (ESI): m/z 334.8 [M + H^+].

Ethyl 2-(((4-amino-6-chloropyrimidin-5-yl)methyl)(methyl)amino)-3-phenylpropanoate 4.12. 585 mg (84%). mp: 57–60°C. ^{1}H-NMR δ 8.18 (s, 1H), 7.34–7.18 (m, 5H), 4.32–4.14 (m, 2H), 4.01 (d, 1H, J = 13.8), 3.76 (d, 1H, J = 13.8), 3.59 (q, 1H, J = 6.0), 3.16–2.97 (m, 2H), 2.31 (s, 3H), 1.30 (t, 3H, J = 7.2). MS (ESI): m/z 348.9 [M + H^+].

Ethyl 1-((4-amino-6-chloropyrimidin-5-yl)methyl)pyrrolidine-2-carboxylate 4.13. 438 mg (77%). mp: 61–62°C. ^{1}H-NMR δ 8.22 (s, 1H), 4.27–4.17 (m, 2H), 3.78 (q, 2H, J = 13.2), 3.26 (q, 1H, J = 7.2), 2.98–2.92 (m, 1H), 2.39 (q, 1H, J = 9.0), 2.30–2.20 (m, 1H), 1.96–1.76 (m, 3H), 1.30 (t, 3H, J = 6.9). MS (ESI): m/z 284.9 [M + H^+].

General procedure for the synthesis of 6,7-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-8(9*H*)-ones 5. NaH (0.84 mmol or 1.54 mmol, 60% dispersion in oil) was added to a stirred solution of compound **4** (0.7 mmol) in THF (4 mL) at 0°C under dry N_2. The reaction mixture was stirred for 10 min and allowed to warm to room temperature. After starting material **4** was consumed completely, as indicated by TLC, saturated aqueous NH_4Cl was added to quench the reaction. The mixture was concentrated *in vacuo* and partitioned between water (4 mL) and EtOAc (3 × 5 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (4 mL) and brine (4 mL), dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (CH_2Cl_2/EtOAc, 10:1–5:1, v/v) to afford the desired product **5**.

4-Chloro-6-methyl-6,7-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-8(9H)-one 5.1. 104 mg (70%). mp: 177–179°C. ^{1}H-NMR δ 9.11 (s, 1H), 8.66 (s, 1H), 4.15 (s, 2H), 3.80 (s, 2H), 2.55 (s, 3H). MS (ESI): m/z 212.8 [M + H^+].

6-Butyl-4-chloro-6,7-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-8(9H)-one 5.2. 136 mg (76%). mp: 144–146°C. ^{1}H-NMR (DMSO-d_6) δ 8.59 (s, 1H), 4.07 (s, 2H), 3.70 (s, 2H), 2.56–2.50 (m, 2H), 1.45–1.21 (m, 4H), 0.86 (t, 3H, J = 7.2). MS (ESI): m/z 254.9 [M + H^+].

4-Chloro-6-cyclohexyl-6,7-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-8(9H)-one 5.3. 157 mg (80%). mp: 212–214°C. ^{1}H-NMR (DMSO-d_6) δ 8.56 (s, 1H), 4.12 (s, 2H), 3.75 (s, 2H), 3.38 (s, 1H), 1.74–1.70 (m, 4H), 1.53–1.51 (m, 1H), 1.22–1.13 (m, 5H). MS (ESI): m/z 280.9 [M + H^+].

4-Chloro-6-phenethyl-6,7-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-8(9H)-one 5.4. 164 mg (77%). mp: 110–111°C. ^{1}H-NMR (DMSO-d_6) δ 8.59 (s, 1H), 7.26–7.19 (m, 5H), 4.11 (s, 2H),

3.75 (s, 2H), 2.81–2.74 (m, 4H). MS (ESI): *m/z* 302.8 [M + H^+].

6-Benzyl-4-chloro-6,7-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-8(9H)-one 5.5. 129 mg (64%). mp: 168–170°C. ^{1}H-NMR (DMSO-d_6) δ 98.62 (s, 1H), 7.36–7.24 (m, 5H), 4.02 (s, 2H), 3.74 (s, 4H). 3.43 (s, 1H). MS (ESI): *m/z* 288.9 [M + H^+].

4-Chloro-6-phenyl-6,7-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-8(9H)-one 5.6. 86 mg (45%). mp: 246–248°C. ^{1}H-NMR (DMSO-d_6) δ 8.52 (s, 1H), 7.22–7.17 (m, 2H), 6.77–6.71 (m, 3H), 4.88 (s, 2H), 4.57 (s, 2H). MS (ESI): *m/z* 274.8 [M + H^+].

4-Chloro-6-(2-hydroxyethyl)-6,7-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-8(9H)-one 5.7. 75 mg (44%). mp: 213–214°C. ^{1}H-NMR (DMSO-d_6) δ 8.14 (s, 1H), 4.28 (t, 2H, J = 4.5), 3.58 (s, 2H), 2.66 (t, 4H, J = 4.5). MS (ESI): *m/z* 242.8 [M + H^+].

4-Chloro-6,7-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-8(9H)-one 5.8. 51 mg (36%). mp: 168–170°C. ^{1}H-NMR (DMSO-d_6) δ 8.54 (s, 1H), 4.01 (s, 2H), 3.67 (s, 2H). MS (ESI): *m/z* 198.8 [M + H^+].

4-Chloro-6,7-dimethyl-6,7-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-8(9H)-one 5.9. 106 mg (67%). mp: 166–168°C. ^{1}H-NMR (DMSO-d_6) δ 8.62 (s, 1H), 4.14 (d, 1H, J = 16.8), 3.98 (d, 1H, J = 17.1), 3.68 (q, 1H, J = 6.9), 2.32 (s, 3H), 1.21 (d, 3H, J = 6.9). MS (ESI): *m/z* 226.8 [M + H^+].

4-Chloro-7-isopropyl-6-methyl-6,7-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-8(9H)-one 5.10. 83 mg (47%). mp: 224–226°C. ^{1}H-NMR (DMSO-d_6) δ 8.61 (s, 1H), 4.00 (q, 2H, J = 16.8), 3.11 (d, 1H, J = 9.9), 2.37 (s, 3H), 1.89–1.81 (m, 1H), 0.96 (d, 3H, J = 6.6), 0.87 (d, 3H, J = 6.6). MS (ESI): *m/z* 254.7[M + H^+].

4-Chloro-6-methyl-7-phenyl-6,7-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-8(9H)-one 5.11. 99 mg (49%). mp: 202–203°C. ^{1}H-NMR (DMSO-d_6) δ 8.66 (s, 1H), 7.36–7.26 (m, 5H), 4.53 (s, 1H), 3.95 (q, 2H, J = 15.9), 2.39 (s, 3H). MS (ESI): *m/z* 288.9 [M + H^+].

7-Benzyl-4-chloro-6-methyl-6,7-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-8(9H)-one 5.12. 152 mg (72%). mp: 177–179°C. ^{1}H-NMR (DMSO-d_6) δ 8.60, (s, 1H), 7.27–7.15 (m, 5H), 4.00 (s, 1H), 3.97 (s, 2H), 3.38 (s, 1H), 3.08–3.03 (m, 1H), 2.89–2.81 (m, 1H), 2.36 (s, 3H). MS (ESI): *m/z* 302.9 [M + H^+].

4-Chloro-7,8,9,9a-tetrahydro-5H-pyrimido[4,5-e]pyrrolo[1,2-a][1,4]diazepin-10(11H)-one 5.13. 105 mg (63%). mp: 169–170°C. ^{1}H-NMR δ 8.77 (br, 1H), 8.63 (s, 1H), 4.33 (d, 1H, J = 16.5), 3.87 (d, 1H, J = 16.5), 3.41 (s, 1H), 3.28–3.24 (m, 1H), 2.70–2.59 (m, 2H), 2.22–2.08 (m, 1H), 1.93–1.90 (m, 2H). MS (ESI): *m/z* 238.9 [M + H^+].

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