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Graphical Abstract

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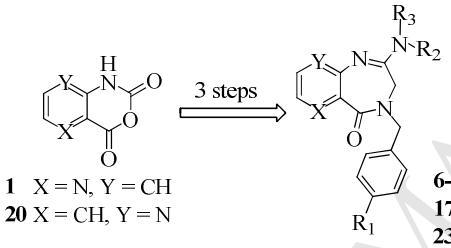

1 X = N, Y = CH
20 X = CH, Y = N

6-16 X = N, Y = CH, R_1 = H
17-19 X = N, Y = CH, R_1 = OCH_3
23-24 X = CH, Y = N, R_1 = H

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ABSTRACT

An efficient synthesis leading to novel 2,4-disubstituted 3*H*-pyrido[3,2-*e*][1,4]diazepin-5-ones and 2,4-disubstituted 3*H*-pyrido[2,3-*e*][1,4]diazepin-5-ones derivatives is presented, using the condensation of ethyl 2-(benzylamino)acetate or ethyl 2-(4-methoxybenzylamino)acetate with 1*H*-pyrido[3,2-*d*][1,3]oxazine-2,4-diones and 1*H*-pyrido[2,3-*d*][1,3]oxazine-2,4-diones. This synthesis gives 4-substituted 3-hydro-1*H*-pyrido[3,2-*e*][1,4]diazepine-2,5-diones and 4-benzyl-3,4-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepine-2,5-diones in good yields. Finally, after a regioselective thionation and nucleophilic substitutions reactions, various bis-functionalized 1,4-diazepines were easily obtained in excellent yields. These results open an access way to a library of novel bis-functionalized pyrido-1,4-diazepines.

1. Introduction

1,4-Benzodiazepines are important biomolecules with a wide array of biological activities and therapeutic uses. The exploration of privileged structures in drug discovery is a rapidly emerging theme in medicinal chemistry. The term “privileged structure” was first coined by Evans et al. in 1988 and was defined as “a single molecular framework able to provide ligands for diverse receptors”. This group noted the ability of polyfunctionalized 1,4-benzodiazepin-2-ones to bind to cholecystokinin family (CCKs) (e.g. **I**), gastrin, or central benzodiazepine receptors.[1] The benzodiazepine scaffold is also found in neurokinin-1 antagonists, enzyme inhibitors such as κ-secretase inhibitors (e.g. **II**) and farnesyl:protein transferase inhibitors (e.g. **III**), as well as in ion channel ligands, such as the delayed rectifier K^+ current modulator (e.g. **IV**)[2,3] (Figure 1).

Benzodiazepines are primarily known for their actions on the central nervous system. In addition to their established anxiolytic activities, 1,4-benzodiazepines also display antibiotic,[4] antimalarial,[5] and anti-HIV[6] activities.

There have also been several reports of benzodiazepines as potential anticancer agents,[7] including BMS-214662,[7a] a known farnesyltransferase (FTase) inhibitor, and Bz-423 **V**[7b] (Figure 1).

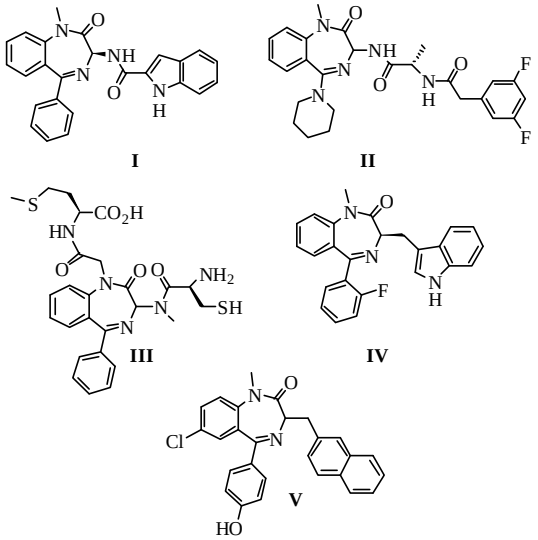

Figure 1. Some polyfunctionalized 1,4-benzodiazepines.

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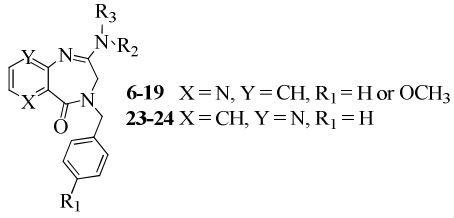
According to medicinal chemists, the true utility of privileged structures is the ability to synthesize a library based upon a particular core scaffold and screen it against a variety of different receptors, yielding several active compounds. This was illustrated by Bunin et al. using the benzodiazepine scaffold. Thus, having developed various series of 1,4-benzodiazepin-2-ones, they selected a small library of 192 molecules and screen it against the cholecystokinin A receptor, yielding active compounds.[8] Therefore, a larger library of 1680 1,4-benzodiazepin-2-ones was synthesized and screened against a large number of receptor and enzyme targets. As a result, inhibitors of pp60s-src tyrosine kinase and ligands that block an autoimmune DNA-antibody interaction implicated in systemic lupus erythematosus were identified.[9]

Thus, intensive attempts have been made to discover new synthetic routes to access this type of skeleton and to produce modified ring systems with potential biological activities.[10] In particular, heterocycle-fused diazepine derivatives, such as the pyridodiazepines, have exhibited anticonvulsant activities.[11]
Our ongoing research program looking for novel bioisosters of 1,4-benzodiazepines[12] led us to develop a short and convenient synthesis of 2,4-disubstituted 3*H*-pyrido[3,2-*e*] [1,4]diazepin-5-ones **6-19** and 2,4-disubstituted 3*H*-pyrido[2,3-*e*][1,4]diazepin-5-ones **23-24** derivatives (Figure 2). Moreover, these compounds have become interesting targets for further modifications aimed at preparing various fused or substituted derivatives.



6-19 X = N, Y = CH, R_1 = H or OCH_3
23-24 X = CH, Y = N, R_1 = H

Figure 2. Targeted structures.

2. Results and discussion

We present here an efficient and rapid synthesis of 2,4-disubtituted 3*H*-pyrido[3,2-*e*][1,4]diazepin-5-ones **6-19** and 2,4-disubtituted 3*H*-pyrido[2,3-*e*][1,4]diazepin-5-ones **23-24** derivatives.

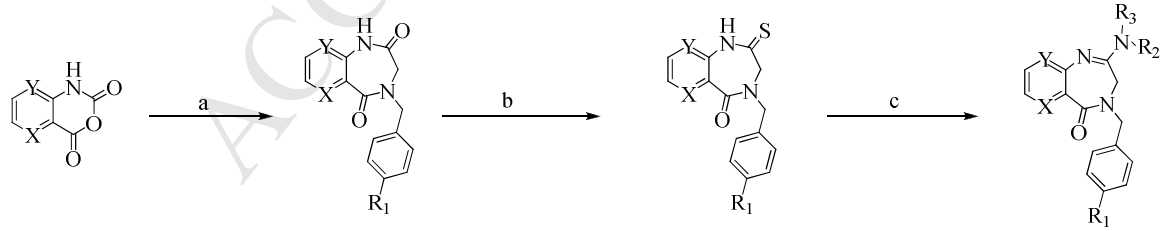
The starting compound in the first serie (compounds **6-16** and **17-19**) was the 1*H*-pyrido[3,2-*d*][1,3]oxazine-2,4-dione **1**, which was obtained starting from the Boc protected 3-aminopyridine-2-carboxylic acid with good yields using an excess of thionyl chloride in CH_2Cl_2 at reflux for 18 h.[13] The latter was synthesized from commercially available pyridine-2,3-dicarboxylic acid.[14]

Compound **1** was then condensed with commercially available ethyl 2-(benzylamino)acetate or ethyl 2-(4-methoxybenzylamino)acetate in DMF at reflux for 18 h in the presence of Et_3N yielding respectively compounds 4-benzyl-3,4-dihydro-1*H*-pyrido[3,2-*e*][1,4]diazepine-2,5-dione **2** and 4-(4-methoxybenzyl)-3,4-dihydro-1*H*-pyrido[3,2-*e*][1,4] diazepine-2,5-dione **3** (75%, 70%).

Subsequently, dilactam **2** or **3** was regioselectively thionated by heating with Lawesson's reagent in THF at 100 °C for 2 h. The reaction mixture was then simply cooled to room temperature and filtered to give pure monothiolactam **4** or **5** in excellent yields (97%, 95%) (Scheme 1). The formation of dithiolactam was not observed in the presence of a large excess of Lawesson reagent or elongation of the reaction time. The highly regioselective formation of monothiolactam may be due to steric effect by the 4-(4-methoxybenzyl) or benzyl groups in compounds **2**, **3** or **21**.

Finally, monothiolactam **4** or **5** was treated with various amines in the presence of $HgCl_2$ providing amidines **6-16** and **17-19** in good yields 78%-98% (Table 1).

To prepare **23-24** regioisomers, we started from 2-amino nicotinic acid, which was converted into 1*H*-pyrido[2,3-*d*] [1,3]oxazine-2,4-dione **20** using ethyl chloroformate for 12 h in toluene at 100 °C.[15] Compound **20** was then condensed with commercially available ethyl 2-(benzylamino)acetate in DMF at reflux for 18 h in the presence of Et_3N yielding 4-benzyl-3,4-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepine-2,5-dione **21** in good yield (70%). The dilactam **21** was subsequently converted to monothiolactam **22** using Lawesson's reagent by heating in THF at 100 °C for 1 h. The reaction mixture was then simply cooled to room temperature and filtered to give pure **22** in excellent yield (98%) (Scheme 1). Finally, thiolactam **22** was treated with morpholine or pyrrolidine in the presence of $HgCl_2$ affording amidines **23** and **24** in good yields (80%, 90%) (Table 1).



1 X = N, Y = CH
20 X = CH, Y = N

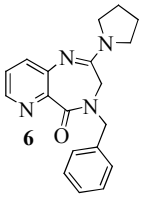
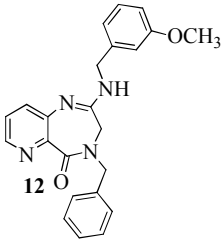
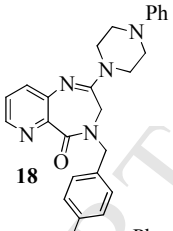
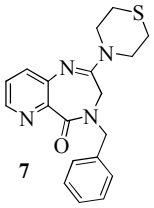
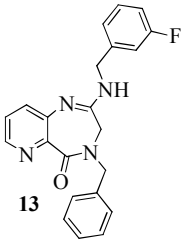
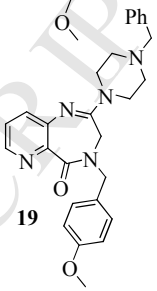
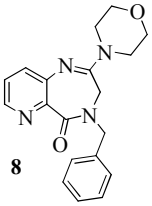
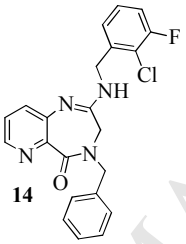
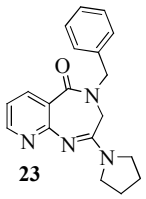
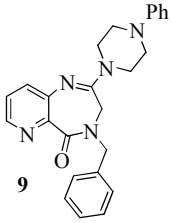
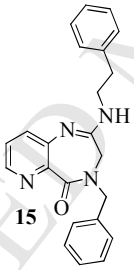
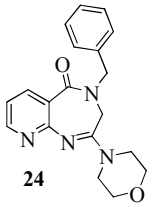
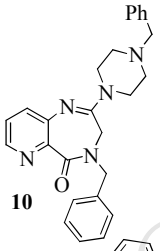
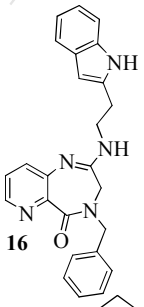
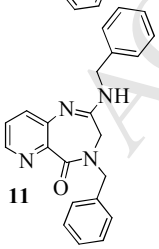
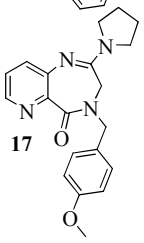
2 X = N, Y = CH, R_1 = H, 75%
3 X = N, Y = CH, R_1 = OCH_3, 70%
21 X = CH, Y = N, R_1 = H, 70%

4 X = N, Y = CH, R_1 = H, 97%
5 X = N, Y = CH, R_1 = OCH_3, 95%
22 X = CH, Y = N, R_1 = H, 98%

6-16 X = N, Y = CH, R_1 = H, 78-98%
17-19 X = N, Y = CH, R_1 = OCH_3, 90-98%
23, 24 X = CH, Y = N, R_1 = H, 90%, 80%

Scheme 1. Reagents and conditions: (a) ethyl 2-(benzylamino)acetate or ethyl 2-(4-methoxybenzylamino)acetate (1.2 equiv), DMF/Et_3N, reflux; 18 h; (b) Lawesson's reagent (1 equiv), THF, 100 °C, 2 h; (c) $HgCl_2$ (1.2 equiv), amines (1.2 equiv), THF, reflux, 1 h.

Table 1. Results of amination of compounds **4**, **5** and **22**.

Entry	product	yield[a]	Entry	product	yield[a]	Entry	product	yield[a]
1	 **6**	89%	7	 **12**	80%	13	 **18**	90%
2	 **7**	80%	8	 **13**	90%	14	 **19**	85%
3	 **8**	85%	9	 **14**	90%	15	 **23**	90%
4	 **9**	88%	10	 **15**	85%	16	 **24**	80%
5	 **10**	97%	11	 **16**	78%			
6	 **11**	85%	12	 **17**	90%			

[a] isolated yields after purification by column chromatography.

3. Conclusion

In summary, we have described the synthesis of novel 2,4-disubstituted 3*H*-pyrido[3,2-*e*][1,4]diazepin-5-ones and 2,4-disubstituted 3*H*-pyrido[2,3-*e*][1,4]diazepin-5-ones derivatives. The reactions all employ commercial or readily-available starting materials, and are performed under very simple experimental conditions and straightforward work-up, which makes them potentially useful for drug synthesis. This efficient strategy should provide easy access to a range of 1,4-pyridodiazepine alkaloids and their analogues.

4. Experimental section

4.1. General

All reactions were carried out under an inert atmosphere. IR spectra were recorded on a Bruker Alpha-T FT-IR spectrometer (ATR platinum Diamond). ^{1}H and ^{13}C NMR were recorded on a Bruker Avance DPX300 spectrometer (300 MHz ^{1}H, 75 MHz ^{13}C), the deuterated solvents indicated were used. For the purification chromatography, silica gel (60-200 mesh) was used. Thin layer chromatography (TLC) was carried out on Merck silica gel $60F_{254}$ precoated plates. Melting points were determined in open capillary tubes and are uncorrected. HRMS were performed on a Thermo Q Exactive LC-MS HR/AM Orbitrap. Commercial starting materials and dry solvents were obtained and used as received. Chemicals products were obtained from the following sources: Aldrich and Acros organics.

4.2. General Procedure for the synthesis of compounds 3, 4 and 23

A suspension of azaisatoic anhydride **1** or **20** [14] (1 g, 6 mmol) and ethyl 2-(benzylamino)acetate or ethyl 2-(4-methoxybenzylamino)acetate (7.25 mmol) in 10 mL of DMF and 2 mL (14.8 mmol) of Et_3N was heated to reflux for 18 h. The solvent was evaporated, and the crude product was purified by chromatography to give **2**, **3** or **21**.

*4.2.1. 4-Benzyl-3,4-dihydro-1H-pyrido[3,2-*e*][1,4]diazepine-2,5-dione (**2**).* Yield 75%; m.p. 240 °C; ν_{max} (neat) 3259 (br), 3076, 2916, 1694, 1634, 1447, 1118 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.94 (s, 2H), 4.78 (s, 2H), 7.26-7.39 (m, 5H), 7.51-7.58 (m, 2H), 8.49-8.51 (m, 1H), 10.53 (s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 50.8, 51.8, 126.7, 127.9, 128.2 (2CH), 129.0 (2CH), 129.5, 134.9, 137.3, 143.0, 146.1, 165.3, 170.3; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{15}H_{13}N_3O_2$: 268.1080, found: 268.1059.

*4.2.2.4-(4-Methoxybenzyl)-3,4-dihydro-1H-pyrido[3,2-e][1,4] diazepine-2,5-dione (**3**).* Yield 70%; m.p. 213 °C; ν_{max} (neat) 3076, 2902, 2837, 1701, 1642, 1232 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.74 (s, 3H), 3.89 (s, 2H), 4.69 (s, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 7.5-7.56 (m, 2H), 8.49-8.50 (m, 1H), 10.48 (s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 50.5, 51.1, 55.5, 114.4 (2CH), 126.6, 129.3, 129.4, 129.8 (2CH), 134.9, 142.7, 145.0, 159.1, 165.2, 170.3; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{16}H_{15}N_3O_3$: 298.1186, found: 298.1163.

*4.2.3. 4-Benzyl-3,4-dihydro-1H-pyrido[2,3-*e*][1,4]diazepine-2,5-dione (**21**).* Yield 70%; m.p. 180 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 2H), 4.88 (s, 2H), 7.28-7.31 (m, 1H), 7.34-7.40 (m, 5H), 8.43-8.46 (m, 1H), 8.60 (d, *J* = 3.1 Hz, 1H), 9.06 (s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.2, 52.1, 120.4, 128.2, 128.4 (2CH), 128.6, 128.9 (2CH), 135.8, 141.8, 148.2, 152.0, 169.1, 176.2; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{15}H_{13}N_3O_2$: 268.1080, found: 268.1059.

4.3. General Procedure for the synthesis of compounds 4, 5 and 22.

Lawesson's reagent (1.87 g, 4.62 mmol) was added to a suspension of dilactam **2**, **3**, or **21** (4.62 mmol) in 100 mL of THF. The mixture was heated at 100 °C for 2 h then the yellow solid was filtered to yield pure **4**, **5** or **22** in excellent yields.

*4.3.1. 4-Benzyl-2-thioxo-3,4-dihydro-1H-pyrido[3,2-e][1,4] diazepin-5(2H)-one (**4**).* Yield 97%; m.p. 255 °C; ν_{max} (neat) 3048, 3031, 1657, 1592, 1386 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.20 (s, 2H), 4.73 (s, 2H), 7.28-7.40 (m, 5H), 7.60-7.64 (m, 1H), 7.68-7.71 (m, 1H), 8.60-8.62 (m, 1H), 12.60 (s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 51.4, 57.3, 126.8, 128.0, 128.3 (2CH), 129.0 (2CH), 129.8, 135.1, 136.0, 143.7, 147.5, 164.7, 199.7; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{15}H_{13}N_3OS$: 284.0852, found: 284.0830.

*4-(4-Methoxybenzyl)-2-thioxo-3,4-dihydro-1H-pyrido [3,2-e][1,4]diazepin-5(2H)-one (**5**).* Yield 95%; m.p. 329 °C; ν_{max} (neat) 3047, 2994, 1661, 1511, 1240 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.74 (s, 3H), 4.17 (s, 2H), 4.89 (s, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.59-7.63 (m, 1H), 7.67-7.70 (m, 1H), 8.59-8.61 (m, 1H), 12.57 (s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 50.7, 55.5, 56.9, 114.4 (2CH), 126.8, 128.9, 129.7, 129.9 (2CH), 135.0, 143.8, 147.5, 159.2, 164.5, 199.8; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{16}H_{15}N_3O_2S$: 314.0958, found: 314.0933.

*4-Benzyl-2-thioxo-3,4-dihydro-1H-pyrido[2,3-e][1,4] diazepin-5(2H)-one (**22**).* Yield 98%; m.p. 213 °C; ν_{max} (neat) 3064, 2928, 1646, 1593, 1352, 1134 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.26 (s, 2H), 4.76 (s, 2H), 7.26-7.39 (m, 5H), 7.42-7.46 (m, 1H), 8.30-8.33 (m, 1H), 8.62-8.64 (m, 1H), 12.78 (s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 51.6, 58.3, 121.9, 123.0, 128.0, 128.3 (2CH), 129.0 (2CH), 136.9, 141.5, 148.9, 152.3, 165.5, 200.3; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{15}H_{13}N_3OS$: 284.0852, found: 284.0830.

4.4. General Procedure for the synthesis of compounds 6-19 and 23-24

A suspension of **4**, **5** or **22** (0.28 mmol) and mercuric chloride (0.9 g, 0.34 mmol) in dry THF (5 mL) was heated to 100 °C and an amine (0.34 mmol) was added. After 1 h, the solution became black (formation of mercuric sulfide). The reaction mixture was filtered through Celite and then washed with methanol. The filtrate was then concentrated, and the crude product was purified by chromatography (DCM/MeOH 96/4) to give respectively **6-16**, **17-19** or **24-25**.

*4.4.1. 4-Benzyl-2-(pyrrolidin-1-yl)-3H-pyrido[3,2-e][1,4] diazepin-5(4H)-one (**6**).* Yield 89%; m.p. 216 °C; ν_{max} (neat) 2978, 2959, 2871, 1631, 1595, 1570 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72-1.82 (m, 4H), 3.05 (s, 2H), 3.45-3.52 (m, 2H), 3.91 (s, 2H), 4.97 (s, 2H), 7.27-7.38 (m, 6H), 7.48-7.52 (m, 1H), 8.45-8.47 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.5, 25.7, 44.3, 47.6, 51.6, 126.1, 127.7 (2CH), 127.9, 128.8 (2CH), 135.1, 142.0, 144.1, 145.0, 157.0, 167.3; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{19}H_{20}N_4O$: 321.1701, found: 321.1684.

*4.4.2. 4-Benzyl-2-thiomorpholino-3H-pyrido[3,2-e][1,4] diazepin-5(4H)-one (**7**).* Yield 80%; m.p. 231 °C; ν_{max} (neat) 3020, 2967, 2914, 2845, 1640, 1567, 1414 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.57 (s, 4H), 3.71 (s, 4H), 3.88 (s, 2H), 4.78 (bs, 1H), 4.98 (bs, 1H), 7.28-7.40 (m, 6H), 7.44-7.47 (m, 1H),

8.50-8.52 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.2, 40.7, 48.1, 51.1, 125.9, 128.0 (2CH), 128.1, 128.9 (2CH), 134.9, 135.1, 142.4, 144.5, 144.7, 157.3, 167.1; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{19}H_{20}N_4OS$: 353.1431, found: 353.1402.

*4.4.3. 4-Benzyl-2-morpholino-3H-pyrido[3,2-e][1,4]diazepin-5(4H)-one (**8**).* Yield 85%; m.p. 227 °C; ν_{max} (neat) 2957, 2856, 1631, 1594, 1569 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.43-3.56 (m, 8H), 3.88 (s, 2H), 4.91 (s, 2H), 7.28-7.41 (m, 6H), 7.49 (d, *J* = 8.2 Hz, 1H), 8.52 (d, *J* = 3.1Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.8, 45.5 ($2CH_2$), 51.3, 66.3, 125.9, 127.9 (2CH), 128.1, 129.0 (2CH), 134.9, 136.3, 142.4, 144.6, 144.7, 158.0, 167.1; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{19}H_{20}N_4O$: 337.1659, found: 337.1631.

*4.4.4. 4-Benzyl-2-(4-phenylpiperazin-1-yl)-3H-pyrido[3,2-e][1,4]diazepin-5(4H)-one (**9**).* Yield 88%; m.p. 199 °C; ν_{max} (neat) 2977, 2959, 2871, 1628, 1592, 1568 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.11 (s, 4H), 3.64 (s, 4H), 3.95 (s, 2H), 4.93 (s, 2H), 6.91-6.96 (m, 3H), 7.28-7.41 (m, 8H), 7.51-7.54 (m, 1H), 8.52-8.54 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.9, 46.8 ($2CH_2$), 49.1, 49.2, 51.2, 116.6 (2CH), 120.7, 126.0, 128.0 (2CH), 128.1, 129.0 (2CH), 129.3 (2CH), 134.9, 136.3, 142.4, 144.6, 144.7, 150.6, 157.8, 167.2; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{25}H_{25}N_5O$: 412.2132, found: 412.2100.

*4.4.5. 4-Benzyl-2-(4-benzylpiperazin-1-yl)-3H-pyrido[3,2-e][1,4]diazepin-5(4H)-one (**10**).* Yield 97%; m.p. 157 °C; ν_{max} (neat) 3030, 2930, 2800, 1631, 1594, 1567 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.4 (s, 4H), 3.46-3.98 (m, 8H), 4.61 (s, 1H), 5.18 (s, 1H), 7.28-7.38 (m, 11H), 7.43-7.47 (m, 1H), 8.48-8.50 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.6, 45.2, 51.0, 62.7, 125.9, 127.4, 128.0, 128.0 (2CH), 128.4 (2CH), 129.0 (2CH), 129.2 (2CH), 134.9, 136.3, 137.2, 142.4, 144.5, 157.7, 167.2; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{26}H_{27}N_5O$: 426.2288, found: 426.2255.

*4.4.6. 4-Benzyl-2-(benzylamino)-3H-pyrido[3,2-e][1,4]diazepin-5(4H)-one (**11**).* Yield 98%; m.p. 213 °C; ν_{max} (neat) 3253 (br), 3030, 2947, 2936, 1606, 1556 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.71 (s, 2H), 4.42 (s, 2H), 4.80 (s, 2H), 5.61 (s, NH), 7.19-7.27 (m, 7H), 7.28-7.34 (m, 4H), 7.47-7.50 (m, 1H), 8.33-8.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.6, 46.8, 51.5, 125.9, 127.5, 127.9, 128.1 (2CH), 128.5 (2CH), 128.6 (2CH), 128.7 (2CH), 135.0, 137.7, 142.8, 144.2, 145.3, 157.3, 166.9; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{22}H_{20}N_4O$: 357.1710, found: 357.1681.

*4.4.7. 4-Benzyl-2-(3-methoxybenzylamino)-3H-pyrido[3,2-e][1,4]diazepin-5(4H)-one (**12**).* Yield 80%; m.p. 163 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.64 (s, 2H), 3.83 (s, 3H), 4.48 (s, 2H), 4.86 (s, 2H), 5.14 (bs, NH), 6.87-6.96 (m, 2H), 7.21-7.29 (m, 4H), 7.30-7.36 (m, 4H), 7.51-7.54 (m, 1H), 8.44-8.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.3, 45.9, 51.4, 55.3, 110.4, 120.6, 125.4, 125.7, 127.9, 128.5 (2CH), 128.7 (2CH), 129.1, 129.1, 130.1, 134.8, 136.2, 143.0, 144.4, 150.9, 156.9, 157.5, 166.7; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{23}H_{22}N_4O_2$: 387.1815, found: 387.1786.

4.4.8. 4-Benzyl-2-(3-fluorobenzylamino)-3H-pyrido[3,2-e][1,4]diazepin-5(4H)-one (**13**). Yield 90%; m.p. 199 °C; ν_{max} (neat) 3252 (br), 2959, 2871, 1597, 1560, 1205 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.78 (s, 2H), 4.43 (s, 2H), 4.78 (s, 2H), 6.30 (s, NH), 6.91-6.99 (m, 3H), 7.17-7.22 (m, 6H), 7.28-7.32 (m, 1H), 7.45-7.48 (m, 1H), 8.29-8.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.9, 46.7, 51.6, 114.1, 114.3, 114.7, 115.0, 123.5, 123.5, 125.9, 127.8, 128.3 (2CH), 128.7 (2CH), 129.9, 130.0, 135.1, 136.4, 140.5, 140.6, 142.7, 144.0, 145.2, 157.5, 161.2, 164.4, 166.9; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{22}H_{19}FN_4O$: 375.1616, found: 375.1585.

*4-Benzyl-2-(2-chloro-3-fluorobenzylamino)-3H-pyrido[3,2-e][1,4]diazepin-5(4H)-one (**14**).* Yield 90%; m.p. 163 °C; ν_{max} (neat) 3282 (br), 3063, 3028, 2919, 1617, 1210, 715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.72 (s, 2H), 4.54 (s, 2H), 4.82 (s, 2H), 5.71 (s, NH), 7.17-7.37 (m, 9H), 7.49 (d, *J* = 8.1 Hz, 1H), 8.35 (d, *J* = 3.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.2, 45.7, 51.5, 125.8, 126.9, 127.9, 128.5 (2CH), 128.8 (2CH), 129.5, 130.4, 133.7, 135.2, 136.3, 142.9, 144.3, 145.1, 157.0, 166.5; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{22}H_{18}ClFN_4O$: 409.1226, found: 391.1289; MS (IS): m/z 409 (M+H).

*4.4.9. 4-Benzyl-2-(phenethylamino)-3H-pyrido[3,2-e][1,4]diazepin-5(4H)-one (**15**).* Yield 85%; m.p. 203 °C; ν_{max} (neat) 3253 (br), 3063, 3027, 2944, 1636, 1611, 1579 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.75-2.80 (m, 2H), 3.48-3.53 (m, 2H), 3.62 (s, 2H), 4.77 (s, 2H), 5.25 (s, NH), 7.14-7.17 (m, 2H), 7.25-7.36 (m, 9H), 7.48-7.51 (m, 1H), 8.39-8.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.6, 42.6, 46.7, 51.3, 125.8, 126.5, 127.9, 128.4, 128.5 (2CH), 128.6 (2CH), 128.7 (2CH), 128.7 (2CH), 134.8, 136.5, 138.8, 143.0, 144.2, 157.3, 166.8; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{23}H_{22}N_4O$: 371.1166, found: 371.1837.

*4.4.10. 2-(2-(1H-indol-2-yl)ethylamino)-4-benzyl-3H-pyrido[3,2-e][1,4]diazepin-5(4H)-one (**16**).* Yield 78%; m.p. 283 °C; ν_{max} (neat) 3270 (br), 3107, 1623, 1600, 1566 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.23-2.97 (m, 2H), 3.56 (d, *J* = 5.1 Hz, 2H), 3.78 (s, 2H), 4.24 (bs, 1H), 5.09 (bs, 1H), 6.97-7.10 (m, 2H), 7.17 (s, 1H), 7.31-7.41 (m, 8H), 7.59 (d, *J* = 7.4 Hz, 1H), 7.87 (s, 1H), 8.29 (s, 1H), 10.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.6, 41.9, 45.6, 51.1, 111.9, 112.2, 118.7, 121.4, 123.3, 126.1, 127.7, 127.9 (2CH), 128.9 (2CH), 134.4, 136.7, 137.8, 143.2, 143.5, 143.5, 145.8, 145.8, 158.8, 166.4; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{25}H_{23}N_5O$: 410.9175, found: 410.1944.

*4.4.11. 4-(4-Methoxybenzyl)-2-(pyrrolidin-1-yl)-3H-pyrido[3,2-e][1,4]diazepin-5(4H)-one (**17**).* Yield 90%; m.p. 174 °C; ν_{max} (neat) 2990, 2968, 2882, 1595, 1561, 1511 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.82 (s, 4H), 3.13 (s, 2H), 3.48-3.56 (m, 2H), 3.81 (s, 3H), 3.90 (s, 2H), 4.90 (s, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 7.2 Hz, 2H), 7.40 (d, *J* = 3.3 Hz, 1H), 7.54 (d, *J* = 7.1 Hz, 1H), 8.45 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.5, 25.8, 44.0, 47.8, 51.0, 55.4, 114.2 (2CH), 126.28, 128.2, 129.2 (2CH), 135.5, 141.6, 144.1, 145.1, 157.0, 159.4, 167.4; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{20}H_{22}N_4O_2$: 351.1815, found: 351.1792.

*4.4.12. 4-(4-Methoxybenzyl)-2-(4-phenylpiperazin-1-yl)-3H-pyrido[3,2-e][1,4]diazepin-5(4H)-one (**18**).* Yield 98%; m.p. 257 °C; ν_{max} (neat) 3006, 2891, 1629, 1597, 1574 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.13 (s, 4H), 3.69 (s, 4H), 3.76 (s, 3H), 4.01 (s, 2H), 4.83 (bs, 2H), 6.87-6.97 (m, 5H), 7.27-7.40 (m, 5H), 7.50-7.53 (m, 1H), 8.51-8.53 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.6 ($2CH_2$), 45.3 ($2CH_2$), 49.3, 50.5, 55.3, 114.4 (2CH), 116.6 (2CH), 118.7, 120.7, 125.9, 128.2, 129.3 (2CH), 129.3 (2CH), 134.8, 142.5, 144.5, 144.7, 150.7, 157.9, 159.5, 167.0; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{26}H_{27}N_5O_2$: 442.2237, found: 442.2205.

*4.4.13. 2-(4-Benzylpiperazin-1-yl)-4-(4-methoxybenzyl)-3H-pyrido[3,2-e][1,4]diazepin-5(4H)-one (**19**).* Yield 95%; m.p. 193 °C; ν_{max} (neat) 3001, 2890, 2832, 1629, 1595, 1573 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.45 (s, 4H), 3.45-3.57 (m, 6H), 3.83 (s, 3H), 4.48 (s, 2H), 4.48 (bs, 1H), 5.15 (bs, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.31-7.37 (m, 6H), 7.42-7.45 (m, 1H), 8.48-8.50 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.3, 50.2 ($2CH_2$), 52.6, 52.6 ($2CH_2$), 55.4, 62.7, 114.4 (2CH), 125.8 (2CH), 127.5, 127.6, 128.3, 128.5 (2CH), 129.2, 129.4 (2CH), 134.8, 142.6, 144.5, 157.8, 159.4, 167.1; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{27}H_{29}N_5O_2$: 456.2394, found: 456.2361.

*4-Benzyl-2-(pyrrolidin-1-yl)-3H-pyrido[2,3-e][1,4]diazepin-5(4H)-one (**23**).* Yield 90%; m.p. 170 °C; ν_{max} (neat) 2967, 2875, 1639, 1596, 1560 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.67-1.73 (m, 4H), 2.94 (s, 2H), 3.60 (s, 2H), 3.96 (s, 2H), 4.22 (s, 2H), 7.12-7.16 (m, 1H), 7.24-7.28 (m, 2H), 7.32-7.36 (m, 3H), 8.45-8.48 (m, 1H), 8.70-8.72 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.2, 25.6, 45.3, 47.7, 48.4, 51.9, 117.6, 122.4, 127.6 (2CH), 128.1, 128.9 (2CH), 136.2, 142.6, 151.6, 156.9, 158.4, 167.2; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{19}H_{20}N_4O$: 321.1710, found: 321.1687.

*4.4.14. 4-Benzyl-2-morpholino-3H-pyrido[2,3-e][1,4]diazepin-5(4H)-one (**24**).* Yield 80%; m.p. 192 °C; ν_{max} (neat) 3051, 2961, 2853, 1618, 1594, 1563 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.02-3.05 (m, 2H), 3.56-3.81 (m, 6H), 3.92 (s, 2H), 4.87 (s, 2H), 7.09-7.13 (m, 1H), 7.24-7.28 (m, 2H), 7.35-7.41 (m, 3H), 8.37-8.41 (m, 1H), 8.61-8.63 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.6, 45.2, 51.5, 66.3, 118.1, 121.7, 127.8 (2CH), 128.2, 129.1 (2CH), 136.1, 140.8, 152.4, 158.0, 158.7, 167.8; HRMS-FIA (m/z): $[M+H]^+$ calcd for $C_{19}H_{20}N_4O_2$: 337.1659, found: 337.1633.

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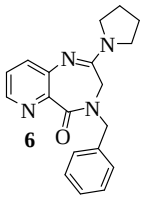
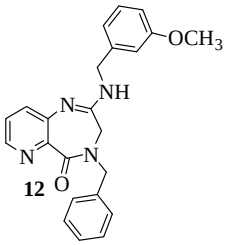
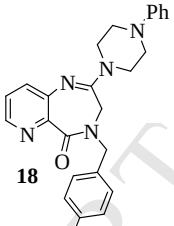
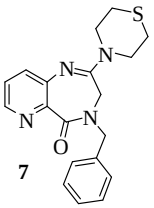
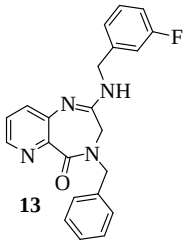
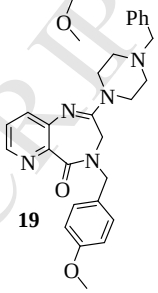
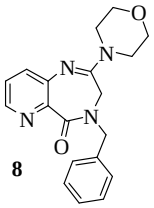
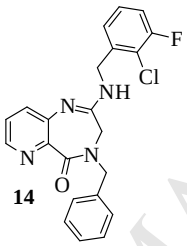
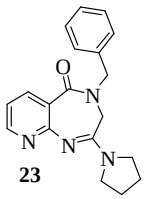
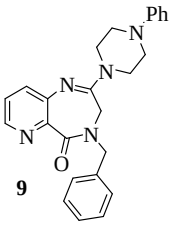
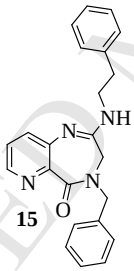
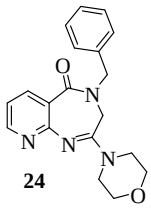
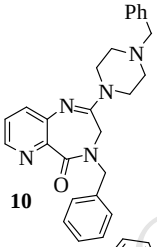
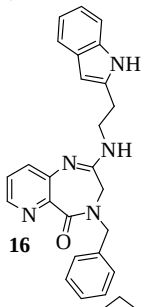
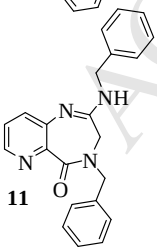
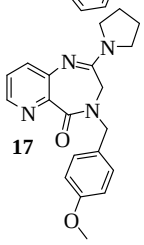
Table 1. Results of amination of compounds **4**, **5** and **22**.

Entry	product	yield[a]	Entry	product	yield[a]	Entry	product	yield[a]
1	 **6**	89%	7	 **12**	80%	13	 **18**	90%
2	 **7**	80%	8	 **13**	90%	14	 **19**	85%
3	 **8**	85%	9	 **14**	90%	15	 **23**	90%
4	 **9**	88%	10	 **15**	85%	16	 **24**	80%
5	 **10**	97%	11	 **16**	78%			
6	 **11**	85%	12	 **17**	90%			

[a] isolated yields after purification by column chromatography.

Figure 1. Some polyfunctionalized 1,4-benzodiazepines.

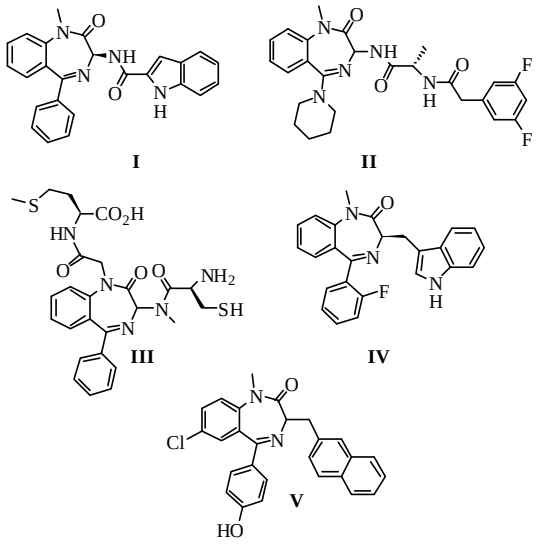
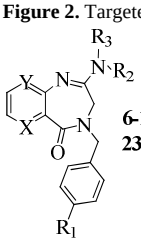
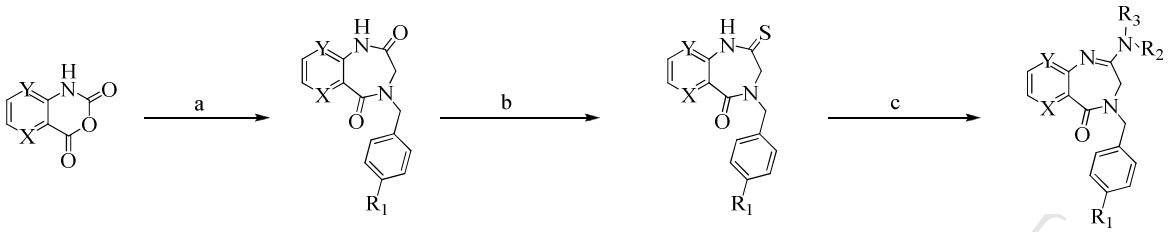


Figure 2. Targeted structures.



6-19 X = N, Y = CH, R_1 = H or OCH_3
23-24 X = CH, Y = N, R_1 = H



1 X = N, Y = CH
20 X = CH, Y = N

2 X = N, Y = CH, R_1 = H, 75%
3 X = N, Y = CH, R_1 = OCH_3, 70%
21 X = CH, Y = N, R_1 = H, 70%

4 X = N, Y = CH, R_1 = H, 97%
5 X = N, Y = CH, R_1 = OCH_3, 95%
22 X = CH, Y = N, R_1 = H, 98%

6-16 X = N, Y = CH, R_1 = H, 78-98%
17-19 X = N, Y = CH, R_1 = OCH_3, 90-98%
23, 24 X = CH, Y = N, R_1 = H, 90%, 80%

Scheme 1. Reagents and conditions: (a) ethyl 2-(benzylamino)acetate or ethyl 2-(4-methoxybenzylamino)acetate (1.2 equiv), DMF/Et_3N, reflux; 18 h; (b) Lawesson's reagent (1 equiv), THF, 100 °C, 2 h; (c) $HgCl_2$ (1.2 equiv), amines (1.2 equiv), THF, reflux, 1 h.