Scientific paper

Synthesis and Structural Characterization of Pyrazino[1,3]diazepines, as a New Ring System

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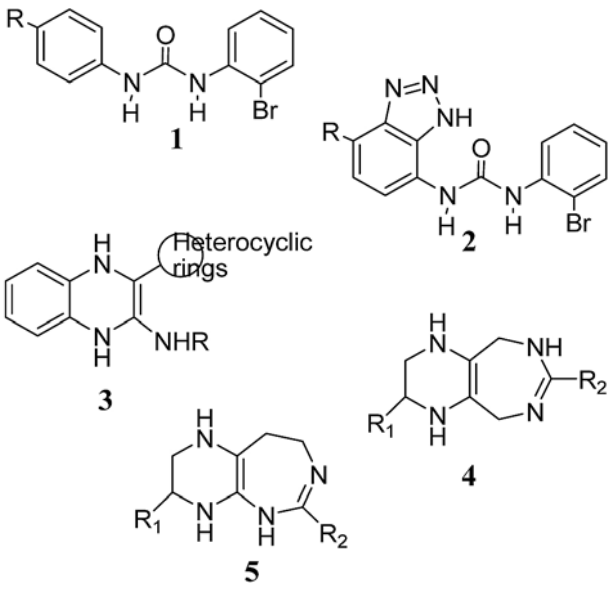
Abstract

Pyrazino[1,3]diazepine represents a new ring system and was synthesized via annulation of the diazepine ring onto the preformed pyrazine derivatives. These compounds were synthesized as potential non-peptide, small-molecule IL-8 receptor antagonists. Different new pyrazine derivatives were also prepared for the syntheses of these new ring systems.

Keywords: Guanidine nitrate; *S*-methylisothiourea sulphate; pyrazine; dimethylacetylene dicarboxylate; non-peptide small-molecule IL-8 receptor antagonists.

1. Introduction

Diarylureas **1**, **2** and 2-amino-3-heteroaryl quinoxalines **3** depicted below are found to be specific non-peptide, small-molecule antagonists of the interleukin (IL) receptor.[1,2,3,4] Herein we describe a synthesis of the new pyrazino[1,3]diazepine ring systems **4** and **5** as potential non-peptide, small-molecule IL-8 receptor antagonists.

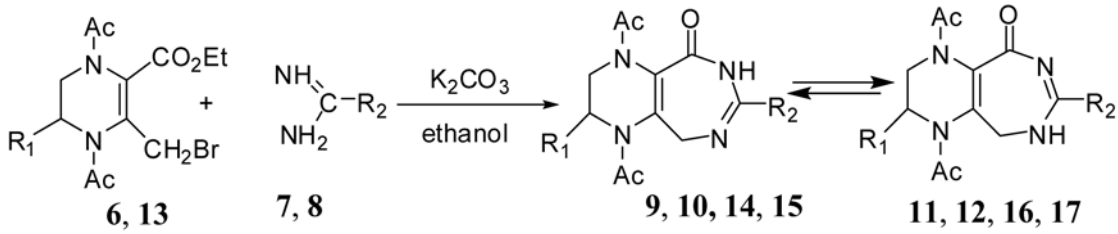


2. Results and Discussion

In our strategy, the [1,3]diazepine nucleus was built onto the preformed piperazine derivatives. Guanidine nitrate and *S*-methylisothiourea sulphate were employed as the sources of nitrogen atoms in [1,3]diazepine syntheses.

For the syntheses of pyrazino[1,3]diazepine derivatives of the structure **4**, reaction of the bromomethylcarboethoxypyrazines **6** or **13** with either guanidine nitrate (**7**) or *S*-methylisothiourea sulphate (**8**), in the presence of potassium carbonate, afforded the pyrazino[1,3]diazepine derivatives **11** and **16**, or **12** and **17**, rather than the alternative tautomers **9** and **14** or **10** and **15**, respectively (Scheme 1). The ^{1}H NMR spectra for the products **11** and **16** showed the presence of two different kinds of activated enamine protons (NH_2 and NH protons), instead of the amide NH protons. In addition, the ^{13}C NMR spectra for compounds **11**, **12**, **16** and **17** showed for the 5-C signals with upfield chemical shift, namely at δ 197.7, 198.4, 201.0 and 199.3 ppm, respectively. These data revealed the amidate[5] not amidic nature for these compounds and supported the existence of the tautomers **11**, **12**, **16** and **17**, respectively. The *S*-methylthio derivatives **12** and **17** showed SMe protons at δ 2.24 and 2.20 ppm.

Compounds **6** and **13** were prepared by condensation of the 1,2-diamino derivatives with ethyl-α-bromoacetoacetate[6] in tetrahydrofuran (THF) and potassium carbonate to pyrazine derivatives **18** and **18a**, respectively. During the separation of the latter compounds we found



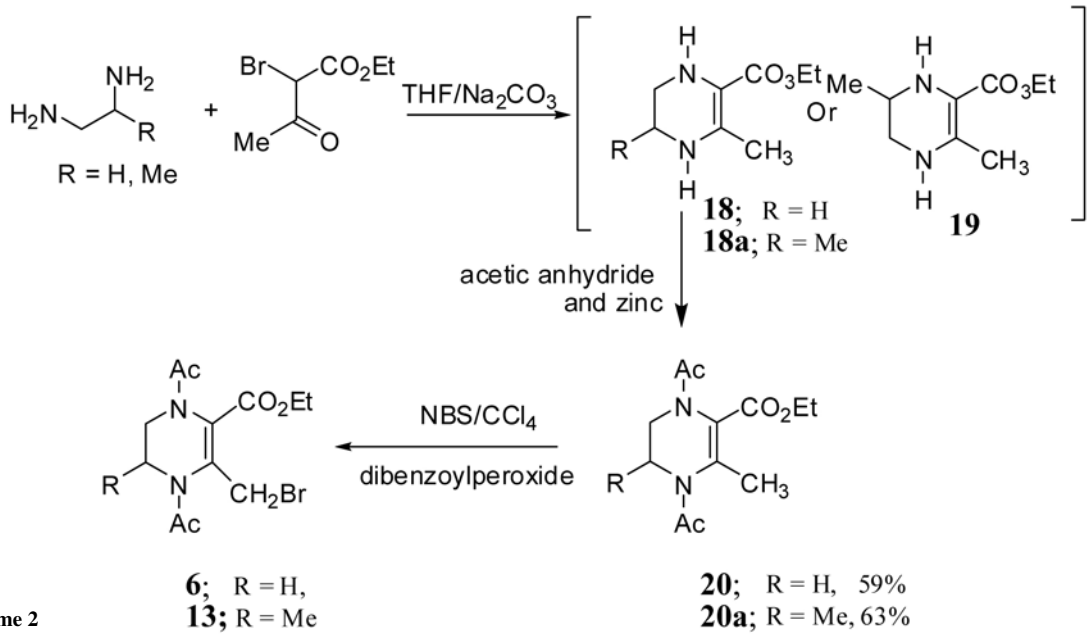
Scheme 1

Compound	R^1	R^2	Yield (%)	Compound	R^1	R^2	Yield (%)
6	H	–	65	**11**	H	NH_2	64
13	Me	–	75	**12**	H	SMe	60
7	–	NH_2	–	**14**	Me	NH_2	–
8	–	SMe	–	**15**	Me	SMe	–
9	H	NH_2	–	**16**	Me	NH_2	52
10	H	SMe	–	**17**	Me	SMe	70

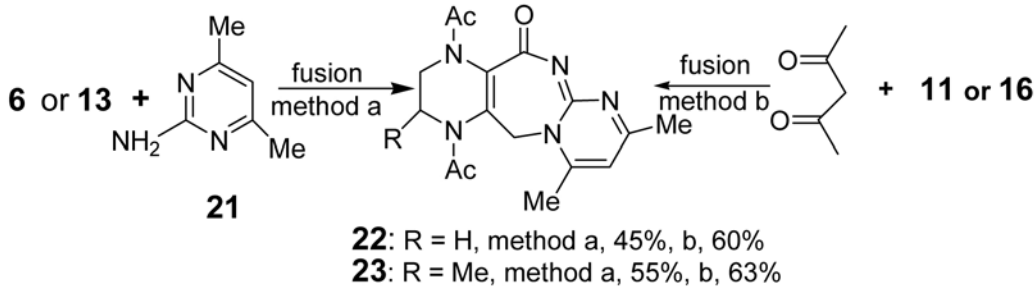
that they were soluble in water and poorly extracted into organic solvents. In addition, they decomposed on standing, so they were diacetylated with acetic anhydride and zinc to compounds **20** and **20a**, respectively (Scheme 2). The 2-C amino group of 1,2-diaminopropane moiety is sterically more hindered than the 1-C amino group, so we proposed that it would add to a carbonyl carbon of the ethyl-α-bromoacetoacetate and produce 5-methylpyrazine derivative **18a**, rather than its alternative isomer **19** (Scheme 2). Bromination of compounds **20** and **20a** with *N*-bromosuccinimide[7] in the presence of dibenzoylperoxide as a catalyst in carbon tetrachloride afforded the bromomethyl pyrazine derivatives **6** and **13**, respectively.

The fused tricyclic ring systems containing pyrazino-pyrimido[1,3]diazepine moiety (i.e. **22** or **23**) were synthesized in a similar procedure, by direct condensation of bromomethyl pyrazines **6** and **13** with 2-amino-4,6-dimethylpyrimidine **21** (method a). A different procedure (method b) involved condensation of acetylacetone with the aminopyrazino[1,3]diazepines **11** or **16** (Scheme 3).

The other pyrazinodiazepine isomer **5** was prepared as shown in Scheme 4. For this, the 1,2-diamine compound reacts with dimethylacetylene dicarboxylate[8] to yield the amide pyrazine derivatives **24** and **25**, via addition of one amino group to the triple bond and condensation of the other one with the ester group, which is present on the same side. The ^{1}H NMR spectra of compounds **24** and **25** showed the presence of vinylic proton signals as singlet at δ 5.28 and 5.17 ppm, respectively, in addition to two different NH protons. The structure of 5-



Scheme 2

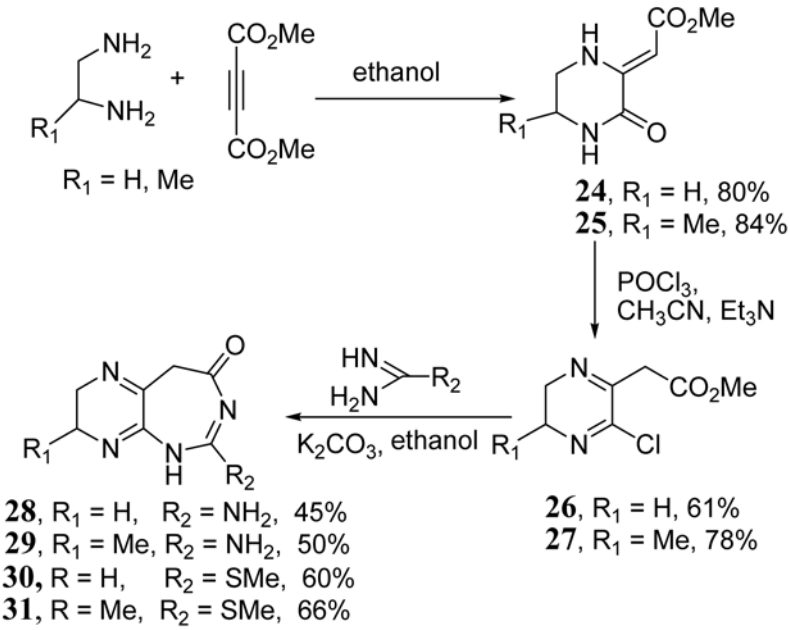


Scheme 3

methylpyrazine derivative **25** was confirmed by 2D ^{1}H NMR (COSY). The 1-NH, at δ 3.34 ppm, makes a weak interaction with 6-C-β-hydrogen at δ 3.45 ppm, this illustrating the presence of a CH_2 moiety in the piperazine ring beside 4-NH, and confirming the proposed structure **25**. Reaction of the amide carbonyl group of compounds **24** and **25** with phosphorous oxychloride gave the chloro derivatives **26** and **27**, respectively. The ^{1}H NMR spectra for latter compounds showed the disappearance of both NH and vinylic protons (in contrast with the starting materials **24** and **25**) and the presence of allylic activated methylene protons at δ 2.55 and 2.35 ppm, which revealed the existence of the tautomeric forms **26** and **27**. IR absorption showed the upfield carbonyl ester at a frequency of 1720 cm^{-1} and disappearance of the amide carbonyl absorption. Condensation of the chloroester derivatives **26** and **27** with guanidine nitrate yielded the aminopyrazino[1,3]diazepines **28** and **29**, respectively. Both compounds **28** and **29** showed the presence of two different signals for enaminic protons (NH_2 and NH) in their ^{1}H NMR spectra. In addition, further condensation of the chloro derivatives **26** and **27** with *S*-methylisothiourea sulphate provided the methylthiopyrazino[1,3]diazepine derivatives **30** and **31**, respectively. The ^{13}C NMR spectra for compounds **28**, **29**, **30** and **31** also showed the upfield shift of 4-C for carbonyl group at δ 205.6, 203.1, 210.4 and 209.2 ppm, respectively. The ^{1}H NMR spectra for the methylthio pyrazino-diazepines **30** and **31**, revealed the presence of the SMe protons at δ 2.22 and 2.15 ppm, respectively.

3. Conclusion

In conclusion, we have presented a facile route to pyrazino[2,3-*e*][1,3]diazepin-5-one derivatives **11**, **12**, **16** and **17** and pyrazino[2,3-*d*][1,3]diazepin-4(5*H*)-one derivatives **28**, **29**, **30** and **31** with amidate functions starting from the condensation of haloester and guanidine or *S*-methylisothiourea. Moreover, pyrazino[1,3]diazepine derivatives **11**, **16**, **28** and **29** with aminal functional group will open access for further structure-activity studies.



Scheme 4

4. Experimental

Silica gel plates (Merck F, 254) and silica gel 60 (Merck, 70–230 mesh) were used for TLC and column chromatography, respectively. Melting points were determined on a Gallenkamp melting point apparatus. Microanalyses were performed with a Perkin-Elmer 260 elemental analyzer for C, H, and N, and the results were within ±0.4% of the theoretical values. The IR spectra were recorded with a Perkin-Elmer 1420 spectrometer in nujol mulls for the solids and mixed with KBr in case of liquids, , wavenumbers are expressed in cm^{-1}, of maximum absorption peaks. The ^1H NMR spectra were recorded with Varian EM 390 instrument at 200 MHz, the two dimensional spectra (^1H–^1H COSY) were taken at 500 MHz and ^{13}C NMR at 50 MHz. The chemical shifts are reported in δ (ppm). All the exchangeable protons were confirmed by the addition of D_2O. Beside standard abbreviations, dm is used for double multiplets.

Ethyl 1,4-diacetyl-1,4,5,6-tetrahydro-3-methylpyrazine-2-carboxylate (20).

1,2-Diaminoethane (0.6 g, 0.01 mol) in tetrahydrofuran (5 mL) was added to a solution of ethyl-α-bromoacetoacetate (2.09 g, 0.01 mol) in tetrahydrofuran (20 mL) and sodium carbonate (3.0 g) at –20 °C during 15 min. The reaction mixture was stirred for 4 h, then the temperature was raised and the room temperature was mantained for 8 h. The reaction mixture was filtered, dried over anhydrous sodium sulphate and evaporated *in vacuo*. The crude material was dissolved in acetic anhydride (30 mL) and zinc (5 g) was added and reaction mixture was refluxed for 6 h. The reaction mixture was poured in water (50 mL), extracted with chloroform, washed with water (3 × 20 mL), dried over anhydrous sodium sulphate and evaporated *in vacuo* to give crude product **20**. It was purified on column chromatography (ethyl acetate: petroleum ether 10%) and recrystallized from ethyl acetate to give pure product **20** (1.5 g, 59%). Mp 190 °C. IR ν_{max} 1640 (C=O, amide), 1690 (C=O, vinyl ester). ^1H NMR ($CDCl_3$) δ 1.2–1.3 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$), 1.75 (3H, s, 3-CH_3), 2.12 (3H, s, CH_3, 4-$NCOCH_3$), 2.43 (3H, s, 1-$NCOCH_3$), 3.12–3.43 (4H, m, 5-CH_2, 6-CH_2), 4.13 (2H, q, J = 7.1 Hz, $CO_2CH_2CH_3$). ^{13}C NMR δ 171.1, 170.0, 169.2, 126.2, 110.3, 65.5, 49.3, 48.1, 22.0, 22.1, 15.7, 13.6. Anal. Calcd for $C_{12}H_{18}N_2O_4$ (254.282): C, 56.68; H, 7.13; N, 11.02. Found: C, 56.75; H, 7.22; N, 11.12.

Ethyl 1,4-diacetyl-1,4,5,6-tetrahydro-3,5-dimethylpyrazine-2-carboxylate (20a).

The same procedure as described for compound **20**, yielding 1.7 g of **20a** (63%). Mp 143–146 °C. IR ν 1710 (C=O, ester), 1650 (C=O, acetyl) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.27 (6H, m, $CO_2CH_2CH_3$, 5-CH_3), 2.01 (3H, s, 4-$NCOCH_3$), 2.10 (3H, s, 1-$NCOCH_3$), 2.80 (3H, s, 3-CH_3), 3.40–3.67 (2H, 2 × m, J = 6.1 Hz, J = 10.1 Hz, 6-CH_2), 3.7 (2H, q, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.80 (1H, m, J = 10.1 Hz, 5-H). ^{13}C NMR δ 171.7, 170.7, 170.2, 125.2, 105.5, 64.2, 63.2, 47.5, 23.2, 22.4,18.4, 15.5, 13.3. Anal. Calcd for $C_{13}H_{20}N_2O_4$ (268.309): C, 58.19; H, 7.51; N, 10.44. Found: C, 58.43; H, 7.32; N, 10.11.

Ethyl 1,4-diacetyl-3-(bromomethyl)-1,4,5,6-tetrahydro pyrazine-2-carboxylate (6)

A mixture of allylic compound **20** (2.54 g, 0.01 mol), *N*-bromosuccinimide (2.1 g, 0.012 mol) and dibenzoyl peroxide (0.01 g, catalyst) in carbon tetrachloride (20 mL) was irradiated with a lamp (60 W) for 8 h. Cold water (50 mL) and chloroform (50 mL) were added and the organic layer was separated, washed with cold water (3 × 20 mL), dried over anhydrous sodium sulphate and evaporated *in vacuo* to give pure product **6** (2.1 g, 65%). Mp 110 °C. IR ν_{max} 1640 (CO, amide), 1700 (CO, ester). ^1H-NMR (DMSO-d_6) δ 1.2–1.3 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$), 2.12 (3H, s, 1-$NCOCH_3$), 2.23 (3H, s, 4-$NCOCH_3$), 3.12–3.43 (4H, m, 5-CH_2, 6-CH_2), 3.9 (2H, s, CH_2Br), 4.13 (2H, q, J = 7.1 Hz, $CO_2CH_2CH_3$). ^{13}C NMR δ 180.2, 172.4, 170.7, 140.4, 136.3, 70.7, 50.5, 50.3, 34.2, 30.1, 24.2, 16.6. Anal. Calcd for $C_{12}H_{17}BrN_2O_4$ (333.178): C, 43.26; H, 5.14; Br, 23.98; N, 8.41. Found: C, 43.44; H, 5.20; Br, 24.00; N, 8.54.

Ethyl 1,4-diacetyl-3-(bromomethyl)-1,4,5,6-tetrahydro -5-methylpyrazine-2-carboxylate (13).

The same procedure as described for compound **6**, yielding 2.6 g of **13** (75%). Mp 116 °C. IR ν 1720 (C=O, ester), 1660 (C=O, acetyl) cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.33 (6H, m, $CO_2CH_2CH_3$, 5-CH_3), 2.22 (3H, s, 4-$NCOCH_3$), 2.25 (3H, s, 1-$NCOCH_3$), 3.34–3.45 (2H, 2 × m, J = 6.1 Hz, J = 10.1 Hz, 6-CH_2), 3.88 (2H, q, J = 7.1 Hz, $CO_2CH_2CH_3$) 4.00 (1H, m, 5-H), 4.30 (2H, s, CH_2Br). ^{13}C NMR δ 177.8, 173.2, 171.0, 139.0, 133.2, 69.2, 64.2, 48.8, 33.4, 28.8, 23.2, 20.1, 16.2. Anal. Calcd for $C_{13}H_{19}BrN_2O_4$ (347.205): C, 44.97; H, 5.52; Br, 23.01; N, 8.07. Found: C, 45.23; H, 5.32; Br, 23.25; N, 8.25.

Methyl 2-(3-oxopiperazin-2-ylidene)acetate (24).

A solution of dimethylacetylene dicarboxylate (7.1 g, 0.05 mol) in absolute ethanol (20 mL) was added to a solution of 1,2-diaminoethane (3.0 g, 0.05 mol) in absolute ethanol (20 mL) dropwise during 30 min with stirring at room temperature. The reaction mixture was further stirred for 4 h and the white precipitate was filtered off. The product was crystallized from ethanol to give pure piperazino-ester derivative **24** (6.8 g, 80%). Mp 170 °C. IR ν 3450 (sh., NH), 1705 (C=O, ester), 1675 (C=O, amide) cm^{-1}. ^1H NMR (DMSO-d_6) δ 3.38–3.48 (4H, m, 5-CH_2, 6-CH_2), 3.63 (3H, s, CO_2CH_3), 5.28 (1H, s, vinylic), 8.42 (1H, br, 4-NH, exch.), 8.51 (1H, br, 1-NH, exch.). Anal. Calcd for $C_7H_{10}N_2O_3$ (170.166): C, 49.41; H, 5.92; N, 16.46. Found: C, 49.63; H, 6.15; N, 16.26.

Methyl 2-(5-methyl-3-oxopiperazin-2-ylidene)aceta te (25).

The same procedure as described for compound **24**, yielding 7.4 g of **25** (84%). Mp 205–207 °C. IR ν 3450 (sh., NH), 1700 (C=O, ester), 1680 (C=O, amide) cm^{-1}. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ 1.05 (3H, d, J = 7.1 Hz, CH_3), 2.92 (1H, t, J = 6.1 Hz, 6-H_α), 3.34 (1H, br, 1-NH, exch.), 3.36–3.45 (1H, dd, J = 6.1 Hz, J = 10.1 Hz, 6-H_β), 3.52 (3H, s, CO_2CH_3), 3.57 (1H, m, 5-H), 5.17 (1H, s, vinylic), 8.28 (1H, br, 4-NH, exch.). ^{13}C NMR δ 170.8, 165.5, 158.5, 110.5, 54.3, 63.3, 50.5, 19.5. Anal. Calcd for $C_8H_{12}N_2O_3$ (184.192): C, 52.17; H, 6.57; N, 15.21. Found: C, 52.33; H, 6.72; N, 15.43.

Methyl 2-(3-chloro-5,6-dihydropyrazin-2-yl)acetate (26).

A mixture of the oxopiperazino-acetate derivative **24** (1.7 g, 0.01 mol), phosphorus oxychloride (5 mL, excess) and triethylamine (10 mL, excess) in acetonitrile (20 mL) was stirred at room temperature for 1 h. It was refluxed for 4 h and after cooling poured into cold water and the yellowish white precipitate was separated. The precipitate was triturated with diethyl ether (5 × 10 mL) to give the pure product **26** (1.1 g, 61%). Mp 80–82 °C. IR ν 3400 (sh., NH), 1720 (C=O, ester) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.55 (2H, s, CH_2CO$_2$Me), 3.44–3.56 (4H, 2 × m, 5-CH_2, 6-CH_2), 3.85 (3H, s, CO_2CH_3). ^{13}C NMR δ 175.5, 173.3, 171.2, 60.6, 59.3, 52.5, 32.6. Anal. Calcd for $C_7H_9ClN_2O_2$ (188.612): C, 44.58; H, 4.81; Cl, 18.80; N, 14.85. Found: C, 44.88; H, 4.58; Cl, 18.63; N, 15.22.

Methyl 2-(3-chloro-5,6-dihydro-5-methylpyrazin-2-yl) acetate (27).

The same procedure as described for compound **26**, yielding 1.6 g of **27** (78%). Mp 105–110 °C. IR ν 3400 (sh., NH), 1716 (C=O, ester) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.35 (3H, d, J = 7.1 Hz, 5-CH_3), 2.35 (2H, s, CH_2CO$_2$Me), 3.20 (1H, m, J = 6.1 Hz, 6-H_α), 3.60 (1H, m, J = 10.1 Hz, 6-H_β), 3.80 (3H, s, CO_2CH_3), 4.65 (1H, m, 5-H). ^{13}C NMR δ 174.3, 173.1, 170.7, 59.0, 58.6, 50.5, 32.0, 20.3. Anal. Calcd for $C_8H_{11}ClN_2O_2$ (202.638): C, 47.42; H, 5.47; Cl, 17.50; N 13.82. Found: C, 47.66; H, 5.23; Cl, 17.30; N, 13.43.

General procedure for the reaction between pyrazinoha loester and guanidine nitrate or *S*-methylisothiourea sulphate.

A mixture of pyrazino-haloester (0.01 mol), guanidine nitrate (1.22 g, 0.01 mol), or *S*-methylisothiourea sulphate (1.88 g, 0.01 mol) and potassium carbonate (3.0 g, 0.03 mol) in absolute ethanol (30 mL) were refluxed for 8 h. The obtained mixture was poured into cold water (75 mL) and the precipitate was filtered off. The pure material was obtained by recrystalization from ethanol (90%).

1,4-Diacetyl-7-amino-1,2,3,4,8,9-hexahydropyrazino [2,3-*e*][1,3]diazepin-5-one (11).

Yielding 1.7 g of **11** (64%). Mp 173–180 °C. IR ν 3350 (br, NH_2), 1690 (C=O, C-5), 1650 (C=O, acetyl, N-4), 1640 (C=O, acetyl, N-1) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 2.02 (3H, s, 1-NCOCH_3), 2.10 (3H, s, 4-NCOCH_3), 3.22–3.44 (4H, 2 × m, 2-CH_2, 3-CH_2), 4.45 (2H, s, 9-CH_2), 7.45 (2H, br, exch., 7-NH_2), 7.65 (1H, br, exch., 8-NH). ^{13}C NMR δ 197.7, 171.0, 170.6, 165.6, 135.5, 115.5, 51.6, 51.4, 40.4, 22.8, 21.4. Anal. Calcd for $C_{11}H_{15}N_5O_3$ (265.269): C, 49.81; H, 5.70; N, 26.40. Found: C, 50.10; H, 5.66; N, 26.23.

1,4-Diacetyl-7-amino-1,2,3,4,8,9-hexahydro-2-methyl pyrazino[2,3-*e*][1,3]diazepin-5-one (16).

Yielding 1.54 g of **16** (52%). Mp 220–225 °C. IR ν 3350 (br, NH_2), 1685 (C=O, C-5), 1640 (C=O, acetyl, N-4), 1635 (C=O, acetyl, N-1) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 1.3 (3H, d, J = 7.1 Hz, 2-CH_3), 2.00 (3H, s, 1-NCOCH_3), 2.10 (3H, s, 4-NCOCH_3), 3.35–3.50 (2H, 2 × m, 3-CH_2), 4.10 (1H, m, 2-H), 4.32 (2H, s, 9-CH_2), 7.50 (2H, br, exch., 7-NH_2), 7.60 (1H, br, exch., 8-NH). ^{13}C NMR δ 201.0, 170.5, 168.9, 165.5, 134.5, 116.4, 60.6, 46.8, 40.2, 22.5, 21.2, 18.2. Anal. Calcd for $C_{12}H_{17}N_5O_3$ (279.295): C, 51.60; H, 6.14; N, 25.08. Found: C, 51.50; H, 6.33; N, 25.32.

2-Amino-7,8-dihydro-1*H*-pyrazino[2,3-*d*][1,3]diazepin -4(5*H*)-one (28).

Yielding 0.8 g of **28** (45%). Mp 215–218 °C. IR ν 3300 (br, NH_2), 1680 (C=O, C-4) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 2.85 (2H, s, 5-CH_2), 3.50–3.75 (4H, 2 × m, 7-CH_2, 8-CH_2), 7.48 (2H, br, exch., 2-NH_2), 7.85 (1H, br, exch., 1-NH). ^{13}C NMR δ 205.6, 171.5, 170.4, 168.1, 55.2, 50.3, 30.3. Anal. Calcd for $C_7H_9N_5O$ (179.179): C, 46.92; H, 5.06; N, 39.09. Found: C, 46.61; H, 5.32; N, 39.29.

2-Amino-7,8-dihydro-8-methyl-1*H*-pyrazino[2,3-*d*][1, 3]diazepin-4(5*H*)-one (29).

Yielding 0.96 g of **29** (50%). Mp 240–245 °C. IR ν 3300 (br, NH_2), 1680 (C=O, C-4) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 1.33 (3H, d, J = 7.1 Hz, 8-CH_3), 2.80 (2H, s, 5-CH_2), 3.20–3.40 (2H, 2 × m, J = 6.1 Hz, J = 10.1 Hz, 7-CH_2), 4.10 (1H, m, J = 10.1 Hz, 8-H), 7.50 (2H, br, exch., 2-NH_2), 7.60 (1H, br, exch., 1-NH). ^{13}C NMR δ 203.1, 168.3, 166.7, 169.5, 60.2, 48.1, 29.8, 20.3. Anal. Calcd for $C_8H_{11}N_5O$ (193.206): C, 49.73; H, 5.74; N, 36.25. Found: C, 49.60; H, 5.55; N, 36.45.

1,4-Diacetyl-1,2,3,4,8,9-hexahydro-7-(methylt- hio)pyrazino[2,3-*e*][1,3]diazepin-5-one (12).

Yielding 1.77 g of **12** (60%). Mp 170 °C. IR ν 3350 (sh., NH), 1692 (C=O, C-5), 1654 (C=O, acetyl, N-4), 1645 (C=O, acetyl, N-1) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 2.00 (3H, s, 1-NCOCH_3), 2.11 (3H, s, 4-NCOCH_3), 2.24 (3H, s, SCH_3), 3.20–3.40 (4H, m, 2-CH_2, 3-CH_2), 4.33 (2H, s, 9-CH_2), 7.75 (1H, br., exch., 8-NH). ^{13}C NMR δ 198.4, 170.8, 170.3, 170.1, 166.1, 137.2, 51.5, 51.0, 42.4,

21.3, 22.7, 15.3. Anal. Calcd for $C_{12}H_{16}N_4O_3S$ (296.345): C, 48.64; H, 5.44; N, 18.91; S, 10.82. Found: C, 48.33; H, 5.34; N, 18.66; S, 10.63.

1,4-Diacetyl-1,2,3,4,8,9-hexahydro-2-methyl-7-(methylthio)pyrazino[2,3-*e*][1,3]diazepin-5-one (17).

Yielding 2.2 g of **17** (70%). Mp 195 °C. IR ν 3350 (sh., NH), 1690 (C=O, C-5), 1640 (C=O, acetyl, N-1), 1635 (C=O, acetyl, N-4) cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.28 (3H, d, J = 7.1 Hz, 2-CH_3), 2.07 (3H, s, 1-$NCOCH_3$), 2.12 (3H, s, 4-$NCOCH_3$), 2.20 (3H, s, SCH_3), 3.30–3.45 (2H, 2 × m, 3-CH_2), 4.20 (1H, m, 2-H), 4.52 (2H, s, 9-CH_2), 7.73 (1H, br, exch., 8-NH). ^{13}C NMR δ 199.3, 170.9, 169.2, 168.1, 135.1, 116.8, 60.9, 47.1, 41.4, 21.5, 22.6, 18.3, 15.2. Anal. Calcd for $C_{13}H_{18}N_4O_3S$ (310.372): C, 50.31; H, 5.85; N, 18.05; S, 10.33. Found: C, 50.51; H, 5.66; N, 18.11; S, 10.23.

7,8-Dihydro-2-(methylthio)-1*H*-pyrazino[2,3-*d*][1,3]diazepin-4(5*H*)-one (30).

Yielding 1.26 g of **30** (60%). Mp 210–212 °C. IR ν 3400 (sh., NH), 1685 (C=O, C-4) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.22 (3H, s, SCH_3), 2.65 (2H, s, 5-CH_2), 3.35–3.65 (4H, 2 × m, 7-CH_2, 8-CH_2), 4.66 (2H, s, 5-CH_2), 8.66 (1H, br, exch., 1-NH).^{13}C NMR δ 210.4, 170.2, 169.2, 166.6, 59.1, 48.8, 29.3, 15.3. Anal. Calcd for $C_8H_{10}N_4OS$ (210.256): C, 45.70; H, 4.79; N, 26.65; S, 15.25. Found: C, 45.34; H, 4.54; N, 26.76; S, 15.33.

7,8-Dihydro-8-methyl-2-(methylthio)-1*H*-pyrazino[2,3-*d*][1,3]diazepin-4(5*H*)-one (31).

Yielding 1.48 g of **31** (66%). Mp 230–233 °C. IR ν 3400 (sh, NH), 1660 (C=O, C-4) cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.33 (3H, d, J = 7.1 Hz, 8-CH_3), 2.15 (3H, s, SCH_3), 2.55 (2H, s, 5-CH_2), 3.11–3.33 (2H, 2 × m, J = 6.1 Hz, J = 10.1 Hz, 7-CH_2), 4.00 (1H, m, J = 10.1 Hz, 8-H), 7.88 (1H, br, exch., 1-NH).^{13}C NMR δ 209.2, 168.0, 167.5, 165.8, 59.3, 48.0, 28.1, 20.1, 15.1. Anal. Calcd for $C_9H_{12}N_4OS$ (224.283): C, 48.20; H, 5.39; N, 24.98; S, 14.30. Found: C, 48.43; H, 5.40; N, 24.77; S, 14.35.

1,4-Diacetyl-8,10-dimetyhl-1,2,3,4,11-pentahydropyrazino[2,3-*e*]-pyrimido[1,2-*a*][1,3]diazepin-5-one (22).

Method a. Fusion of the pyrazinobromoester derivative **6** (0.9 g, 0.003 mol) with 2-amino-4,6-dimethylpyrimidine (0.34 g, 0.003 mol) was carried out in an oil bath (140 °C) for 3 h. The residue was then dissolved in absolute ethanol (5 mL) and poured into a cold solution of sodium carbonate. The precipitate was collected and recrystallized from mixture of *N*,*N*-dimethylformamide and water (3:1) to give pure product **22** (0.44 g, 45%). Mp >300 °C. IR ν 1680 (C=O, C-5), 1660 (C=O, acetyl, N-4), 1650 (C=O, acetyl, N-1) cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.72 (3H, s, 10-CH_3), 1.92 (3H, s, 8-CH_3), 2.11 (3H, s, 1-$NCOCH_3$), 2.20 (3H, s, 4-$NCOCH_3$), 3.33–3.54 (4H, dm, 2-CH_2, 3-CH_2), 4.82 (2H, s, 11-CH_2), 6.54 (1H, s, 9-H).^{13}C NMR δ 202.4, 177.8, 176.1, 171.8, 169.3, 162.3, 138.2, 118.1, 105.5, 50.3, 49.9, 44.5, 25.2, 23.5, 21.4, 21.1. Anal. Calcd for $C_{16}H_{19}N_5O_3$ (329.354): C, 58.35; H, 5.81; N, 21.26. Found: C, 58.55; H, 6.00; N, 21.30.

Method b. Fusion of the aminopyrazino-diazepine derivative **11** (1.33 g, 0.005 mol) with acetylacetone (0.5 g, 0.005 mol) and anhydrous sodium acetate (1.65 g, 0.02 mol) was carried out in an oil bath (140 °C) for 8 h. The residue was then dissolved in absolute ethanol (8 mL) and poured into cold water. The precipitate was collected and recrystallized from mixture of *N*,*N*-dimethylformamide and water (3 : 1) to give pure product identical to the compound **22** (same TLC and IR, 0.98 g, yield 60%).

1,4-Diacetyl-2,8,10-trimetyhl-1,3,4,11-tetrahydropyrazino[2,3-*e*]-pyrimido[1,2-*a*] [1,3]diazepin-5-one (23).

Same procedures as for compound **22**; *method a* gave 0.56 g (55%) of the compound **23**, whereas the *method b* gave 1.0 g (63%) of the same compound **23** (TLC and IR). Mp >300 °C. IR ν 1680 (C=O, C-5), 1660 (C=O, acetyl, N-4), 1650 (C=O, acetyl, N-1) cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.13 (3H, d, J = 7.1 Hz, 2-CH_3), 1.68 (3H, s, 10-CH_3), 1.90 (3H, s, 8-CH_3), 2.00 (3H, s, 1-$NCOCH_3$), 2.10 (3H, s, 4-$NCOCH_3$), 3.30–3.40 (2H, dm, 3-CH_2), 4.12 (1H, m, 2-H), 4.80 (2H, s, 11-CH_2), 6.44 (1H, s, 9-H). ^{13}C NMR δ 200.2, 175.8, 175.5, 171.3, 170.3, 169.9, 136.2, 116.6, 101.2, 60.6, 47.5, 42.5, 24.8, 22.5, 21.0, 20.8, 18.1. Anal. Calcd for $C_{17}H_{21}N_5O_3$ (343.38): C, 59.46; H, 6.16; N, 20.40. Found: C, 59.50; H, 6.10; N, 20.33.

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Povzetek

S pripajanjem diazepinskega obroča na že v naprej pripravljene pirazinske derivate so bili sintetizirani nekateri novi pirazino[1,3]diazepinski ciklični sistemi. V ta namen so bili pripravljeni različni novi, kot tudi že znani, pirazinski derivati. Produkti bi morda lahko učinkovali kot nepeptidni antagonisti IL-8 receptorjev z majhno molekulsko maso.