Tetrahedron 66 (2010) 2514–2519

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A traceless solid-supported synthesis of novel pyrazinediazepinedione derivatives

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ARTICLE INFO

Article history:
Received 29 July 2009
Received in revised form 9 December 2009
Accepted 18 January 2010
Available online 22 January 2010

ABSTRACT

A simple, convenient, six-step synthesis of novel, tricyclic pyrazinebenzodiazepinedione derivatives has been described. The strategy is based on the use of the orthogonally-protected, optically pure, (*S*)-piperazine-2-carboxylic acid, in a Petasis reaction, followed by coupling with anthranilic acid and finally cyclizing cleavage. The investigated method was applied for the synthesis of novel bicyclic pyrazinediazepinedione derivatives. This traceless, solid-supported approach allows the preparation of a wide variety of compounds in moderate yields from commercially available or easily obtainable reagents.

1. Introduction

Due to their biological and pharmacological activities, a large number of tricyclic and tetracyclic benzodiazepine derivatives have been synthesized recently. Much synthetic effort has been directed toward the synthesis of benzodiazepines condensed to various heterocyclic rings, such as: triazole,[1] tetrazole,[2] imidazole,[3] isoindole,[4] pyridine,[5] pyrimidine,[6] isoxazole,[7] or pyrrole.[8] Just recently,[9] a novel group of pyrazinebenzodiazepine derivatives, such as **1** (Fig. 1) was identified as potent antagonists of the vasopressin receptor.

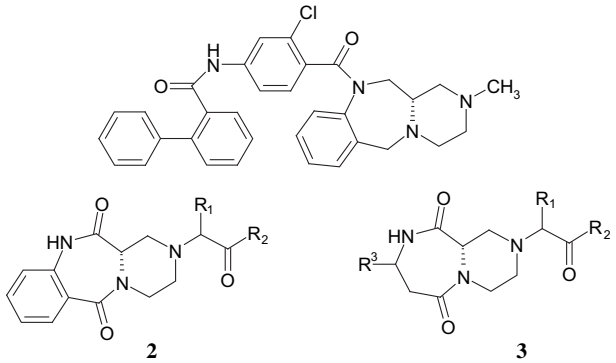
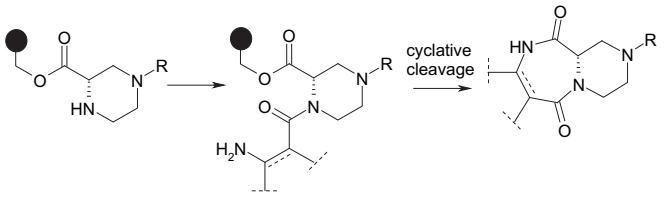


Figure 1.

The compound **1** binds to human V2 receptors with a high affinity and is very selective with respect to V1a receptors, consequently exhibiting a pronounced aquaretic activity. These properties motivated us to investigate the synthetic routes to novel pyrazinebenzodiazepines of type **2**.

The preparation of small molecules on solid phase appears to be an expedient method, being utilized to generate compounds for screening against biological systems, and to enhance the drug discovery effort.[10] Multi-component reactions (MCR) are especially attractive for automated parallel synthesis and prove to be powerful tools for producing diverse arrays of compounds, often in one step and high yield.[11] The time- and cost-saving advantage of an efficient MCR over an equivalent multi-step linear synthesis is obvious and is the driving force behind the recent resurgence of their studies.

We report here a novel, solid-phase synthesis of 1,4-benzodiazepine derivatives containing the 1,2,3,4,6,11,12,12a-octahydrobenzo[*e*]pyrazin[1,2-*a*][1,4]diazepin-6,12-dione core **2** (Scheme 1). Surprisingly, only one research group has reported the synthesis of such compounds and their analogs to date.[9,12a–c] While extending the developed method, we also investigated the synthetic availability of compounds possessing the perhydropyrazine[1,2-*a*][1,4]diazepine-6,12-dione core **3** (Scheme 1). To the best of our knowledge, these compounds have not been described in the literature yet.



Scheme 1. Construction of bi- and tricyclic pyrazinediazepinedione ring systems **2** and **3**.

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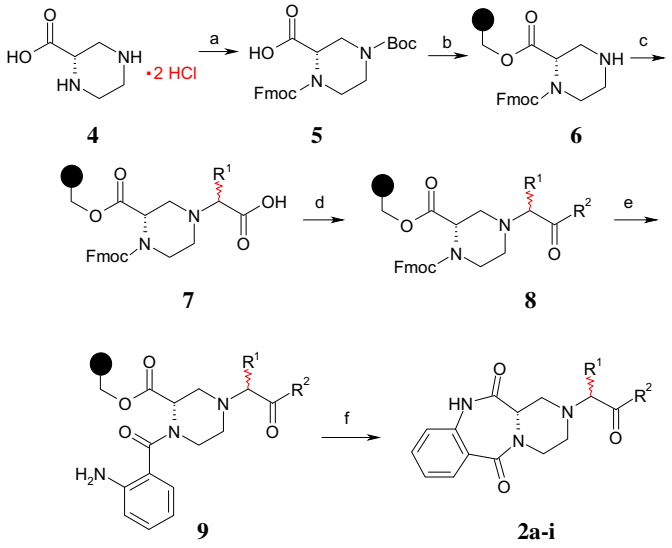
doi:10.1016/j.tet.2010.01.064

2. Results and discussion

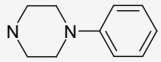
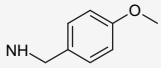
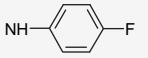
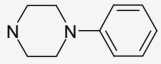
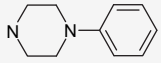
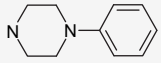
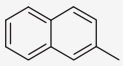
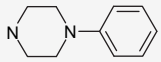
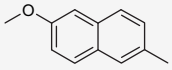
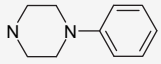
We started our research by synthesizing the pyrazinebenzodiazepines of type **2**. The presented synthetic route assumes the use of optically pure (*S*)-piperazine-2-carboxylic acid hydrochloride (**3**) as a main substrate, which is converted into an appropriate resin-bound amino derivative **4** (Scheme 2). We decided to involve the three-component Petasis condensation to extend the side chains, followed by the coupling of anthranilic acid and cyclizing cleavage, leading to the desired compounds **2**. It was reported that the coupling with anthranilic acid proceeded smoothly in the presence of carbodiimides, and no additional protection of the aromatic amine group was required.[13] Based on these results, we suggested the synthetic route to the fused heterocyclic system **2** (Scheme 2).



Scheme 2. Reagents and conditions: (a) (i) Boc_2O, $NaOH_{aq}$, dioxane:H_2O 2:1, 0 °C→rt, then FmocCl, Na_2CO_3; (b) (i) 4-hydroxymethyl polystyrene resin DEAD, Ph_3P, THF:CH_2Cl_2 3:1, 0 °C→rt; (ii) 40% TFA in CH_2Cl_2; (c) OHC–COOH·H_2O, R_1-$B(OH)_2$, CH_2Cl_2–MeOH 4:1, rt; (d) DIC, HOBt, R′R″NH, DMF; (e) (i) 10% piperidine in DMF, rt; (ii) DIC, HOBt, o-NH_2–Ph–COOH, DMF, rt; (f) 20% CH_3COOH in *i*-PrOH, 65 °C.

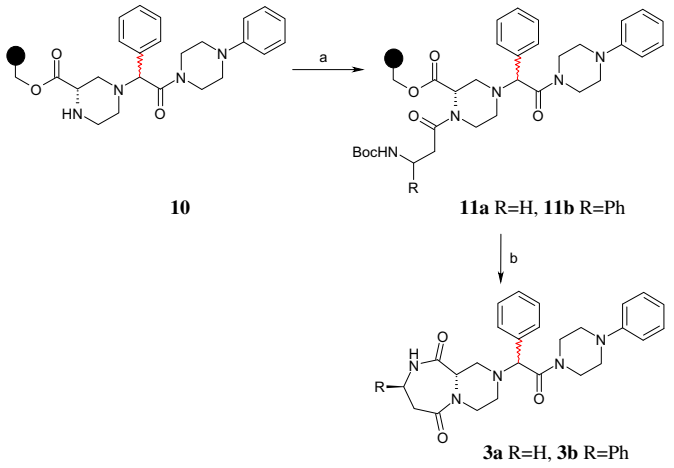
The solid-supported synthesis could facilitate and improve the multi-step syntheses of complex organic molecules, although with some limitations and disadvantages. All by-products, generated in the previous steps of the synthesis, would be cleaved in the final step along with the required product, giving a mixture of various compounds. Consequently, the purification of final product would extend the time of synthesis. We assumed that, in the projected synthesis, only the cyclic product would be cleaved from resin, and the non-cyclized intermediates would not be detached from the solid support. Before the coupling with the 4-hydroxymethyl polystyrene resin, (*S*)-piperazine-2-carboxylic acid was orthogonally protected with two different protecting groups (Boc, Fmoc), giving the intermediate **5**, and then attached to the resin by the ester linkage. In this step, we decided to use the Mitsunobu reaction,[14] which was a very useful procedure for synthesis of esters. The elemental analysis of resin with attached amino acid showed 1.55% of N, which corresponds to 0.74 mmol/g of resing loading (90% yield). In the next step, in order to remove the Boc protecting group, the solid phase was treated with a solution of TFA. This deprotected the β-nitrogen atom of the piperazine-2-carboxylic acid and led to the monoprotected amino derivative **6**, which was used in the next step as an amine substrate for the Petasis reaction. The Petasis product **7** was treated with a DIC/HOBt mixture and then the appropriate amine was added to yield the amide derivative **8**. In order to deprotect the remaining α-nitrogen atom, the intermediate **8** was then treated with a piperidine solution. Then the anthranilic acid activated with DIC/HOBt was added to give the amino derivative **9**. The final step, the cyclizing cleavage, proceeded smoothly at 65 °C in the presence of 20% CH_3COOH in *i*-PrOH. When either the temperature or the concentration was lower than recommended, a significant decrease of yield was observed. Several amines and boronic acids were also applied for the studied synthesis. The obtained results are summarized in Table 1. Obtained yields were calculated based on the loading of the resin with (*S*)-piperazine-2-carboxylic acid.

Table 1
Syntheses of the pyrazinebenzodiazepinones **2**

Product No.	R^1	R^2	Crude yield [%]	Purified yield [%]
2a	Ph		38	24
2b	Ph		50	24
2c	Ph		48	28
2d	Ph		48	22
2e	4-Et-Ph		61	33
2f	4-MeO-Ph		58	32
2g			69	26
2h			75	36
2i			63	21

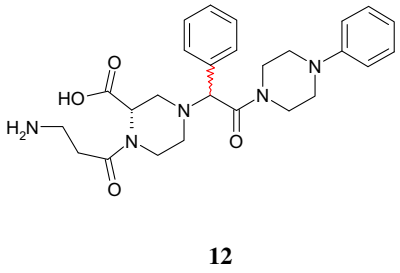
The synthesized tricyclic pyrazinebenzodiazepine derivatives possess two stereogenic centers: the first one originates from the optically-pure chiral substrate and the second one is created in the Petasis reaction. For this reason, all the described compounds were obtained as pairs of diastereomers in an equimolar ratio (based on ^{1}H NMR spectra). These pairs are inseparable by chromatographic methods and are characterized as mixtures of diastereomers. In order to assign correctly the signals in the ^{1}H NMR spectra to the appropriate protons in the molecule, additional correlation spectra (COSY, HSQC, HMBC, NOE) were taken for the selected products, these confirmed indisputably the assumed structures. In all these syntheses, after cleavage with 20% acetic acid in *i*-PrOH, we found no trace of any non-cyclized product in the reaction mixture.

In the next part of our research, we decided to use β-amino acids, which should result in formation of the bicyclic azepinedione derivatives **3**. Thus the amino derivative **10** was coupled with either Boc-protected β-alanine or β-D-phenylalanine using DIC/HOBt as a coupling agent. Further treatment of the obtained intermediate **11b** with 40% TFA followed by heating to 65 °C with 20% CH_3COOH in *i*-PrOH led to the formation of the perhydropyrazinediazepinedione **3b** in 30% total yield (63% yield of the crude product (Scheme 3)).



Scheme 3. Reagents and conditions: (a) DIC, HOBt, BocNH–CH(*R*)–CH_2–COOH, DMF, rt; (b) (i) 40% TFA in CH_2Cl_2 (ii) 20% CH_3COOH in *i*-PrOH, 65 °C.

Surprisingly, the treatment of **11a** with 40% TFA, followed by heating with 20% CH_3COOH in *i*-PrOH at 65 °C didn't result in cleavage of any product, including required **3a**. After treatment the resin with a 95:5 mixture of TFA–H_2O, a complex mixture of polar compounds was obtained. MS analysis revealed, that one of the compound possessed molecular weight 479, which suggested the formation of non-cyclized derivative **12** (Fig. 2) as a one of the products. Because of the failure of the cyclization-cleavage step and formation of complex mixture, the cyclization of β-alanine intermediate was not further investigated.



12

Figure 2.

The synthesized bicyclic pyrazinediazepine derivative **3b** possesses three stereogenic centers: two of them originate from the optically-pure chiral amino acids and the third one is created in the Petasis reaction. The compound **3b** was obtained as an equimolar pair of diastereomers (based on ^{1}H NMR spectra) inseparable by chromatographic methods. As in the case of the tricyclic pyrazinebenzodiazepines **2**, the appropriate 2D NMR spectra confirmed the structure of the desired product. No traces of other products were detected in the reaction mixture after cleavage of **3b** from the resin.

3. Conclusion and perspectives

In conclusion, a novel, traceless, solid-supported synthesis leading to the new pyrazinebenzodiazepine derivatives was developed. Using this approach, an array of new products was synthesized. The use of the Petasis reaction for the development of side chains led to the compounds having a great structural diversity. The cyclizing cleavage, applied in the last step, led to only one detectable product cleaved from the resin. This mild cleavage method left the by-products resulting from incomplete or undesired reactions on the solid support. The obtained pyrazinebenzodiazepinedione derivatives could be easily reduced to the pyrazinebenzodiazepines of type **1** using lithium borohydride.[12a,15] Additionally, the developed method could be utilized for the synthesis of benzodiazepine derivatives incorporated into cyclic peptides, since the benzodiazepine structure could stabilize the loop conformations.[16] The biological activity of the synthesized compounds will be reported in due course.

4. Experimental

4.1. General

All reagents were obtained from Fluka and Merck and were used without further purification. Dry dichloromethane (DCM) and dimethylformamide (DMF) were obtained by distillation from over calcium hydride. The optically pure (*S*)-piperazine-2-carboxylic acid was obtained from ChemPacific. The Wang resin was obtained from Novabiochem. ^{1}H and ^{13}C spectra were recorded on a Varian 500 MHz instrument using CD_3OD as a solvent, with TMS as an internal standard. The abbreviations used in the descriptions of NMR spectra are as follows: H_a—a signal from an axial proton, H_e—a signal from an equatorial proton, H_p—a signal from the piperazine substituent. All ESI-MS spectra were recorded on a Quattro LC Micromass instrument. The IR spectra were recorded on a Nicolet Magna 550 FTIR instrument. The IR band positions are reported in cm^{-1}. The preparative flash chromatographic experiments were performed using Merck Kieselgel 60, 230–400 mesh. The TLC analyses were done on Merck 60 F_{254} aluminum plates and visualized by using iodine vapor and UV light (254 nm) or by spraying with an aqueous solution of $(NH_4)_6Mo_7O_{24}$ (2.5%) and $(NH_4)_4Ce(SO_4)_4$ (1%) in 10% H_2SO_4 and heating to 110 °C. The numbering scheme of carbon atoms in the heterocyclic cores is shown in Figure 3.

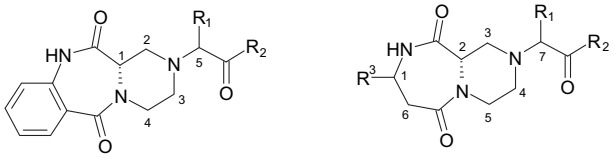


Figure 3.

4.1.1. Protection of (S)-piperazine-2-carboxylic acid. To a solution of 3.0 g (14.8 mmol) of (*S*)-piperazine-2-carboxylic acid dihydrochloride (**3**) in 30 mL of dioxane and 15 mL of water, the solution of 1.5 g of NaOH (29.6 mmol) in 5 mL of water was added slowly at 0 °C followed by 3.6 g (16.3 mmol) of di-*tert*-butyl dicarbonate. After 5 h of stirring at the rt, 1.7 g (16.0 mmol) of solid sodium carbonate and 4.7 g (18.2 mmol) of FmocCl were added, and the reaction was stirred overnight. The solvent was rotary evaporated, the obtained residue was partitioned between 100 mL of ethyl acetate and 100 mL of 1 N HCl. The organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated. The crude product was crystallized once from ethyl acetate. The yield of N_α-Fmoc-N_β-Boc-(*S*)-piperazine-2-carboxylic acid is 4.4 g (43%) as amorphous, cotton-like solid.

4.2. A typical procedure for the synthesis of the pyrazinebenzodiazepinedione derivative 2a

(a) Wang resin (1.0 g, 0.82 mmol/g, Novabiochem) was swelled in anhydrous dichloromethane (10 mL). To this slurry, triphenylphosphine (643 mg, 2.46 mmol) and N_α-Fmoc-N_β-Boc-(*S*)-piperazine-2-carboxylic acid (**4**) (111 mg, 2.46 mmol) were added, the reaction mixture was cooled to 0 °C under the argon atmosphere,

and diethyl azadicarboxylate (428 mg, 2.46 mmol) in 2 mL of THF was added slowly. The reaction was stirred for three days, then the resin was filtered off and washed with 50 mL of THF (3×), 50 mL of CH_2Cl_2 (3×), 50 mL of MeOH (3×), then alternately with CH_2Cl_2 and MeOH (3×50 mL each). The orthogonally-protected piperazinic resin ester was swelled in 10 mL of CH_2Cl_2 and then 3.3 mL of TFA was added dropwise. After one hour, the resin was filtered off and washed with 50 mL of THF (3×), 50 mL of CH_2Cl_2 (3×), 50 mL of MeOH (3×), then alternately with CH_2Cl_2 and MeOH (3×50 mL each). The resin-bound amine TFA salt was then neutralized with 10% of diisopropylethylamine in CH_2Cl_2 and washed again with 50 mL of THF (3×), 50 mL of CH_2Cl_2 (3×), 50 mL of MeOH (3×), then alternately with CH_2Cl_2 and MeOH (3×50 mL each). (b) The resin-bound amino derivative **4** was swelled in CH_2Cl_2 (10 mL), and glyoxylic acid (151 mg, 1.64 mmol) and phenylboronic acid (200 mg, 1.64 mol) in 2 mL of MeOH were added. The reaction mixture was agitated for 5 h, then filtered off and washed with CH_2Cl_2 (3×50 mL). The above procedure was repeated again for the 12 h after which the resin was filtered off again and washed again with 50 mL of THF (3×), 50 mL of CH_2Cl_2 (3×), 50 mL of MeOH (3×), then alternately with CH_2Cl_2 and MeOH (3×50 mL each). (c) The β-amino acid **6** from the previous step was swelled in dry DMF (10 mL), and HOBt (626 mg, 4.1 mmol) followed by DIC (0.63 mL, 4.1 mmol) were added. The reaction was agitated for 3 h, after which the resin was washed with dry DMF (3×50 mL). The resin was swelled again in DMF (10 mL) and to this slurry was added *N*-phenylpiperazine (0.63 mL, 4.1 mmol) and the reaction was allowed to agitate for 12 h. The intermediate **7** was filtered off and washed with DMF (3×50 mL) followed by 50 mL of THF (3×), 50 mL of CH_2Cl_2 (3×), 50 mL of MeOH (3×), then alternately with CH_2Cl_2 and MeOH (3×50 mL each). (d) The intermediate **7** was treated with 50 mL of 25% piperidine in DMF, then filtered off and washed with 50 mL of THF (3×), 50 mL of CH_2Cl_2 (3×), 50 mL of MeOH (3×), then alternately with CH_2Cl_2 and MeOH (3×50 mL each). Anthranilic acid (562 mg, 4.1 mL) was dissolved in 10 ml of dry DMF and then HOBt (626 mg, 4.1 mmol) followed by DIC (0.63 ml, 4.1 mmol) was added. The reaction mixture was agitated for 1 h; in the meantime, the resin was swelled in 10 mL of dry DMF, and to this heterogeneous slurry, the solution of the activated anthranilic acid was added. The reaction was agitated for 5 h and rinsed with dry DMF (3×50 mL) before repeating the coupling procedure for 15 h. Then the resin was filtered off and washed with 50 mL of THF (3×), 50 mL of CH_2Cl_2 (3×), 50 mL of MeOH (3x), then alternately with CH_2Cl_2 and MeOH (3×50 mL each). (e) The free amine **8** was taken up in 50 mL of 20% AcOH/*i*-PrOH and heated for 12 h at 60 °C. The resin was filtered off and washed several times with MeOH. The filtrate and washings were combined and concentrated to give a brown solid. To obtain the analytically pure samples, the crude product **2a** was purified by a column chromatography on silica gel (1–2% MeOH in $CHCl_3$). All final products were obtained as white amorphous solids.

4.3. A procedure for the synthesis of the perhydropyrazinediazepinedione derivative 3b

(a) The amino derivative **10**, was obtained by the procedure used for the synthesis of the pyrazinebenzodiazepinedione derivatives **2**. 1.09 g of Boc-protected β-D-phenylalanine (4.1 mmol) was dissolved in 10 mL of dry DMF and then HOBt (626 mg, 4.1 mmol) followed by DIC (0.63 mL, 4.1 mmol) were added. The reaction mixture was agitated for 1 h; in the meantime, the resin was swelled in 10 mL of dry DMF, and the solution of the activated amino acid was added to slurry of the amino derivative **10**. The reaction was agitated for 5 h and rinsed with dry DMF (3×50 mL) before repeating the coupling procedure for 15 h. Then the resin was filtered off and washed with 50 mL of THF (3×), 50 mL of CH_2Cl_2 (3×), 50 mL of MeOH (3×), then alternately with CH_2Cl_2 and MeOH (3×50 mL each). (b) The resin was treated with 50 mL of 25% solution of TFA in DCM for one hour in rt and washed with 50 mL of THF (3×), 50 mL of CH_2Cl_2 (3×), 50 mL of MeOH (3×), then alternately with CH_2Cl_2 and MeOH (3×50 mL each). Finally, the resin-bound intermediate was taken up in 50 mL of 10% AcOH/*i*-PrOH and heated for 12 h at 50 °C. The resin was filtered off and washed with MeOH (4×25 mL). The filtrate and washings were combined and concentrated to give a brown solid. The crude product was purified by a column chromatography on silica gel (1–2% MeOH in $CHCl_3$).

*4.3.1. (S)-2-(R)- and (S)-2-((S)-[-oxo-1-phenyl-2-(4-phenyl-piperazin-1-yl)ethyl)]-1,2,3,4-tetrahydrobenzo[e]pyrazino[1,2-a][1,4]diazepine-6,12(11H,12aH)-dione (**2a**).* Mixture of diastereomers; isolated yield: 92 mg (24%); R_f=0.39 (3% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, DMSO-d_6), δ: 7.74–7.66 (m, 1H, H_{Ar}); 7.60 (d, 1H, J=7, H_{Ar}); 7.54–7.25 (m, 4H, H_{Ar}); 7.25–7.14 (m, 5H, H_{Ar}); 7.07 (t, 1H, J=8, H_{Ar}); 6.90 (d, 2H, J=7, H_{Ar}); 6.82–6.74 (m, 1H, H_{Ar}); 4.92, 4.73 (2×s, 1H, H-5); 4.30 (t, 2H, J=11, H-4$_a$); 4.11 (d, 2H, J=3, H-4$_e$); 4.08–4.00 (m, 0.5H, H_pCH_2NC=O); 3.92–3.70 (m, 2H, H_pCH_2NC=O); 3.70–3.54 (m, 1.5H, H_pCH_2NC=O+0.5H-2$_a$); 3.54–3.42 (m, 0.5H, H_pCH_2NC=O); 3.31 (d, 0.5H, J=11.5, 0.5H-2$_a$); 3.24 (d, 0.5H, J=11.5, 0.5H-2$_e$); 3.20–2.82 (m, 5.5H, 4H_pCH_2NPh+H-3$_a$+0.5H-2$_e$); ~2.49 (dt, 0.5H, 0.5H-3$_e$, under signal DMSO); 2.46–2.36 (m, 1H, H-1); 2.27 (dt, J_1=3, J_2=11, 0.5H-3$_e$); ^{13}C NMR (125 MHz, DMSO-d_6), δ: 170.6, 170.5, 168.3, 168.0, 167.4, 167.3, 150.8, 150.6, 137.0, 136.9, 136.1, 134.3, 131.9, 130.4, 130.3, 129.7, 129.0, 128.9, 128.8, 128.1, 127.9, 127.6, 127.5, 126.5, 126.4, 123.8, 120.5, 120.4, 119.3, 119.2, 115.8, 115.7, 79.1, 68.4, 51.3, 51.2, 49.1, 48.4, 48.3, 48.1, 47.8, 47.2, 46.4, 45.0, 44.6, 41.3, 41.3; IR: 3454, 3228, 2917, 2823, 1698, 1638, 1599, 1478, 1438, 1410, 1284, 1228, 1160, 1022, 758, 698; HR ESI MS: m/z for $[M+Na]^+$ calculated: 532.2325, found: 532.2318.

*4.3.2. (S)-2-(R)- and (S)-2-((S)-2-morpholino-2-oxo-1-phenyl-ethyl)-1,2,3,4-tetrahydrobenzo[e]pyrazino[1,2-a][1,4] diazepine-6,12(11H,12aH)-dione (**2b**).* Mixture of diastereomers; isolated yield: 78 mg (24%); R_f=0.45 (3% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, CD_3OD), δ: 7.72 (t, 1H, J=7, H_{Ar}); 7.57 (d, 1H, J=7.5, H_{Ar}); 7.48 (t, 1H, J=8, H_{Ar}); 7.43 (d, 1H, J=7, H_{Ar}); 7.40–7.28 (m, 1H, H_{Ar}); 7.26–7.20 (m, 1H, H_{Ar}); 7.07 (t, 1H, J=7, H_{Ar}); 4.79, 4.77 (2×d, 1H, H-5); 4.37, 4.33 (2×d, 1H, H-4$_e$); 4.16–4.08 (m, 1H, H-4$_e$); 3.90–3.35 (m, 8.5H, 8H$_m$+0.5H-2$_a$); 3.27 (d, 0.5H, J=11.5, H-2$_a$); 3.20 (dt, 0.5H, 0.5H-3$_a$); 3.16–3.00 (m, 1H, 0.5H-2$_e$+0.5H-3$_a$); 2.89 (d, J=11.5, 0.5H, 0.5H-2$_e$); 2.70–2.60 (m, 1H, 0.5H-1+0.5H-3$_e$); 2.57 (dd, 0.5H, J_1=5.5, J_2=12.5, 0.5H-1); 2.46 (dt, J_1=4, J_2=11.5, 0.5H, H-3$_e$); ^{13}C NMR (125 MHz, CD_3OD), δ: 172.6, 172.3, 171.4, 170.9, 170.4, 170.2, 133.7, 133.6, 131.6, 131.6, 131.0, 130.7, 130.4, 129.8, 129.5, 129.4, 129.3, 127.8, 127.7, 125.8, 121.9, 79.5, 71.7, 71.3, 67.9, 67.8, 67.7, 67.4, 53.4, 53.3, 47.8, 47.6, 47.3, 43.7, 41.6, 41.5; IR: 3475, 3227, 2963, 2919, 2855, 1698, 1634, 1479, 1437, 1411, 1302, 1227, 1162, 1111, 1025, 1004, 761, 702; HR ESI MS: m/z for $[M+Na]^+$ calculated: 457.1852, found: 457.1871.

*4.3.3. (S)-2-(R)- and (S)-2-((S)-2-(4-methoxybenzylamino)-2-oxo-1-phenylethyl)-1,2,3,4-tetrahydrobenzo[e]pyrazino [1,2-a][1,4] diazepine-6,12(11H,12aH)-dione (**2c**).* Mixture of diastereomers; isolated yield: 99 mg (28%); R_f=0.47 (3% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, CD_3OD), δ: 7.73–7.67 (m, 1H, H_{Ar}); 7.47–7.42 (m, 1H, H_{Ar}); 7.36–7.23 (m, 1H, H_{Ar}); 7.23–7.18 (m, 3H, H_{Ar}); 7.06–7.01 (m, 1H, H_{Ar}); 6.85–6.80 (m, 1H, H_{Ar}); 4.49, 4.39 (2×d_{AB}, 1H, J=14.5, NH_2CH_2Ph); 4.36 (s, 1H, H-5); 4.32 (s, 1H, H-5); 3.97 (d, 1H, J=3.5, H-4$_e$); 3.72 (s, 3H, OCH_3); 3.17–3.06 (m, 2H, H-3$_e$+H-2$_e$); 3.03 (d, 1H, J=11.5, H-3$_e$); 2.28 (dt, 1H, J_1=11.5, J_2=11.5 H-3$_e$); 1.75 (dd, 1H, J_1=5, J_2=12.5, H-1); ^{13}C NMR (125 MHz, CD_3OD), δ: 173.2, 172.9, 172.7, 170.5, 170.4, 160.3, 138.0, 135.0, 133.7, 132.4,

131.5, 131.1, 131.0, 130.3, 130.2, 129.9, 129.3, 129.1, 128.1, 126.0, 122.0, 114.8, 114.7, 55.7, 55.6, 52.4, 52.3, 47.5, 43.5, 42.3; IR: 3443, 3287, 3061, 2921, 2835, 1692, 1643, 1513, 1478, 1438, 1409, 1303, 1249, 1175, 1162, 1032, 761, 701; HR ESI MS: m/z for $[M+Na]^+$ calculated: 507.2008, found: 507.2011.

*4.3.4. (S)-2-(R)- and (S)-2-(S)-2-(4-fluorophenylamino)-2-oxo-1-phenylethyl-1,2,3,4-tetrahydrobenzo[e]pyrazino [1,2-a][1,4] diazepine-6,12(11H,12aH)-dione (**2d**).* Mixture of diastereomers; Isolated yield: 75 mg (22%); R_f=0.51 (3% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, CD_3OD), δ: 7.96–7.88 (m, 1H, H_{Ar}); 7.86–7.72 (m, 2H, H_{Ar}); 7.56–7.44 (m, 2H, H_{Ar}); 7.42–7.21 (m, 1H, H_{Ar}); 7.15–6.98 (m, 1H, H_{Ar}); 4.64, 3.89, (2×s, 1H, H-5); 4.40 (d, 0.5H, J=13, H-4$_a$); 4.37–4.30 (m, 1H, H-4$_e$+H-4$_a$); 4.11 (d, 0.5H, J=3.5, 0.5H-4$_e$); 3.56 (d, 0.5H, J=12, H-2$_a$); 3.30 (m, 1H, 0.5H-3$_a$+0.5H-2$_a$); 3.17, 2.68 (2×d, J=12, H-2$_e$); 3.10 (dt, 0.5H, J_1=3.5, J_2=12, H-3$_a$); 2.49, 1.88 (2×dd, 1H, J_1=4.5, J_2=12.5, H-1); 2.43, 2.04 (2×dt, J_1=3.5, J_2=12, H-3$_e$); ^{13}C NMR (125 MHz, CD_3OD), δ: 172.8, 172.6, 172.0, 171.9, 170.7, 161.8, 159.9, 138.2, 135.9, 135.6, 134.4, 133.8, 133.7, 131.5, 131.4, 130.1, 129.9, 129.8, 129.6, 129.3, 129.2, 128.4, 128.2, 127.1, 126.1, 126.0, 123.9, 123.8, 123.7, 122.0, 121.9, 116.2, 116.1, 116.0, 115.9, 77.4, 75.7, 52.8, 52.5, 52.3, 52.2, 47.5, 42.5; IR: 3456, 3258, 2966, 2923, 2852, 1692, 1643, 1608, 1529, 1509, 1477, 1408, 1306, 1211, 1159, 1033, 838, 760, 701; HR ESI MS: m/z for $[M]^+$ calculated: 459.1848, found: 459.1827.

*4.3.5. (S)-2-(R)- and (S)-2-((S)-1-(4-ethylphenyl)-2-oxo-2-(4-phenylpiperazin-1-yl)ethyl)-1,2,3,4-tetrahydrobenzo [e]pyrazino[1,2-a][1,4]diazepine-6,12(11H,12aH)-dione (**2e**).* Mixture of diastereomers; isolated yield: 132 mg (33%); R_f=0.41 (3% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, DMSO-d_6), δ: 7.74–7.64 (m, 1H, H_{Ar}); 7.52–7.44 (m, 2H, H_{Ar}); 7.34 (d, 1H, J=13, H_{Ar}); 7.25–7.14 (m, 5H, H_{Ar}); 7.07 (t, 1H, J=8, H_{Ar}); 6.93–6.87 (m, 2H, H_{Ar}); 6.81–6.78 (m, 1H, H_{Ar}); 4.86, 4.68 (2×s, 1H, H-5); 4.36–4.24 (m, 1H, H-4$_a$); 4.09 (s, 1H, H-4$_e$); 4.06–3.98 (m, 0.5H, 0.5H$_p$CH_2NC=O); 3.90–3.70 (m, 1.5H, 1.5H$_p$CH_2NC=O); 3.70–3.63 (m, 1.5H, H$_p$CH_2NC=O+0.5H-2$_a$); 3.51–3.42 (m, 0.5H, H$_p$CH$_2$NC=O); 3.30 (m, 0.5H, H-2$_a$); 3.26–3.14 (m, 1H, 0.5H-2$_e$+0.5H$_p$CH_2NC=O); 3.12–2.80 (m, 5.5H, 4H$_p$CH_2NPh+H-3$_a$+0.5H-2$_e$); 2.59 (q, 2H, J=7, CH_2CH$_3$); 2.45–2.35 (m, 1H, H-1); 2.30–2.22 (m, 0.5H, 0.5H-3$_e$); 1.16 (t, 3H, J=7,CH$_2$CH_3). Half peak of H-3$_e$ covered by DMSO peak; ^{13}C NMR (125 MHz, DMSO-d_6), δ: 170.4, 168.4, 168.1, 167.3, 167.2, 150.7, 150.6, 143.0, 142.9, 136.9, 136.8, 133.3, 131.8, 131.5, 130.3, 130.2, 129.7, 129.3, 128.9, 128.8, 127.6, 127.5, 127.2, 126.4, 126.3, 123.8, 120.4, 119.2, 119.1, 115.7, 115.6, 68.1, 51.2, 49.1, 48.4, 48.2, 48.1, 47.0, 46.3, 44.9, 44.6, 41.3, 27.7, 15.4, 15.3; IR: 3446, 3226, 2963, 2925, 2870, 1696, 1640, 1600, 1495, 1478, 1439, 1411, 1284, 1228, 1160, 1021, 759, 694; HR ESI MS: m/z for $[M]^+$ calculated: 538.2818, found: 538.2817.

*4.3.6. (S)-2-(R)- and (S)-2-((S)-1-(4-methoxyphenyl)-2-oxo-2-(4-phenylpiperazin-1-yl)ethyl)-1,2,3,4-tetrahydro- benzo[e]pyrazino[1,2-a][1,4]diazepine-6,12(11H,12aH)-dione (**2f**).* Mixture of diastereomers; isolated yield: 128 mg (32%); R_f=0.37 (3% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, DMSO-d_6), δ: 7.74–7.66 (m, 1H, H_{Ar}); 7.52–7.44 (m, 2H, H_{Ar}); 7.35 (d, 1H, J=8.5H_{Ar}); 7.24–7.18 (m, 3H, H_{Ar}); 7.07 (t, 1H, H_{Ar}); 6.95–6.86 (m, 4H, H_{Ar}); 6.84–6.74 (m, 1H, H_{Ar}); 4.85, 4.67 (2×s, 1H, H-5); 4.29 (t, 1H, J=12, H-4$_a$); 4.09 (s, 1H, H-4$_e$); 4.07–4.00 (m, 0.5H, 0.5CH_2NC=O); 3.91–3.52 (m, 6H, 2.5CH_2NC=O+OCH$_3$+0.5H-2$_a$); 3.51–3.41 (m, 0.5H, CH_2NC=O); 3.29 (d, 0.5H, J=12.5, 0.5H-2$_a$); 3.24–3.13 (m, 1H, 0.5H, 0.5CH$_2$NC=O+H-2$_e$); 3.13–2.78 (m, 5.5H, 4CH_2NPh+H-5$_a$+0.5H-2$_e$), ~2.48 (dt, 0.5H, 0.5H-3$_e$, under the signal of DMSO); 2.44–2.35 (m, 1H, H-1); 2.25 (dt, 0.5H, J_1=3.5, J_2=11.5, 0.5H-3$_e$); ^{13}C NMR (125 MHz, DMSO-d_6), δ: 170.5, 170.4, 168.6, 168.3, 167.3, 167.2, 158.6, 158.5, 150.8, 150.6, 136.9, 136.8, 131.8, 130.9, 130.3, 130.2, 130.1, 128.9, 128.8, 127.9, 126.4, 126.3, 126.1, 123.8, 120.4, 120.4, 120.0, 119.2, 115.7, 115.6, 113.5, 113.2, 51.3, 51.2, 49.1, 48.4, 48.2, 48.0, 47.7, 46.9, 46.8, 46.3, 44.9, 44.6, 41.2; IR: 3455, 3239, 2911, 2832, 1703, 1643, 1615, 1598, 1511, 1475, 1452, 1435, 1409, 1291, 1228, 1176, 1162, 1020, 756, 697; HR ESI MS: m/z for $[M+Na]^+$ calculated: 562.2430, found: 562.2409.

*4.3.7. (S)-2-(R)- and (S)-2-((R)-2-oxo-2-(4-phenylpiperazin-1-yl)-1-(thiophen-2-yl)ethyl)-1,2,3,4-tetrahydrobenzo [e]pyrazino[1,2-a][1,4]diazepine-6,12(11H,12aH)-dione (**2g**).* Mixture of diastereomers; isolated yield: 101 mg (26%); R_f=0.47 (3% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, CD_3OD), δ: 7.50–7.46 (m, 1H, H_{Ar}); 7.45–7.42 (m, 1H, H_{Ar}); 7.26–7.20 (m, 1H, H_{Ar}); 7.10–7.05 (m, 1H, H_{Ar}); 7.03–6.98 (m, 1H, H_{Ar}); 6.94 (d, 1H, J=8, H_{Ar}); 6.83 (t, 1H, J=7, H_{Ar}); 5.30 (s, 1H, H-5); 4.36 (d, 1H, J=13, H-4$_a$); 4.14 (dd, 1H, J_1=2.5, J_2=5.5, H-4$_e$); 4.00–3.89 (m, 1H, H$_p$CH_2NC=O); 3.89–3.79 (m, 2H, 2H$_p$CH_2NC=O); 3.79–3.70 (m, 1H, H$_p$CH_2NC=O); 3.43 (d, 1H, J=13, H-2$_a$); 3.29–3.21 (m, 2H, 2H$_p$CH2NPh); 3.20–3.12 (m, 1H, H-5$_a$); 3.12–3.04 (m, 1H, H$_p$CH2NPh); 3.04–2.90 (m, 2H, H$_p$CH_2NPh+H-2$_e$); 2.67–2.56 (m, 2H, H-5$_e$+H-1); ^{13}C NMR (125 MHz, CD_3OD), δ: 172.5, 170.5, 170.4, 142.5, 138.4, 139.0, 133.7, 131.6, 130.1, 129.4, 128.2, 127.8, 127.2, 125.7, 121.8, 121.4, 117.8, 113.9, 53.3, 52.0, 50.8, 50.4, 47.2, 46.9, 44.1, 43.4, 41.8; IR: 3239, 3092, 2923, 1694, 1641, 1599, 1496, 1478, 1438, 1408, 1286, 1229, 1161, 1031, 760, 697; HR ESI MS: m/z for $[M+Na]^+$ calculated: 538.1889, found: 538.1892.

*4.3.8. (S)-2-(R)- and (S)-2-((S)-1-(naphthalen-2-yl)-2-oxo-2-(4-phenylpiperazin-1-yl)ethyl)-1,2,3,4-tetrahydrobenzo [e]pyrazino[1,2-a][1,4]diazepine-6,12(11H,12aH)-dione (**2h**).* Mixture of diastereomers; isolated yield: 147 mg (36%); R_f=0.58 (3% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, CD_3OD), δ: 7.95–7.70 (m, 7H, H_{Ar}); 7.75–7.45 (m, 5H, H_{Ar}); 7.29–7.24 (m, H, H_{Ar}); 7.21–7.15 (m, 2H, H_{Ar}); 7.12–7.00 (m, 1H, H_{Ar}); 4.60, 4.49 (2×s, 1H, H-5); 4.37 (d, 1H, J=12.5, H-4$_a$); 4.21 (dd, 1H, J_1=2.5, J_2=5.5, H-4$_e$); 4.03–3.94 (m, 1H, H$_p$CH_2NC=O); 3.88–3.70 (m, 3H, 3H$_p$CH_2NC=O); 3.53 (d, 1H, J=13, H-2$_a$); 3.24–3.05 (m, 4H, 2H$_p$CH_2NPh+H-2$_e$+H-3$_a$); 3.05–2.92 (m, 2H, 2H$_p$CH_2NC=O); 2.87–2.79 (m, 1H, H$_p$CH_2NC=O); 2.79–2.70 (m, 2H, H-1+H-3$_e$); ^{13}C NMR (125 MHz, CD_3OD), δ: 173.0, 172.7, 171.4, 170.5, 152.4, 138.4, 138.1, 134.8, 134.4, 133.7, 132.5, 131.6, 131.5, 131.1, 130.8, 130.2, 130.1, 130.0, 129.6, 129.5, 129.3, 128.2, 127.9, 127.6, 127.5, 126.1, 126.0, 125.8, 122.0, 121.9, 121.5, 117.8, 114.8, 113.9, 75.6, 75.3, 66.7, 55.7, 53.4, 52.9, 52.6, 52.5, 52.4, 50.8, 50.6, 47.7, 47.5, 44.2, 43.5, 43.4, 42.4, 41.7; IR: 3454, 3217, 3056, 2910, 2814, 1695, 1637, 1599, 1478, 1439, 1413, 1280, 1227, 1060, 1021, 757, 694; HR ESI MS: m/z for $[M+Na]^+$ calculated: 582.248, found: 582.2474.

*4.3.9. (S)-2-(R)- and (S)-2-((S)-1-(6-methoxynaphthalen-2-yl)-2-oxo-2-(4-phenylpiperazin-1-yl)ethyl)-1,2,3,4-tetrahydrobenzo[e]pyrazino[1,2-a][1,4]diazepine-6,12(11H,12aH)-dione (**2i**).* Mixture of diastereomers; isolated yield: 91 mg (21%); R_f=0.55 (3% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, DMSO-d_6), δ: 7.90–7.60 (m, 4H, H_{Ar}); 7.60–7.54 (m, 1H, H_{Ar}); 7.52–7.44 (m, 1H, H_{Ar}); 7.32–7.27 (m, 1H, H_{Ar}); 7.24–7.12 (m, 1H, H_{Ar}); 7.07 (t, 1H, J=9, H_{Ar}); 6.93–6.83 (m, 2H, H_{Ar}); 6.78 (q, 1H, J=6, H_{Ar}); 5.05, 4.86 (2×s, 1H, H-6); 4.31 (t, 1H, J=13, H-4$_a$); 4.41–4.01 (m, 1.5H, H-4$_e$+0.5H$_p$CH_2NC=O); 3.96–3.74 (m, 5H, 2H$_p$CH_2NC=O+OCH$_3$); 2.72–3.58 (m, 1.5H, H$_p$CH_2NC=O+0.5H-2$_a$); 3.32–3.10 (m, 1H, 0.5H$_p$CH_2NC=O+0.5H-2$_e$); 3.10–2.79 (m, 5.5H, 4H$_p$CH_2NPh+H-3$_a$+0.5H-2$_e$); 2.62, 2.44 (m, 1.5H, H-1+0.5H-3$_e$, partially under DMSO peak); 2.37 (dt, J_1=3, J_2=11, 0.5H-3$_e$); ^{13}C NMR (125 MHz, DMSO-d_6), δ: 170.6, 170.4, 168.4, 168.2, 167.3, 167.2, 157.4, 150.7, 150.6, 137.0, 136.8, 133.7, 133.6, 131.9, 131.3, 130.3, 129.9, 129.3, 128.9, 128.8, 128.3, 128.2, 128.0, 127.9, 127.5, 126.6, 126.4, 126.3, 126.1, 123.8, 120.4, 119.2, 119.1, 118.6, 118.5, 115.7, 115.6, 105.7, 105.6, 55.9, 55.1, 51.3, 49.1, 48.4, 48.3, 48.1, 47.7, 47.3, 47.2, 46.2, 45.0, 44.7, 41.3; IR: 3455, 3229, 2918, 2826, 1696, 1636, 1604, 1504, 1495, 1480, 1438, 1410, 1392, 1268, 1227,

1161, 1025, 759, 695; HR ESI MS: m/z for $[M+Na]^+$ calculated: 612.2587; found: 612.2610.

*4.3.10. (8S,10aS)-2-(R)- and (8S,10aS)-2-((S)-2-oxo-1-phenyl-2-(4-phenylpiperazin-1-yl)ethyl)-8-phenylhexahydropyra-zino[1,2-a][1,4]diazepine-6,10(7H,10aH)-dione (**3b**).* Mixture of diastereomers; isolated yield: 119 mg (30%); R_f=0.48 (3% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, CD_3OD), δ: 7.40–7.25 (m, 8H, H_{Ar}); 7.22–7.17 (m, 2H, H_{Ar}); 7.14–7.05 (m, 1H, H_{Ar}); 6.89–6.79 (m, 2H, H_{Ar}); 4.56, 4.51 (2×s, 1H, H-7); 4.32–4.20 (m, 2H, H-$5_{a,e}$); 3.80–3.46 (m, 4H, H_pCH_2NC=O); 3.27–3.20 (m, 2H, H–$6_{a,e}$); 3.15–3.05, 3.05–2.85, 2.66–4.49 (3×m, 6H, $4H_pCH_2$NPh+H-$3_{a,e}$+H-1); 2.44, 2.40 (2×dt, 1H, J_1=3, J_2=12, H-4_a); 2.24, 1.94; (2×dt, 1H, J_1=3, J_2=12, H-4_e); 2.09, 1.89 (2×t, 1H, J=11.5, H-2); ^{13}C NMR (125 MHz, CD_3OD), δ:170.9, 170.8, 167.8, 167.8, 167.1, 167.0, 136.1, 136.0, 131.7, 131.6, 130.5, 130.4, 130.1, 130.0, 129.8, 129.7, 129.6, 128.8, 128.7, 121.6, 117.8, 57.1, 56.8, 56.6, 55.2, 54.4, 50.7, 50.6, 50.4, 50.2, 46.7, 46.6, 44.9, 43.3, 43.2, 42.2, 42.0, 41.7; IR: 3446, 3254, 2922, 2857, 2822, 1684, 1656, 1599, 1495, 1439, 1336, 1273, 1154, 1018, 759, 702; HR ESI MS: m/z for $[M+Na]^+$ calculated: 560.2637, found: 560.2646.

Acknowledgements

The authors are grateful to Prof. Wiktor Kozminski for the help in analysis of the correlation NMR spectra.

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