A Traceless, Solid-Supported Synthesis of β-Turn Mimetics Based on the Hexahydropyrazino[1,2-*a*]pyrazine-1,2-dione Scaffold

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Abstract: The solid-supported synthesis of a library of β-turn mimetics based on the three-component Petasis condensation and 2,5-diketopiperazine formation is reported. The eight-step sequence starts from optically pure (*S*)-piperazine-2-carboxylic acid dihydrochloride, which is first converted into an orthogonally protected, resin-bound amino derivative. The subsequent transformations lead to compounds having the common hexahydropyrazino[1,2-*a*]pyrazine-1,2-dione core and diverse side chains, which mimic the β-turn structure. This synthetic route includes protection of the initial amino acid with two different protecting groups, followed by attachment to the Wang resin using the Mitsunobu reaction, deprotection of the β-nitrogen atom, then Petasis reaction, amidation, deprotection of the α-nitrogen atom, coupling with a Boc-protected α-amino acid, cleavage of the Boc group, and the cyclizative cleavage from the resin, resulting in the requested bicyclic products obtained in good yields and having good to moderate purities. Six different boronic acids, four amines, and nine α-amino acids were applied to this synthetic route, to explore the efficiency and limitations of the described method.

Key words: solid-phase synthesis, cyclizative cleavage, multicomponent reactions, β-turn mimetics

The 2,5-diketopiperazine structure is common in many natural products and can be found as a structural element of various compounds isolated from many species of microorganisms. Such compounds include, but are not limited to, polychlorinated piperazines (e.g., **1**) obtained from cyanobacterial symbionts living on sea sponges *Disidea spp.*,[1] the *Asperigillus ustus* metabolite phenylahistin (**2**), which exhibits a promising antitumor activity,[2] and the *N*-methyltyrosine derivative **3** isolated from *Streptomyces griseus*, which inhibits calpain, the calcium-activated cysteine protease.[3] The 2,5-diketopiperazine ring occurs also in some complex molecules such as tetracyclic roquefortine E (**4**) isolated from *Penicillium roquefortii*,[4] the pentacyclic alkaloids spirotryprostatins[5] represented by spirotryprostatin A (**5**), or hepta- and octacyclic biologically active antibiotics okaramines[6] isolated from *Penicillium simplicissimum* such as okaramine N (**6**) (Figure 1).

However, the 2,5-diketopiperazines (2,5-DKPs) are of great interest for organic chemists not only because they are structural elements of many natural compounds. 2,5-DKPs possess structural similarity to peptides, but without the limitations inherent to peptides. Poor sub-receptor selectivity, poor biostability, and the fact that interaction between peptides and macromolecular receptors is highly depended on the conformation of the peptide means that the peptides are not always good materials in drug design.

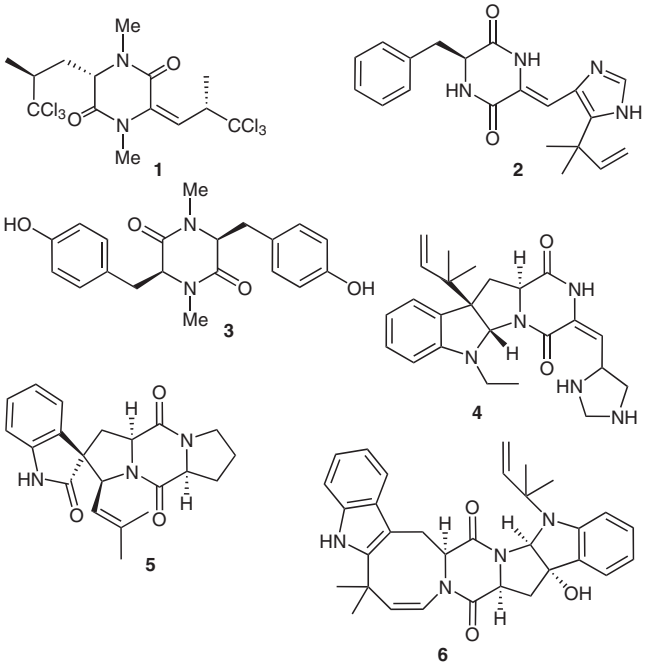

Figure 1 Naturally occurring compounds possessing a 2,5-diketopiperazine fragment

Consequently, much effort has been devoted to the design and synthesis of metabolically stable and conformationally restricted therapeutic peptide equivalents, which are called peptidomimetics. The appearance of 2,5-DKPs in biological natural products inspired and stimulated organic chemists to investigate the possibility of replacing peptide-based active compounds with 2,5-DKP derivatives to overcome the limitations of peptides. The use of 2,5-DKPs improves the resistance of the amide bond to metabolic cleavage reactions and reduces conformational mobility, which strengthens the favorable interactions of 2,5-DKPs with macromolecules. During the course of drug discovery, 2,5-diketopiperazine derivatives have been synthesized that are antagonistic activity to human oxytocin receptor,[7] highly cytotoxic,[8] selective inhibitors of collagenase-1,[9] and novel neuroprotective compounds.[10]

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These results showed a wide range of activity of 2,5-diketopiperazines, thus proving the usefulness of 2,5-DKPs as potent biologically active substances and focusing the attention of medicinal chemists on this class of compounds. The design, synthesis, and investigation of biochemical interactions of mimetics of the peptide turn structure has captured the interest of scientists and it has resulted in significant numbers of reviews and opinions published in biochemical journals.[11]

The β-turn structure **A** (Figure 2) is defined as any tetrapeptide sequence with a ten-membered intramolecularly hydrogen-bonded ring, in which the distance between four carbon atoms in the peptide chain varies from 4 to 7 Å. Depending on the dihedral angle values, there are at least 14 types of known β-turn structure. The β-turns are one of the three major structural elements of the peptides and play a key role in many molecular recognition events. These events include, but are not limited to, the interactions between peptide hormones and their receptors, antibodies, and antigens and between regulatory enzymes and their corresponding substrates. Recently, a solid-supported synthesis of new β-turn structure mimetics, based on the bicyclic 2,5-diketopiperazine structure **B**, was announced by Golebiowski et al. (Figure 2).[12]

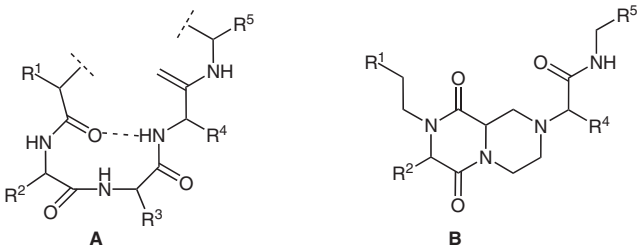


Figure 2 β-Turn motif

Given the fact that only a few structures of type **B** have been reported in the literature, all obtained from racemic substrates and with no spectral data for the synthesized compounds, we focused our synthetic efforts on the synthesis of a library of β-turn mimetics of type **B** based on the hexahydropyrazino[1,2-*a*]pyrazine-1,2-dione core. As opposed to the initial research, we planned to use optically pure (*S*)-piperazine-2-carboxylic acid as the major substrate in our synthesis, which should limit to two the number of the diastereomers of the final product. The use of optically pure building blocks should make possible the separation the obtained pairs of diastereomers by column chromatography and facilitate analysis of the NMR spectra. In this article, we would like to present extensive work detailed investigation on the synthesis of β-turn mimetics possessing the 2,5-diketopiperazine moiety from optically pure amino acids. The use of various building blocks revealed the scope and limitations of the investigation method and led to a significant number of novel products.

Planning the synthesis of the library of β-turn mimetics of type **B**, we faced the problem of selection of the appropriate building blocks, which could determine the R^1, R^2, R^4, and R^5 substituents in the designed structure **B**. The R^4 substituent comes from a boronic acid and it is incorporated in the Petasis reaction, the R^5 substituent comes from a primary or secondary amine and it is incorporated to the structure in the amidation reaction. The R^1 and R^2 substituents originate from an α-amino acid and they are incorporated in the amidation reaction. The R^3 substituent of β-turn **A** is missing in the mimetic structure **B**. The selected boronic acids, amines, and α-amino acids are presented in Figure 3.

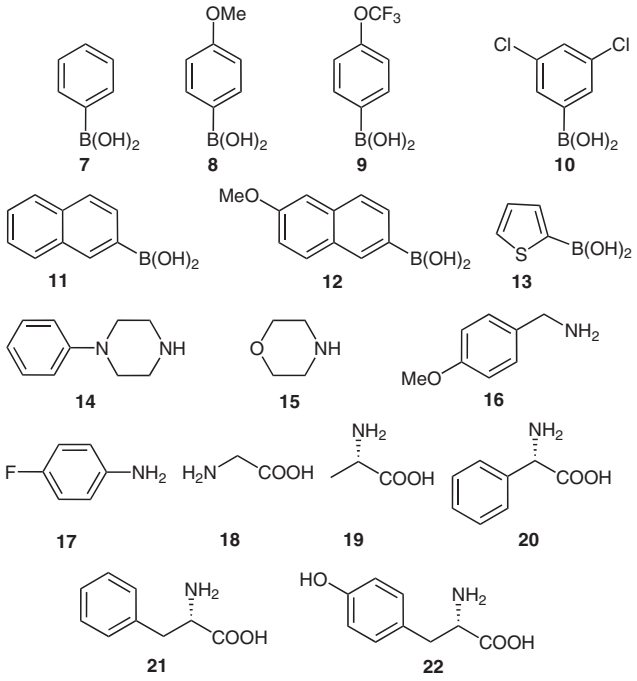
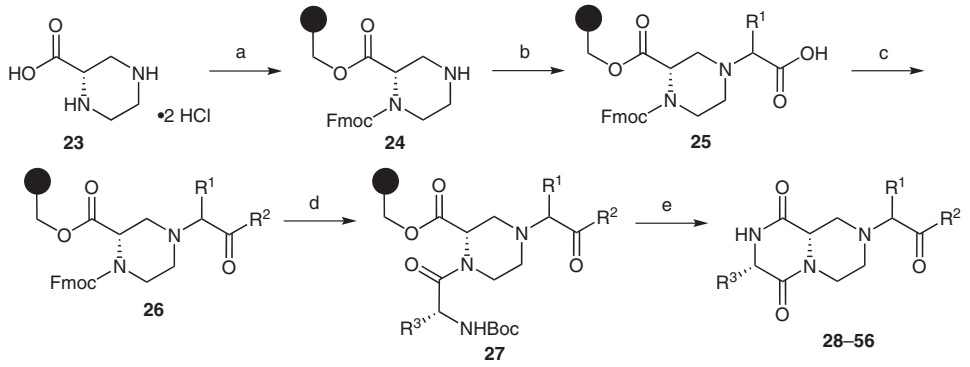


Figure 3 Selection of building blocks

As shown in Figure 3, seven aromatic boronic acid, having either electrophilic or nucleophilic substituents in the aromatic ring, were chosen: phenylboronic acid (**7**), 4-methoxyphenylboronic acid (**8**), 4-(trifluoromethoxy)phenylboronic acid (**9**), 3,5-dichlorophenylboronic acid (**10**), 2-naphthylboronic acid (**11**), 6-methoxy-2-naphthylboronic acid (**12**), and 2-thienylboronic acid (**13**). We decided to use four different aromatic or aliphatic, primary or secondary amines: *N*-phenylpiperazine (**14**), morpholine (**15**), 4-methoxybenzylamine (**16**), and 4-fluoroaniline (**17**), as well as five different amino acids: achiral glycine (**18**), and chiral L-α-alanine (**19**), L-α-phenylglycine (**20**), L-α-phenylalanine (**21**), and L-α-tyrosine (**22**). Where possible, the D-α-enantiomers of the presented amino acids have also been used.

The synthetic route is shown in Scheme 1. In the first step, the major substrate, optically pure (*S*)-piperazine-2-carboxylic acid dihydrochloride salt (**23**), was protected with two different protecting groups that made it possible to deprotect either of the amine groups selectively. Then it was attached to the Wang resin. In this step, we used the Mitsunobu reaction, a very facile and useful method often utilized in the solid-supported synthesis of esters. The



Scheme 1 *Reagents and conditions:* (a) (i) Boc_2O, aq NaOH, dioxane–H_2O (2:1), 0 °C to r.t., then FmocCl, Na_2CO_3 (ii) DEAD, Ph_3P, THF–CH_2Cl_2 (3:1), 0 °C to r.t.; (iii) 40% TFA–CH_2Cl_2; (b) $OHCCOOH·H_2O$, $R^1B(OH)_2$ **7–13**, CH_2Cl_2–MeOH (4:1), r.t.; (c) DIC, HOBt, **14–17**, DMF; (d) (i) 25% piperidine–DMF, r.t.; (ii) DIC, HOBt, $R^3NH(Boc)CO_2H$ **18–22**, DMF, r.t.; (iii) 25% TFA–CH_2Cl_2; (e) 10% AcOH–*i*-PrOH, 50 °C.

ester-linked, orthogonally protected (*S*)-piperazine-2-carboxylic acid was treated with a trifluoroacetic acid solution, which resulted in cleavage of the Boc protecting group and deprotection of the β-nitrogen. In the next step of the synthesis, the monoprotected amino derivative **24** was subjected to the Petasis reaction with glyoxylic acid and an appropriate boronic acid. The Petasis product **25** was treated with a diisopropylcarbodiimide/1-hydroxybenzotriazole (DIC/HOBt) mixture and then the appropriate amine was added, which led to the amide derivative **26**.

From among a wide range of coupling reagents, we decided to use the DIC/HOBt mixture as the most effective and best fitted to the conditions and requirements of our synthesis. In order to cleave the Fmoc protecting group and release the remaining α-nitrogen atom, the intermediate **26** was treated with a piperidine solution, followed by coupling with an appropriate Boc-protected α-amino acid, which led to the intermediate **27**; for the second amide bond formation, we also decided to use the DIC/HOBt mixture. In the final part of our synthesis, the amino derivative **27** was treated with trifluoroacetic acid solution, which resulted in deprotection of the nitrogen atom of the coupled α-amino acid. In the final step, the resin was treated with 10% acetic acid in isopropyl alcohol at 50 °C for 12 hours; the cyclizative cleavage occurred smoothly, giving final products of type **B**, **28–56**. The obtained compounds were purified by column chromatography on silica gel (1–2% MeOH–CH_2Cl_2).

At the beginning of our research, we decided to use unsubstituted phenylboronic acid (**7**), glycine (**18**), and four selected amines to synthesize the first series of compounds **28–31** (Table 1, entries 1–4). Encouraged with the results obtained, we repeated this scheme for each of the remaining α-amino acids **19–22** (Table 1, entries 5–20). Then we decided to check the usefulness of other boronic acids and synthesized a series of compounds from L-α-phenylglycine (**20**), *N*-phenylpiperazine (**14**), and various aromatic boronic acids **7–13** (Table 2, entries 1–6). Finally we decided to use three D-α-amino acids (Table 3, entries 1–3).

Table 1 Compounds Obtained from Phenylboronic Acid (R^1 = Ph)

Entry	Product	R^2	R^3	Yield (%)	
				Crude	Purified[a]
1	**28**	4-phenylpiperazinyl	H	73	22
2	**29**	morpholin-4-yl	H	87	36
3	**30**	4-$MeOC_6H_4CH_2NH$	H	64	22
4	**31**	4-FC_6H_4NH	H	71	28
5	**32**	4-phenylpiperazinyl	Me	68	47
6	**33**	morpholin-4-yl	Me	79	24
7	**34**	4-$MeOC_6H_4CH_2NH$	Me	66	21
8	**35**	4-FC_6H_4NH	Me	69	37
9	**36**[b]	4-phenylpiperazinyl	Ph	52	21
10	**37**[b]	morpholin-4-yl	Ph	65	35
11	**38**[b]	4-$MeOC_6H_4CH_2NH$	Ph	57	28
12	**39**[b]	4-FC_6H_4NH	Ph	48	29
13	**40**	4-phenylpiperazinyl	Bn	67	22
14	**41**	morpholin-4-yl	Bn	74	29
15	**42**	4-$MeOC_6H_4CH_2NH$	Bn	56	23
16	**43**	4-FC_6H_4NH	Bn	65	18
17	**44**	4-phenylpiperazinyl	4-HOBn[c]	64	31
18	**45**	morpholin-4-yl	4-HOBn[c]	58	36
19	**46**	4-$MeOC_6H_4CH_2NH$	4-HOBn[c]	53	28
20	**47**	4-FC_6H_4NH	4-HOBn[c]	43	20

[a] Purified by column chromatography.
[b] Partial racemization during reaction.
[c] 4-Hydroxybenzyl.

The following conclusions can be drawn from a comparison of the results shown in Tables 1– 3: (1) In most cases (Table 1, entries 2, 5, 10, 17, 18), the use of secondary

amines [*N*-phenylpiperazine (**14**) and morpholine (**15**)] slightly decreased the yields of the obtained products, which could indicate that secondary amines are more suitable than primary amines under the amidation reaction conditions in the presence of HOBt/DIC. (2) The best crude yields were achieved for reactions with glycine (**18**) (Table 1, entries 1–4), the yields for the sterically hindered amino acids were noticeably worse, which could indicate that sterical interactions could play an important role in cyclization, the last step of the synthesis. (3) In the most cases, the use of the phenylboronic acids containing electron-donating groups (Table 2, entries 1, 5, 6) led to higher yields than the use of unsubstituted boronic acid. (4) The use of the phenylboronic acids containing electron-withdrawing groups (Cl, OCF_3) did not lead to the desired products. It was assumed that these reagents were not effective in the Petasis reaction under the applied conditions. This assumption could be verified by ESI-MS spectroscopy of the reaction mixture after cleavage, which, in both cases, indicated the presence of products with *m*/*z* = 245 and 378. These masses could be assigned to compounds **57** and **58**, respectively (Figure 4), which could be the byproducts when the Petasis reaction failed.

Table 2 Compounds Obtained from Other Boronic Acids (R^2 = 4-phenylpiperazin-1-yl, R^3 = Ph)

Entry	Product	R^1	Yield (%) Crude	Purified[a]
1	**48**[b]	4-$MeOC_6H_4$	71	32
2	**49**[b]	4-$F_3COC_6H_4$	–	–
3	**50**[b]	3,5-$Cl_2C_6H_3$	–	–
4	**51**[b]	2-thienyl	52	18
5	**52**[b]	2-naphthyl	91	45
6	**53**[b]	6-MeO-2-naphthyl	50	31

[a] Purified by column chromatography.
[b] Partial racemization during reaction.

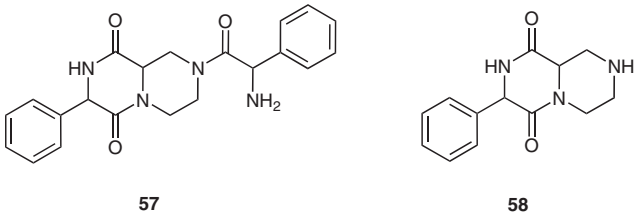
The synthesized products possess either two (when using glycine) or three (when using other α-amino acids) stereogenic centers: the first one originates from optically pure (*S*)-piperazine-2-carboxylic acid, the second one is created in the Petasis reaction, and the third could be incorporated with the optically pure chiral α-amino acid. 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 they 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 recorded for the selected products. These confirmed indisputably the assumed structures.

Table 3 Compounds Obtained from D-α-Amino Acids (R^1 = Ph, R^2 = 4-phenylpiperazin-1-yl)

Entry	Product	R^3	Yield (%) Crude	Purified[a]
1	**54**[b]	Me	58	16
2	**55**[b]	Bn	59	22
3	**56**[b]	4-HOBn	44	26

[a] Purified by column chromatography.
[b] Partial racemization during reaction.

After cleavage with 10% acetic acid in isopropyl alcohol, we found no traces of any uncyclized products in the reaction mixture.



57 58

Figure 4

Due to the partial racemization of phenylglycine, the compounds synthesized from this amino acid were obtained as a mixture of four diastereomers. The racemization of phenylglycine could occur during Boc protection, coupling the protecting amino acid by amide bond, or during cyclizative cleavage of the final product. Although racemization of phenylglycine under basic conditions, resulting from the acidity of the benzylic proton, is well described in literature,[13] this process has not been investigated, neither for the coupling reaction nor for the cyclization. The compounds obtained from phenylglycine were easily separated by column chromatography into two pairs of diastereomers, the major and minor pairs. The representative 2D COSY correlation spectrum for the major pair of diastereomers of **39** is shown in Figure 5.

In summary, we have successfully synthesized a library of β-turn mimetics of type **B** based on the hexahydropyrazino[1,2-*a*]pyrazine-1,2-dione core. Starting from optically pure, orthogonally protected (*S*)-piperazine-2-carboxylic acid attached to the Wang resin, and varying the boronic acids, the amines, and the α-amino acids, we obtained a wide range of compounds having diverse side chains and substituents in the heterocyclic core. The use of the optically pure substrates allows decreases the number of diastereomers of the final products. Unfortunately, the efforts to separate these diastereomers failed and all products were described as pairs of diastereomers. In our opinion, the described synthetic route, which offers the potential biologically active compounds, deepens the knowledge of β-turn mimetics. The investigated method could also be utilized in the synthesis of diketopiperazine derivatives

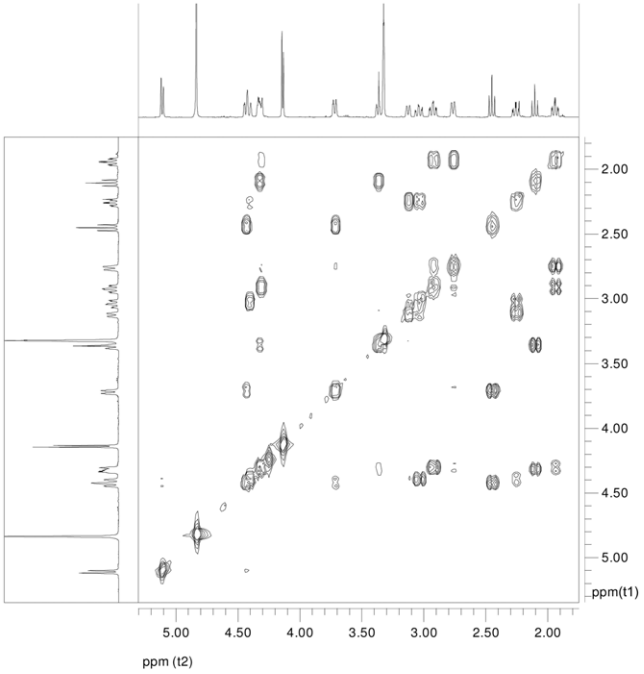


Figure 5 2D COSY spectrum spectra for the major pair of diastereomers of **39**

incorporated into cyclic peptides, as diketopiperazine-based templates stabilize loop conformations.[14] The biological activity of synthesized compounds will be reported in due course.

All reagents were obtained from Fluka and Merck and were used without further purification. Anhyd CH_2Cl_2 and DMF were obtained by distillation from CaH_2. The enantiomerically pure (*S*)-piperazine-2-carboxylic acid was obtained from ChemPacific. The Wang resin was obtained from Novabiochem. ^1H and ^{13}C spectra were recorded on Varian 500 MHz 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: signal from axial proton, H_e: signal from equatorial proton, H_p: signal from the piperazine substituent, H_m: signal from the morpholine substituent. All ESI-MS spectra were recorded on Quattro LC Micromass. The IR spectra were recorded on Nicolet Magna 550 FTIR. 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 F254 aluminum plates and analyzed using iodine vapor and UV light (254 nm), or by spraying with an aqueous soln 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 6.

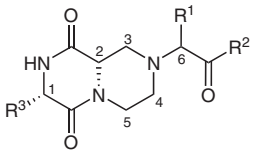


Figure 6

(*S*)-4-(*tert*-Butoxycarbonyl)-1-(9-fluorenylmethoxycarbonyl)piperazine-2-carboxylic Acid

To a soln of **23** (3.0 g, 14.8 mmol) in dioxane (30 mL) and H_2O (15 mL), a soln of NaOH (1.5 g, 29.6 mmol) in H_2O (5 mL) was added slowly at 0 °C, followed by $(Boc)_2O$ (3.6 g, 16.3 mmol). The mixture was stirred at r.t. for 5 h then solid Na_2CO_3 (1.7 g, 16.0 mmol) and FmocCl (4.7 g) were added and the reaction was stirred overnight. The solvent was removed on a rotary evaporator and the residue obtained was partitioned between EtOAc and 1 M HCl. The organic layer was washed with brine, dried ($MgSO_4$) and the solvent was evaporated. The crude product was crystallized once (EtOAc) to give the product (4.4 g, 43%) as a colorless crystalline solid.

Hexahydropyrazino[1,2-*a*]pyrazine-1,2-dione Derivatives 28–56; General Procedure

(a) The Wang resin (1.0 g, 0.82 mmol/g, Novabiochem) was allowed to swell in anhyd CH_2Cl_2 (10 mL). To this slurry, Ph_3P (643 mg, 2.46 mmol) and N^{α}-Fmoc-N^{β}-Boc-(*S*)-piperazine-2-carboxylic acid (111 mg, 2.46 mmol) were added. The mixture was cooled to 0 °C under argon and DEAD (428 mg, 2.46 mmol) in THF (2 mL) was added slowly. The mixture was stirred for 3 d, then the resin was filtered off and washed with THF (3 ×), CH_2Cl_2 (3 ×), MeOH (3 ×), then alternately with CH_2Cl_2 and MeOH. The orthogonally protected piperazinic resin ester was allowed to swell in CH_2Cl_2 (10 mL) and then TFA (3.3 mL) was added dropwise. After 1 h, the resin was filtered off and washed in a standard manner. The resin-bound amine TFA salt was then neutralized with 10% DIPEA in CH_2Cl_2 and washed again in a standard manner.

(b) The resin-bound amino derivative **24** was allowed to swell in CH_2Cl_2 (10 mL), and glyoxylic acid (151 mg, 1.64 mmol) and $PhB(OH)_2$ (200 mg, 1.64 mol) in MeOH (2 mL) were added. The mixture was agitated for 5 h, then filtered off and washed with CH_2Cl_2 (3 ×). The above procedure was repeated again for 12 h after which the resin was again filtered off and washed in a standard manner.

(c) The piperazinic ester **25** from the previous step was allowed to swell in anhyd DMF (10 mL) and HOBt (626 mg, 4.1 mmol) was added followed addition of by DIC (0.63 mL, 4.1 mmol). The reaction was agitated for 3 h, after which the resin was washed with anhyd DMF (3 ×). The resin was allowed to swell again in DMF (10 mL) and to this slurry was added *N*-phenylpiperazine (**14**, 0.63 mL, 4.1 mmol) and the reaction was agitated for 12 h. The resin **26** was filtered off and washed with DMF (3 ×) followed by the standard protocol.

(d) The resin **26** was treated with 25% piperidine in DMF, then filtered off and washed in a standard manner. The Boc-protected amino acid (4.1 mmol) was dissolved in anhyd DMF (10 mL) and then HOBt (626 mg, 4.1 mmol) was added followed by addition of DIC (0.63 mL, 4.1 mmol). The mixture was agitated for 1 h; in the meantime, the resin was allowed to swell in anhyd DMF (10 mL), and the soln of activated amino acid was added to this heterogeneous slurry. The reaction was agitated for 5 h and rinsed with anhyd DMF (3 ×) before repeating the coupling procedure for 15 h. Then the resin was filtered off and washed in a standard manner. The resin was then treated with 25% TFA in CH_2Cl_2 for 1 h and washed in the standard manner.

(e) The resin-bound intermediate **27** was taken up in 10% AcOH–*i*-PrOH and heated at 50 °C for 12 h. The resin was filtered off and washed several times with MeOH. The filtrate and washings were combined and concentrated to give a brown solid. The crude product was purified by column chromatography (silica gel, 1–2% MeOH–$CHCl_3$).

(*S*)-8-[2-Oxo-1-phenyl-2-(4-phenylpiperazin-1-yl)ethyl]tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (28)
IR: 3449, 3260, 3061, 2919, 2853, 2822, 1649, 1598, 1495, 1443, 1331, 1274, 1228, 1154, 1114, 1017, 759, 698 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.52–7.26 (m, 5 H, H_{Ar}), 7.19 (t, *J* = 8 Hz, 2 H, H_{Ar}), 6.87 (d, *J* = 8 Hz, 2 H, H_{Ar}), 6.83 (t, *J* = 8 Hz, 1 H, H_{Ar}), 4.68, 4.67 (2 s, 1 H, H6), 4.40, 4.35 (2 d, 1 H, $H5_a$), 4.18, 4.13 (2 d, 1 H, $H5_e$), 4.03–3.87 (m, 2 H, $H1_{a,e}$), 3.86–3.78 (m, 1 H, $H_pCH_2NC{=}O$), 3.78–3.71 (m, 1 H, $H_pCH_2NC{=}O$), 3.71–3.64 (m, 1 H, $H_pCH_2NC{=}O$), 3.64–3.55 (m, 1 H, $H_pCH_2NC{=}O$), 3.20–3.09 (m, 1 H, H_pCH_2NPh), 3.08–2.99 (m, 1 H, H_pCH_2NPh), 2.99–2.92 (m, 1.5 H, H_pCH_2NPh, 0.5 $H3_e$), 3.47, 3.26 (2 d, *J* = 11 Hz, 1 H, $H3_a$), 2.87, 2.83 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.76 (d, *J* = 11 Hz, 0.5 H, 0.5 $H3_e$), 2.62–2.55 (m, 1 H, H_pCH_2NPh), 2.41, 2.15 (2 t, *J* = 11 Hz, 1 H, H2), 2.38, 2.10 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$).

^{13}C NMR (125 MHz, CD_3OD): δ = 171.06, 171.07, 152.40, 136.33, 136.31, 130.50, 130.48, 130.11, 130.09, 130.07, 129.82, 121.56, 117.81, 70.85, 58.04, 57.94, 55.28, 54.77, 51.09, 50.72, 50.50, 46.67, 45.11, 43.34, 42.46, 42.42.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{29}N_5NaO_3$: 470.2168; found: 470.2191.

(*S*)-8-(2-Morpholin-4-yl-2-oxo-1-phenylethyl)tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (29)
IR: 3443, 3261, 3092, 2924, 2859, 1675, 1464, 1444, 1334, 1274, 1202, 1179, 1116, 1020, 799, 720 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.49–7.32 (m, 5 H, H_{Ar}), 4.63, 4.61 (2 s, 1 H, H6), 4.39–4.35 (2 d, *J* = 13 Hz, 1 H, $H5_a$), 4.17, 4.12 (2 d, *J* = 13 Hz, 1 H, $H5_e$), 4.02–3.86 (m, 2 H, $H1_{a,e}$), 3.71–3.36 (m, 7.5 H, 7 H_m, 0.5 $H3_a$), 3.25 (d, 0.5 H, 0.5 $H3_a$), 3.14 (t, *J* = 9 Hz, 1 H, H_m), 2.86, 2.82 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.97, 2.74 (2 d, *J* = 11 Hz, 1 H, $H3_e$), 2.40, 2.14 (2 t, *J* = 11 Hz, 1 H, H2), 2.38, 2.09 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$).

^{13}C NMR (125 MHz, CD_3OD): δ = 171.20, 171.19, 167.33, 167.25, 164.81, 164.75, 136.19, 136.16, 130.46, 130.44, 130.07, 130.05, 129.81, 79.51, 70.69, 70.63, 67.69, 67.39, 58.03, 57.94, 55.19, 54.72, 50.98, 50.45, 47.36, 47.34, 45.14, 45.10, 43.79, 42.45, 42.41.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{24}N_4NaO_4$: 395.1695; found: 395.1713.

(*S*)-8-[2-(4-Methoxybenzylamino)-2-oxo-1-phenylethyl]tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (30)
IR: 3442, 3300, 3064, 2924, 2836, 1687, 1667, 1613, 1513, 1464, 1443, 1331, 1247, 1174, 1113, 1031, 820, 753, 701 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.47–4.42 (m, 2 H, H_{Ar}), 7.37–7.30 (m, 3 H, H_{Ar}), 7.11–7.06 (m, 2 H, H_{Ar}), 6.79 (d, *J* = 8 Hz, 2 H, H_{Ar}), 4.40 (d, *J* = 13 Hz, 0.5 H, 0.5 $H5_a$), 4.35–4.26 (m, 2.5 H, 2 $PhCH_2NH$, 0.5 $H5_a$), 4.24, 4.12 (2 d, 1 H, $H5_e$), 4.00–3.85 (m, 3 H, $H1_{a,e}$, H6), 3.73 (2 s, 3 H, OCH_3), 3.56, 3.17 (2 d, *J* = 11 Hz, 1 H, $H3_a$), 3.00, 2.66 (2 d, *J* = 11 Hz, 1 H, $H3_e$), 2.91, 2.80 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.22, 1.90 (2 t, *J* = 11 Hz, 1 H, H2), 2.15, 1.86 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$).

^{13}C NMR (125 MHz, CD_3OD): δ = 173.20, 173.18, 167.13, 167.07, 164.78, 164.69, 160.35, 160.30, 137.39, 137.34, 131.87, 131.78, 129.99, 129.92, 129.82, 129.77, 129.73, 129.71, 129.60, 129.58, 114.91, 114.86, 76.23, 76.17, 57.92, 57.67, 56.10, 55.68, 55.67, 54.48, 51.99, 50.30, 45.13, 45.06, 43.41, 42.29, 42.19.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{26}N_2NaO_4$: 445.1852; found: 445.1850.

(*S*)-8-[2-(4-Fluorophenylamino)-2-oxo-1-phenylethyl]tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (31)
IR: 3442, 3281, 3070, 2923, 2853, 1671, 1510, 1467, 1454, 1407, 1331, 1274, 1211, 1155, 1113, 1028, 838, 810, 765, 729, 701 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.61–7.50 (m, 4 H, H_{Ar}), 7.43–7.30 (m, 3 H, H_{Ar}), 7.08–6.98 (m, 2 H, H_{Ar}), 4.47, 4.36 (2 d, *J* = 13 Hz, 1 H, $H5_a$), 4.31, 4.18 (2 d, *J* = 13 Hz, 1 H, $H5_e$), 4.09 (s, 1 H, H6), 4.03–3.88 (m, 2 H, $H1_{a,e}$), 3.57, 3.23 (2 d, *J* = 11 Hz, 1 H, $H3_a$), 3.10, 2.73 (2 d, *J* = 11 Hz, 1 H, $H3_e$), 2.99, 2.87 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.32, 2.01 (2 t, *J* = 11 Hz, 1 H, H2), 2.29, 1.96 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$).

^{13}C NMR (125 MHz, CD_3OD): δ = 171.56, 167.20, 167.14, 164.82, 164.76, 161.91, 159.99, 135.44, 135.42, 130.05, 129.98, 129.91, 129.86, 129.79, 129.77, 123.76, 123.70, 123.64, 116.41, 116.39, 116.23, 116.21, 76.40, 76.29, 57.96, 57.74, 55.92, 54.53, 51.94, 50.33, 45.15, 45.10, 42.31, 42.28.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{21}FN_4NaO_3$: 419.1495; found: 419.1507.

(3*S*,9a*S*)-3-Methyl-8-[2-oxo-1-phenyl-2-(4-phenylpiperazin-1-yl)ethyl]tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (32)
IR: 3452, 3205, 3062, 2985, 2921, 2817, 1689, 1659, 1643, 1599, 1504, 1452, 1432, 1326, 1264, 1232, 1154, 1015, 755, 697 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.56–7.28 (m, 5 H, H_{Ar}), 7.19 (t, *J* = 8 Hz, 2 H, H_{Ar}), 6.90 (d, *J* = 8 Hz, 2 H, H_{Ar}), 6.82 (t, *J* = 7 Hz, 1 H, H_{Ar}), 4.70, 4.69 (2 s, 1 H, H6), 4.37, 4.33 (2 d, *J* = 13 Hz, 1 H, $H5_a$), 4.15, 4.11 (2 d, *J* = 13 Hz, 1 H, $H5_e$), 4.04 (quintet, *J* = 7 Hz, 1 H, H1), 3.88–3.77 (m, 1 H, $H_pCH_2NC{=}O$), 3.77–3.63 (m, 2 H, $H_pCH_2NC{=}O$), 3.63–3.52 (m, 1 H, $H_pCH_2NC{=}O$), 3.47, 3.26 (2 d, *J* = 11 Hz, 1 H, $H3_a$), 3.18–3.08 (m, 1 H, H_pCH_2NPh), 3.08–2.98 (m, 1 H, H_pCH_2NPh), 2.98–2.90 (m, 1.5 H, H_pCH_2NPh, 0.5 $H3_e$), 2.86, 2.81 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.76 (d, *J* = 11 Hz, 0.5 H, 0.5 $H3_e$), 2.66–2.54 (m, 1 H, H_pCH_2NPh), 2.41, 2.13 (2 t, *J* = 11 Hz, 1 H, H2), 2.38, 2.11 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$), 1.41 (t, *J* = 7 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, CD_3OD): δ = 171.07, 167.98, 167.92, 152.37, 136.31, 130.48, 130.09, 129.81, 121.53, 117.78, 112.06, 70.72, 58.50, 55.46, 55.17, 51.46, 51.15, 50.68, 50.46, 46.66, 43.29, 42.58, 21.27, 21.20.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{31}N_5NaO_3$: 484.2325; found: 484.2356.

(3*S*,9a*S*)-3-Methyl-8-(2-morpholin-4-yl-2-oxo-1-phenylethyl)tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (33)
IR: 3475, 3243, 2969, 2923, 2857, 1683, 1651, 1453, 1322, 1269, 1230, 1154, 1114, 1025, 733, 701 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.60–7.31 (m, 5 H, H_{Ar}), 4.65, 4.64 (2 s, 1 H, H6), 4.38, 4.33 (2 d, *J* = 13 Hz, 1 H, $H5_a$), 4.15, 4.11 (2 d, *J* = 13 Hz, 1 H, $H5_e$), 4.05 (quintet, *J* = 7 Hz, 1 H, H1), 3.70–3.34 (m, 7.5 H, 7 H_m, 0.5 $H3_a$), 3.25 (d, 0.5 H, 0.5 $H3_a$), 3.14 (t, *J* = 9 Hz, 1 H, H_m), 2.98, 2.76 (2 d, *J* = 11 Hz, 1 H, $H3_e$), 2.85, 2.81 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.41, 2.13 (2 t, *J* = 11 Hz, 1 H, H2), 2.38, 2.10 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$), 1.41 (t, *J* = 7 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, CD_3OD): δ = 171.10, 167.96, 167.90, 167.05, 166.96, 136.09, 130.44, 130.42, 130.07, 130.05, 129.83, 129.81, 70.55, 70.53, 67.65, 67.35, 58.44, 58.40, 58.31, 55.38, 55.09, 51.45, 51.44, 51.08, 50.62, 47.33, 47.31, 43.73, 42.55, 42.51, 21.25, 21.19.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{26}N_4NaO_4$: 387.2032; found: 387.2036.

(3*S*,9a*S*)-8-[2-(4-Methoxybenzylamino)-2-oxo-1-phenylethyl]-3-methyltetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (34)

IR: 3456, 3282, 3065, 2928, 2835, 1683, 1661, 1613, 1513, 1453, 1322, 1247, 1175, 1151, 1303, 1030, 700 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.50–7.41 (m, 2 H, H_{Ar}), 7.38–7.28 (m, 3 H, H_{Ar}), 7.12–7.05 (m, 2 H, H_{Ar}), 6.85–6.76 (m, 2 H, H_{Ar}), 4.35–4.26 (m, 2.5 H, $PhCH_2NH$, 0.5 $H5_a$), 4.37 (d, 0.5 H, 0.5 $H5_a$), 4.23, 4.10 (2 d, 1 H, $H5_e$), 4.02 (q, *J* = 7 Hz, 1 H, H1), 3.95, 3.94 (2 s, 1 H, H6), 3.73, 3.72 (2 s, 3 H, OCH_3), 3.58, 3.18 (d, *J* = 11 Hz, 1 H, $H3_a$), 3.00, 2.67 (2 d, *J* = 11 Hz, 1 H, $H3_e$), 2.90, 2.79 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.19, 1.86 (2 t, *J* = 11 Hz, 1 H, H2), 2.14, 1.84 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$), 1.38, 1.41 (2 d, *J* = 7 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, CD_3OD): δ = 173.16, 168.00, 167.91, 166.94, 166.86, 160.35, 160.31, 137.39, 137.45, 131.87, 131.78, 129.98, 129.92, 129.83, 129.78, 129.73, 129.61, 129.58, 114.91, 114.87, 76.19, 76.17, 76.09, 58.39, 58.16, 56.41, 55.69, 55.68, 55.67, 55.66, 54.92, 52.14, 51.46, 51.42, 50.50, 43.41, 42.46, 42.35, 21.20, 21.13.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{28}N_4NaO_4$: 459.2008; found: 459.2014.

(3*S*,9a*S*)-8-[2-(4-Fluorophenylamino)-2-oxo-1-phenylethyl]-3-methyltetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (35)

IR: 3456, 3277, 3071, 2977, 2925, 2851, 1683, 1668, 1509, 1453, 1408, 1366, 1322, 1266, 1212, 1155, 1030, 838, 810, 788, 764, 699 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.62–7.50 (m, 4 H, H_{Ar}), 7.44–7.30 (m, 3 H, H_{Ar}), 7.04 (t, 2 H, H_{Ar}), 4.45, 4.38 (2 d, *J* = 13 Hz, 1 H, $H5_a$), 4.30, 4.18 (2 d, *J* = 13 Hz, 1 H, $H4_e$), 4.09, 4.08 (2 d, *J* = 13 Hz, 1 H, $H4_e$), 4.05 (q, *J* = 7 Hz, 1 H, H1), 3.59, 3.24 (2 d, *J* = 11 Hz, 1 H, $H3_a$), 3.12, 2.75 (2 d, *J* = 11 Hz, 1 H, $H3_e$), 2.99, 2.87 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.29, 1.96 (2 t, *J* = 11 Hz, 1 H, H2), 2.27, 1.95 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$), 1.41, 1.43 (2 d, *J* = 7 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, CD_3OD): δ = 171.61, 168.10, 168.03, 167.03, 166.95, 160.03, 137.10, 135.45, 130.05, 130.00, 129.95, 129.89, 129.84, 129.81, 123.78, 123.71, 123.66, 116.43, 116.41, 116.25, 116.23, 76.43, 76.28, 58.43, 58.22, 56.26, 54.98, 52.17, 51.50, 50.56, 42.48, 42.44, 21.19, 21.09.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{23}FN_4O_3$: 411.1833; found: 411.1846.

(9a*S*)-8-[2-Oxo-1-phenyl-2-(4-phenylpiperazin-1-yl)ethyl]-3-phenyltetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (36)

Major pair of diastereomers

IR: 3457, 3229, 2922, 2854, 2818, 1681, 1651, 1598, 1495, 1452, 1303, 1271, 1228, 1152, 1124, 1016, 757, 698 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.53–7.44 (m, 2 H, H_{Ar}), 7.44–7.29 (m, 8 H, H_{Ar}), 7.20 (t, *J* = 8 Hz, 2 H, H_{Ar}), 6.89 (d, *J* = 9 Hz, 2 H, H_{Ar}), 6.83 (t, *J* = 7 Hz, 1 H, H_{Ar}), 5.08, 5.06 (2 s, 1 H, H1), 4.72 (s, 1 H, H6), 4.38–4.20 (m, 2 H, H5), 3.92–3.77 (m, 1 H, $H_pCH_2NC{=}O$), 3.77–3.64 (m, 2 H, $H_pCH_2NC{=}O$), 3.64–3.54 (m, 1.5 H, $H_pCH_2NC{=}O$, 0.5 $H3_a$), 3.36 (d, *J* = 11 Hz, 0.5 H, 0.5 $H3_a$), 3.20–3.08 (m, 1 H, H_pCH_2NPh), 3.08–2.91 (m, 2.5 H, 2 H_pCH_2NPh, 0.5 $H3_e$), 2.89, 2.85 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.75 (d, *J* = 11 Hz, 0.5 H, 0.5 $H3_e$), 2.66–2.52 (m, 1.5 H, H_pCH_2NPh, 0.5 H2), 2.34, 2.10 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$), 2.27 (t, *J* = 11 Hz, 0.5 H, 0.5 H2).

^{13}C NMR (125 MHz, CD_3OD): δ = 171.27, 171.22, 166.80, 166.76, 165.39, 165.33, 152.31, 152.30, 140.08, 140.05, 131.67, 131.64, 130.10, 129.82, 129.80, 129.54, 128.62, 128.57, 127.95, 121.46, 117.71, 115.39, 115.35, 79.70, 69.93, 60.20, 60.14, 58.76, 55.80, 55.78, 55.72, 55.46, 51.22, 50.65, 50.62, 50.37, 46.58, 43.20, 42.81.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{31}H_{33}N_5NaO_3$: 546.2482; found: 546.2497.

Minor pair of diastereomers

^1H NMR (500 MHz, CD_3OD): δ = 7.52–7.45 (m, 2 H, H_{Ar}), 7.45–7.28 (m, 8 H, H_{Ar}), 7.19 (t, *J* = 8 Hz, 2 H, H_{Ar}), 6.88 (d, *J* = 9 Hz, 2 H, H_{Ar}), 6.83 (t, *J* = 7.5 Hz, 1 H, H_{Ar}), 5.05, 5.04 (2 s, 1 H, H1), 4.71, 4.69 (2 s, 1 H, H6), 4.40–4.20 (m, 2 H, H5), 3.88–3.79 (m, 1 H, $H_pCH_2NC{=}O$), 3.79–3.72 (m, 1 H, $H_pCH_2NC{=}O$), 3.72–3.64 (m, 1 H, $H_pCH_2NC{=}O$), 3.64–3.58 (m, 1 H, $H_pCH_2NC{=}O$), 3.56, 3.36 (2 d, *J* = 11 Hz, 1 H, $H3_a$), 3.18–3.10 (m, 1 H, H_pCH_2NPh), 3.08–2.90 (m, 2.5 H, 2 H_pCH_2NPh, 0.5 $H3_e$), 2.89, 2.83 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.75 (d, *J* = 11 Hz, 0.5 H, 0.5 $H3_e$), 2.59 (t, *J* = 8.5 Hz, 1 H, H_pCH_2NPh), 2.46, 2.21 (2 t, *J* = 11 Hz, 1 H, H2), 2.42, 2.13 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$).

^{13}C NMR (125 MHz, CD_3OD): δ = 171.30, 171.29, 167.31, 167.23, 165.87, 165.83, 152.36, 152.35, 140.04, 140.01, 131.68, 131.65, 130.12, 129.95, 129.94, 129.61, 128.28, 1228.25, 127.93, 121.51, 117.77, 115.41, 115.38, 79.48, 70.12, 60.26, 60.22, 57.79, 57.67, 55.68, 55.03, 51.15, 50.69, 50.44, 46.62, 43.27, 42.60.

(9a*S*)-8-(2-Morpholin-4-yl-2-oxo-1-phenylethyl)-3-phenyltetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (37)

Major pair of diastereomers

IR: 3456, 3242, 3063, 2960, 2922, 2856, 1652, 1494, 1454, 1340, 1303, 1270, 1230, 1114, 1022, 757, 702 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.50–7.28 (m, 10 H, H_{Ar}), 5.07, 5.06 (2 s, 1 H, H1), 4.66 (s, 1 H, H6), 4.36–4.18 (m, 2 H, $H5_{a,e}$), 3.73–3.32 (8 H, 7 H_m, $H3_a$), 3.20–3.08 (m, 1 H, H_m), 2.87, 2.85 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.96, 2.74 (2 d, *J* = 11 Hz, 1 H, $H3_e$), 2.56, 2.26 (2 t, *J* = 11 Hz, 1 H, H2), 2.33 Hz), 2.08 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$).

^{13}C NMR (125 MHz, CD_3OD): δ = 171.22, 171.19, 166.83, 166.79, 165.49, 165.44, 140.11, 140.08, 136.20, 130.46, 130.45, 130.09, 130.06, 129.84, 129.82, 129.57, 128.65, 128.59, 70.51, 70.47, 67.67, 67.38, 60.23, 60.17, 58.82, 55.73, 55.56, 51.15, 50.78, 47.35, 43.75, 42.85, 42.84.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{28}N_4O_4$: 449.2189; found: 449.2189.

Minor pair of diastereomers

^1H NMR (500 MHz, CD_3OD): δ = 7.48–7.30 (m, 10 H, H_{Ar}), 5.05, 5.04 (2 s, 1 H, H1), 4.65, 4.63 (2 s, 1 H, H6), 4.43–2.28 (m, 2 H, $H4_{a,e}$), 3.72–3.37 (m, 7.5 H, 7 H_m, 0.5 $H3_a$), 3.34 (d, *J* = 11 Hz, 0.5 H, 0.5 $H3_a$), 3.19–3.11 (m, 1 H, H_m), 2.98, 2.75 (2 d, *J* = 11 Hz, 1 H, $H3_e$), 2.87, 2.82 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.45, 2.19 (2 t, *J* = 11 Hz, 1 H, H2), 2.41, 2.12 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$).

^{13}C NMR (125 MHz, CD_3OD): δ = 171.21, 167.31, 167.22, 165.92, 165.89, 140.06, 140.04, 136.15, 130.47, 130.45, 130.11, 130.09, 129.97, 129.96, 129.84, 129.64, 128.30, 128.27, 70.68, 70.65, 67.70, 67.40, 60.27, 57.80, 57.71, 55.66, 55.12, 50.46, 47.36, 43.83, 43.80, 42.63, 42.60.

(9a*S*)-8-[2-(4-Methoxybenzylamino)-2-oxo-1-phenylethyl]-3-phenyltetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (38)

Major pair of diastereomers

IR: 3462, 3300, 3063, 2925, 2835, 1664, 1613, 1513, 1454, 1303, 1247, 1176, 1124, 1030, 817, 752, 701 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.50–7.41 (m, 2 H, H_{Ar}), 7.40–7.27 (m, 8 H, H_{Ar}), 7.12–7.07 (m, 2 H, H_{Ar}), 6.84–6.76 (m, 2 H,

H_{Ar}), 5.04, 5.02 (2 s, 1 H, H1), 4.40–4.25 (m, 3 H, 2 $NHCH_2Ar$, $H5_a$), 4.21 (d, J = 13 Hz, 1 H, $H5_e$), 3.96, 3.95 (2 s, 1 H, H6), 3.72, 3.71 (2 s, 3 H, OCH_3), 3.69, 3.28 (2 d, J = 11 Hz, 1 H, $H3_a$), 2.97, 2.64 (2 d, J = 11 Hz, 1 H, $H3_e$), 2.91, 2.80 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.32, 1.98 (2 t, J = 11 Hz, 1 H, H2), 2.08, 1.79 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$).

^{13}C NMR (125 MHz, CD_3OD): δ = 173.12, 166.68, 166.64, 165.48, 165.40, 160.34, 160.31, 139.94, 137.37, 137.29, 131.86, 131.80, 129.97, 129.95, 129.82, 129.76, 129.73, 129.64, 129.58, 128.59, 128.53, 128.23, 128.18, 114.93, 114.87, 76.09, 76.00, 60.20, 60.10, 58.71, 56.79, 55.68, 55.33, 52.21, 50.63, 52.21, 50.63, 43.43, 43.41, 42.71, 42.59.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{29}H_{30}N_4O_4$: 499.2345; found: 499.2350.

Minor pair of diastereomers

^{1}H NMR (500 MHz, CD_3OD): δ = 7.50–7.43 (m, 2 H, H_{Ar}), 7.42–7.26 (m, 8 H, H_{Ar}), 7.13–7.06 (m, 2 H, H_{Ar}), 6.83–6.76 (m, 2 H, H_{Ar}), 5.05, 5.02 (2 s, 1 H, H1), 4.40–4.20 (m, 4 H, 2 $NHCH_2Ph$, $H5_{a,e}$), 3.96 (s, 1 H, H6), 3.74, 3.73 (2 s, 3 H, OCH_3), 3.65, 3.27 (2 d, J = 11 Hz, 1 H, $H3_a$), 2.99, 2.66 (2 d, J = 11 Hz, 1 H, $H3_e$), 2.92, 2.81 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.28, 1.96 (2 t, J = 11 Hz, 1 H, H2), 2.20, 1.90 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$).

^{13}C NMR (125 MHz, CD_3OD): δ = 173.27, 167.27, 167.15, 166.03, 165.93, 160.39, 139.97, 137.38, 137.35, 131.90, 131.82, 129.98, 129.96, 129.90, 129.85, 129.81, 129.77, 129.69, 129.64, 128.61, 128.56, 128.26, 128.21, 114.95, 114.89, 76.21, 76.17, 60.26, 57.69, 57.42, 56.48, 55.71, 55.68, 54.85, 52.01, 50.29, 46.28, 44.94, 44.01, 43.44, 42.56, 42.41.

(9a*S*)-8-[2-(4-Fluorophenylamino)-2-oxo-1-phenylethyl]-3-phenyltetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (39)

Major pair of diastereomers

IR: 3463, 3279, 3064, 3032, 2921, 2826, 1672, 1509, 1454, 1407, 1304, 1269, 1211, 1125, 1029, 838, 810, 763, 739, 700 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.59–7.50 (m, 4 H, H_{Ar}), 7.42–7.30 (m, 8 H, H_{Ar}), 7.07–7.00 (m, 3 H, H_{Ar}), 4.45–4.24 (m, 2 H, $H5_{a,e}$), 5.09, 5.07 (2 s, 1 H, H1), 4.12, 4.10 (s, 1 H, H6), 3.70, 3.35 (2 d, J = 11 Hz, 1 H, $H3_a$), 3.10, 2.73 (2 d, J = 11 Hz, 1 H, $H3_e$), 3.01, 2.89 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.42, 2.08 (2 t, J = 11 Hz, 1 H, H2), 2.22, 1.90 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$).

^{13}C NMR (125 MHz, CD_3OD): δ = 172.99, 171.52, 166.76, 166.75, 165.58, 165.52, 161.92, 160.01, 159.99, 140.01, 139.97, 137.03, 137.00, 135.44, 135.42, 135.39, 130.05, 130.01, 129.94, 129.86, 129.85, 129.84, 129.77, 129.62, 129.61, 128.61, 128.55, 123.80, 123.74, 123.66, 116.40, 116.23, 76.30, 76.17, 61.54, 60.23, 60.16, 58.75, 58.58, 56.62, 55.37, 52.20, 50.67, 42.75, 42.69.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{27}H_{25}FN_4NaO_3$: 495.1808; found: 495.1830.

Minor pair of diastereomers

^{1}H NMR (500 MHz, CD_3OD): δ = 7.58–7.51 (m, 4 H, H_{Ar}), 7.44–7.30 (m, 8 H, H_{Ar}), 7.08–7.00 (m, 3 H, H_{Ar}), 4.47–4.31 (m, 2 H, $H5_{a,e}$), 5.07, 5.05 (2 s, 1 H, H1), 4.12 (s, 1 H, H6), 3.66, 3.32 (2 d, J = 11 Hz, 1 H, $H3_a$), 3.10, 2.74 (2 d, J = 11 Hz, 1 H, $H3_e$), 3.00, 2.88 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.38, 2.06 (2 t, J = 11 Hz, 1 H, H2), 2.33, 1.99 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$).

^{13}C NMR (125 MHz, CD_3OD): δ = 172.96, 171.58, 167.13, 166.59, 165.80, 165.59, 161.92, 161.91, 159.99, 159.98, 140.03, 137.04, 137.02, 135.46, 135.44, 135.42, 130.05, 130.00, 129.98, 129.96, 129.89, 129.88, 129.78, 129.68, 129.65, 128.61, 128.56, 123.77, 123.71, 123.65, 116.41, 116.24, 116.24, 76.37, 76.27, 61.53, 60.29, 60.22, 58.64, 56.31, 54.54, 51.97, 50.32, 43.44, 42.61, 42.47.

(3*S*,9a*S*)-3-Benzyl-8-[2-oxo-1-phenyl-2-(4-phenylpiperazin-1-yl)ethyl]tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (40)

IR: 3454, 3243, 3062, 3028, 2919, 2822, 1682, 1651, 1599, 1495, 1454, 1442, 1339, 1274, 1228, 1154, 1017, 759, 701 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.44–7.33 (m, 4 H, H_{Ar}), 7.33–7.24 (m, 4 H, H_{Ar}), 7.24–7.16 (m, 2 H, H_{Ar}), 7.16–7.08 (m, 3 H, H_{Ar}), 6.92–6.80 (m, 2 H, H_{Ar}), 4.42–4.26 (m, 2 H, H1, $H5_a$), 4.15, 4.12 (2 s, 1 H, H6), 3.98, 3.87 (2 d, J = 13 Hz, 1 H, $H5_e$), 3.84–3.50 (m, 4 H, 4 $H_pCH_2NC{=}O$), 3.30–3.24 (m, 1 H, $PhCH_2CH$), 3.18–2.80, 2.79–2.60, 2.60–2.48 (3 m, 8 H, 4 (m, 1 H, H_pCH_2NPh, $H3_{a,e}$, $H4_a$, $PhCH_2CH$), 1.80, 1.50 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$), 0.42, 0.22 (2 t, J = 11 Hz, 1 H, H2).

^{13}C NMR (125 MHz, CD_3OD): δ = 170.69, 170.55, 166.81, 164.85, 152.39, 152.37, 136.38, 136.32, 135.91, 135.90, 130.44, 130.31, 130.14, 130.12, 130.10, 130.05, 129.81, 129.79, 129.76, 129.74, 128.63, 128.60, 121.58, 71.04, 58.44, 58.27, 56.75, 55.52, 54.05, 51.56, 50.85, 50.64, 50.44, 49.88, 46.71, 43.44, 42.24, 40.89.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{32}H_{35}N_5O_3$: 538.2818; found: 538.2840.

(3*S*,9a*S*)-3-Benzyl-8-(2-morpholin-4-yl-2-oxo-1-phenylethyl)tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (41)

IR: 3459, 3242, 3086, 3029, 2961, 2923, 2856, 1683, 1650, 1495, 1454, 1442, 1340, 1323, 1272, 1229, 1205, 1113, 1020, 750, 702 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.45–7.31 (m, 4 H, H_{Ar}), 7.30–7.18 (m, 4 H, H_{Ar}), 7.13–7.05 (m, 2 H, H_{Ar}), 4.40–4.34 (m, 1.5 H, H1, 0.5 $H5_a$), 4.29 (d, 0.5 H, 0.5 $H4_a$), 4.08, 4.06 (2 s, 1 H, H6), 3.97, 3.86 (2 d, J = 13 Hz, 1 H, $H5_e$), 3.68–3.33 (m, 7 H, 7 H_m), 3.29–3.26 (m, 1 H, $PhCH_2CH$), 3.24–3.16, 3.12–3.04 (2 m, 1 H, H_m), 2.94, 2.66 (2 d, J = 11 Hz, 1 H, $H3_a$), 2.92–2.84 (m, 1 H, $PhCH_2CH$), 2.82, 2.53 (2 d, J = 11 Hz, 1 H, $H3_e$), 2.74, 2.64 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 1.79, 1.49 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$), 0.40, 0.19 (2 t, J = 11 Hz, 1 H, H2).

^{13}C NMR (125 MHz, CD_3OD): δ = 170.83, 170.68, 166.81, 164.88, 164.87, 136.37, 136.30, 135.75, 132.25, 132.19, 130.42, 130.30, 130.12, 130.06, 129.85, 129.81, 129.75, 129.73, 128.63, 128.58, 70.98, 70.91, 67.70, 67.66, 67.51, 67.35, 58.41, 58.27, 56.75, 56.73, 5545, 53.97, 51.56, 47.41, 47.35, 43.90, 42.23, 40.88, 40.85.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{26}H_{30}N_4NaO_4$: 485.2165; found: 485.2183.

(3*S*,9a*S*)-3-Benzyl-8-[2-(4-methoxybenzylamino)-2-oxo-1-phenylethyl]tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (42)

IR: 3281, 3063, 3029, 2926, 2835, 1683, 1659, 1614, 1513, 1454, 1441, 1339, 1322, 1301, 1247, 1206, 1117, 1108, 1031, 820, 783, 749, 701 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.42–7.18 (m, 8 H, H_{Ar}), 7.16–7.00 (m, 4 H, H_{Ar}), 6.82–6.76 (m, 2 H, H_{Ar}), 4.40–4.17 (m, 4 H, 2 $PhCH_2H$, H1, $H5_a$), 4.01, 3.83 (2 d, J = 13 Hz, 1 H, $H5_e$), 3.74 (s, 3 H, OCH_3), 3.51, 3.49 (2 s, 1 H, H6), 3.30–3.26 (m, 1 H, $PhCH_2CH$), 2.99, 2.49 (2 d, J = 11 Hz, 1 H, $H3_a$), 2.94–2.81 (m, 1 H, $PhCH_2CH$), 2.76, 2.40 (2 d, J = 11 Hz, 1 H, $H3_e$), 2.74, 2.62 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 1.68, 1.38 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$), 0.34, –0.07 (2 t, J = 11 Hz, 1 H, H2).

^{13}C NMR (125 MHz, CD_3OD): δ = 173.24, 173.01, 166.81, 166.78, 164.85, 164.79, 160.38, 160.24, 137.14, 137.10, 136.26, 132.28, 132.24, 131.89, 131.84, 130.03, 129.86, 129.81, 129.79, 129.6, 129.74, 129.67, 129.62, 129.60, 128.75, 128.69, 114.89, 114.84, 76.30, 76.11, 58.46, 58.22, 56.78, 56.72, 55.68, 55.62, 53.71, 51.92, 3.37, 43.34, 42.24, 42.14, 40.990, 40.84.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{32}N_4O_4$: 513.2502; found: 513.2512.

(3*S*,9a*S*)-3-Benzyl-8-[2-(4-fluorophenylamino)-2-oxo-1-phenylethyl]tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (43)

IR: 3455, 3269, 3064, 3030, 2924, 2838, 1683, 1510, 1454, 1442, 1407, 1339, 1322, 1272, 1210, 1188, 1155, 1101, 1030, 838, 810, 764, 748, 701 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.56–7.48 (m, 2 H, H_{Ar}), 7.40–7.21 (m, 8 H, H_{Ar}),, 7.13–7.08 (m, 2 H, H_{Ar}), 7.05–6.98 (m, 2 H, H_{Ar}), 4.34, 4.32 (2 d, 1 H, H1), 4.42, 4.31 (2 d, 1 H, H5$_a$), 4.07, 3.90 (2 d, 1 H, H5$_e$), 3.70, 3.69 (2 s, 1 H, H6), 3.33–3.27 (m, 1 H, $PhCH_2CH$), 3.02, 2.57 (2 d, *J* = 11 Hz, 1 H, H3$_a$), 2.93–2.84 (m, 1.5 H, $PhCH_2CH$, 0.5 H3$_a$), 2.80, 2.68 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, H4$_a$), 2.48 (d, *J* = 11 Hz, 0.5 H, H3$_e$), 1.80, 1.45 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, H4$_e$), 0.49, 0.07 (2 t, *J* = 11 Hz, 1 H, H2).

^{13}C NMR (125 MHz, CD_3OD): δ = 171.46, 171.32, 166.79, 166.72, 164.80, 164.76, 161.92, 161.88, 156.99, 159.96, 136.75, 136.56, 136.24, 136.21, 135.41, 135.39, 135.30, 135.28, 132.24, 132.16, 130.14, 129.88, 129.85, 129.73, 129.66, 128.69, 128.64, 123.89, 123.83, 123.71, 123.64, 116.39, 116.35, 116.21, 116.17, 76.21, 76.19, 76.09, 76.07, 58.50, 58.22, 56.75, 56.72, 55.51, 53.72, 51.76, 49.89, 42.22, 40.86, 40.82.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{27}FN_4O_3$: 487.2145; found: 487.2130.

(3*S*,9a*S*)-3-(4-Hydroxybenzyl)-8-[2-oxo-1-phenyl-2-(4-phenylpiperazin-1-yl)ethyl]tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (44)

IR: 3240, 3063, 3025, 2921, 2822, 1680, 1639, 1598, 1414, 1495, 1443, 1337, 1272, 1229, 1186, 1152, 1115, 1016, 759, 698 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.46–7.28 (m, 6 H, H_{Ar}), 7.25–7.16 (m, 2 H, H_{Ar}), 7.02–6.94 (m, 2 H, H_{Ar}), 6.93–6.78 (m, 4 H, H_{Ar}), 4.39 (d, *J* = 13 Hz, 0.5 H, 0.5 H5$_a$), 4.32–4.26 (m, 1.5 H, H1, 0.5 H5$_a$), 4.00 (d, *J* = 13 Hz, 0.5 H, H5$_e$), 3.94, 3.91 (2 s, 1 H, H6), 3.88–3.56 (m, 4.5 H, 4 $H_pCH_2NC{=}O$, 0.5 H5$_e$), 3.27–3.19 (m, 1 H, $PhCH_2CH$), 3.15–3.03 (m, 2 H, 2 H_pCH_2NPh), 3.00, 2.38 (2 d, *J* = 11 Hz, 1 H, H3$_a$), 2.97–2.84 (m, 1.5 H, H_pCH_2NPh, 0.5 H3$_e$), 2.83–2.74 (m, 1 H, $PhCH_2CH$), 2.74–2.68 (m, 1 H, H_pCH_2NCPh), 2.60 (dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, H4$_a$), 2.24 (d, *J* = 11 Hz, 0.5 H, 0.5 H3$_e$), 1.73, 1.55 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, H4$_e$), 0.31, 0.09 (2 t, *J* = 11 Hz, 1 H, H2).

^{13}C NMR (125 MHz, CD_3OD): δ = 170.50, 170.40, 166.94, 164.94, 158.16, 158.14, 152.38, 152.34, 136.40, 136.33, 133.70, 133.65, 130.25, 130.17, 130.13, 129.97, 129.92, 127.04, 127.01, 121.57, 117.82, 117.79, 116.82, 116.71, 71.80, 71.57, 58.28, 57.95, 57.04, 55.95, 54.44, 51.86, 51.01, 50.80, 50.45, 49.96, 46.72, 43.55, 42.11, 42.07, 40.21, 40.15.

(3*S*,9a*S*)-3-(4-Hydroxybenzyl)-8-(2-morpholin-4-yl-2-oxo-1-phenylethyl)tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (45)

IR: 3241, 2967, 2924, 2855, 1683, 1637, 1613, 1592, 1514, 1464, 1441, 1338, 1264, 1232, 1206, 1185, 1147, 1113, 1032, 1018, 863, 817, 757, 700 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.44–7.29 (m, 5 H, H_{Ar}), 7.0–6.93 (m, 2 H, H_{Ar}), 6.84–6.77 (m, 2 H, H_{Ar}), 4.39 (d, *J* = 13 Hz, 0.5 H, H5$_a$), 4.32–4.22 (m, 1.5 H, H1, 0.5 H5$_a$), 4.00, 3.81 (2 d, *J* = 13 Hz, 1 H, H5$_e$), 3.87, 3.84 (2 s, 1 H, H6), 3.74–3.36 (m, 7 H, H_m), 3.27–3.17 (m, 1.5 H, $PhCH_2CH$, 0.5 H_m), 3.18–3.08 (m, 0.5 H, H_m), 2.84–2.70 (m, 1.5 H, $PhCH_2CH$, 0.5 H4$_a$), 2.99, 2.35 (2 d, *J* = 11 Hz, 1 H, H3$_a$), 2.88, 2.22 (2 d, *J* = 11 Hz, 1 H, H3$_e$), 2.59 (dt, J_1 = 3 Hz, J_2 = 13 Hz, 0.5 H, H4$_a$), 1.73, 1.53 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, H4$_e$), 0.28, 0.10 (2 t, *J* = 11 Hz, 1 H, H2).

^{13}C NMR (125 MHz, CD_3OD): δ = 170.60, 170.53, 166.94, 164.96, 158.15, 158.11, 136.28, 136.19, 133.67, 133.65, 132.48, 130.22, 130.16, 129.98, 129.93, 127.03, 127.01, 116.79, 116.67, 71.65, 71.43, 67.66, 67.44, 64.76, 58.29, 57.97, 57.01, 56.98, 55.86, 54.40, 51.78, 49.95, 47.39, 44.01, 42.11, 42.05, 40.21, 40.15.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{30}N_4O_5$: 479.2294; found: 479.2316.

(3*S*,9a*S*)-3-(4-Hydroxybenzyl)-8-[2-(4-methoxybenzylamino)-2-oxo-1-phenylethyl]tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (46)

IR: 3280, 3030, 2927, 2836, 1664, 1613, 1513, 1455, 1442, 1337, 1304, 1269, 1247, 1207, 1175, 1114, 1030, 817, 783, 754, 727, 700 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.40–7.28 (m, 5 H, H_{Ar}), 7.10–7.02 (m, 4 H, H_{Ar}), 6.97–6.87 (m, 2 H, H_{Ar}), 6.86–6.70 (m, 2 H, H_{Ar}), 4.42–4.20 (m, 4 H, 2 $PhCH_2N$, H1, H5$_a$), 4.02, 3.81 (2 d, *J* = 13 Hz, 1 H, H5$_e$), 3.74 (s, 3 H, OCH_3), 3.45, 3.41 (2 s, 1 H, H6), 3.25–3.17 (m, 1 H, $PhCH_2CH$), 3.04, 2.41 (2 d, *J* = 11 Hz, 1 H, H3$_a$), 2.86–2.68 (m, 2 H, $PhCH_2CH$, 0.5 H4$_a$, 0.5 H3$_e$), 2.60 (dt, J_1 = 3 Hz, J_2 = 13 Hz, 0.5 H, H4$_a$), 2.32 (d, *J* = 11 Hz, 0.5 H, H3$_e$), 1.74, 1.40 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, H4$_e$), 0.49 (t, *J*–11 Hz, 0.5 H, 0.5 H2), the other 'half' of the H2 signal probably overlapping with TMS signal.

^{13}C NMR (125 MHz, CD_3OD): δ = 173.40, 173.18, 166.96, 166.84, 164.97, 160.39, 160.34, 158.07, 157.95, 137.43, 137.31, 133.44, 133.35, 132.47, 131.89, 131.77, 129.89, 129.85, 129.79, 129.71, 129.67, 126.96, 126.73, 116.77, 116.64, 116.42, 114.91, 114.84, 77.08, 76.76, 58.57, 58.09, 56.03, 55.68, 53.80, 52.141, 43.35, 42.27, 42.12, 40.19, 40.08.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{30}H_{32}N_4NaO_5$: 551.2271; found: 551.2294.

(3*S*,9a*S*)-8-[2-(4-Fluorophenylamino)-2-oxo-1-phenylethyl]-3-(4-hydroxybenzyl)tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (47)

IR: 3265, 3088, 2960, 2925, 1843, 1677, 1646, 1614, 1510, 1454, 1444, 1408, 1337, 1309, 1269, 1210, 1175, 1156, 1114, 838, 813, 765, 726, 700 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.60–7.48 (m, 5 H, H_{Ar}), 7.46 (d, *J* = 7 Hz, 2 H, H_{Ar}), 7.41–7.26 (m, 2 H, H_{Ar}), 7.09–6.86 (m, 2 H, H_{Ar}), 6.83–6.70 (m, 2 H, H_{Ar}), 4.45 (d, *J* = 13 Hz, 0.5 H, H5$_a$), 4.33–4.23 (m, 1.5 H, H1, 0.5 H5$_a$), 4.09, 3.90 (2 d, *J* = 13 Hz, 1 H, H5$_e$), 3.58, 3.55 (2 s, 1 H, H6), 3.23–3.18 (m, 1 H, $PhCH_2CH$), 3.06, 2.45 (2 d, *J* = 11 Hz, 1 H, H3$_a$), 2.90, 2.38 (2 d, *J* = 11 Hz, 1 H, H3$_e$), 2.88–2.77 (m, 1.5 H, $PhCH_2CH$, 0.5 H4$_a$), 2.67 (dt, J_1 = 3 Hz, J_2 = 13 Hz, 0.5 H, H4$_a$), 1.86, 1.48 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, H4$_e$), 0.60, 0.09 (2 t, *J* = 11 Hz, 1 H, H2).

^{13}C NMR (125 MHz, CD_3OD): δ = 172.73, 172.59, 171.80, 171.50, 166.96, 166.85, 165.01, 161.97, 160.05, 158.07, 157.94, 127.12, 136.99, 135.24, 135.22, 133.46, 133.38, 129.96, 129.94, 129.89, 129.86, 127.00, 126.78, 123.98, 123.91, 116.72, 116.65, 116.38, 116.35, 116.21, 116.17, 77.34, 76.92, 58.54, 58.11, 57.02, 56.96, 55.90, 53.74, 52.36, 42.23, 42.15, 40.13, 40.09.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{27}FN_4O_4$: 503.2095; found: 503.2078.

(9a*S*)-8-[1-(4-Methoxyphenyl)-2-oxo-2-(4-phenylpiperazin-1-yl)ethyl]-3-phenyltetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (48)

Major pair of diastereomers

IR: 3457, 3239, 3031, 2929, 2853, 2834, 1684, 1655, 1609, 1598, 1512, 1495, 1454, 1440, 1339, 1304, 1250, 1229, 1177, 1154, 1124, 1017, 808, 758, 694 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.43–7.28 (m, 7 H, H_{Ar}), 7.23–7.18 (m, 2 H, H_{Ar}), 6.97–6.91 (m, 2 H, H_{Ar}), 6.87 (d, *J* = 8 Hz, 2 H, H_{Ar}), 6.82 (t, *J* = 7 Hz, 1 H, H_{Ar}), 5.04, 5.03 (2 s, 1 H, H1), 4.62, 4.61 (2 s, 1 H, H6), 4.33–4.17 (m, 2 H, $H5_{a,e}$), 3.84–3.75 (m, 4 H, OCH_3, H_pCH_2NC=O), 3.73–3.60 (m, 2 H, H_pCH_2NC=O), 3.60–3.49 (m, 1.5 H, H_pCH_2NC=O, 0.5), 3.35 (2 d, *J* = 11 Hz, 0.5 H, 0.5 $H3_a$), 3.16–3.06 (m, 1 H, H_pCH_2NPh), 3.06–2.98 (m, 1 H, H_pCH_2NPh), 2.97–2.90 (m, 1.5 H, H_pCH_2NPh, 0.5 $H3_e$), 2.86, 2.82 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.73 (d, *J* = 11 Hz, 0.5 H, 0.5 $H3_e$), 2.65–2.58 (m, 1 H, H_pCH_2NPh), 2.57, 2.24 (2 t, *J* = 11 Hz, 1 H, H2), 2.30, 2.06 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$).

^{13}C NMR (125 MHz, CD_3OD): δ = 171.27, 171.22, 166.80, 166.76, 165.39, 165.33, 161.38, 161.35, 152.31, 152.30, 140.08, 140.05, 131.67, 131.64, 130.10, 129.82, 129.80, 129.54, 128.62, 128.57, 127.95, 121.46, 117.71, 115.39, 115.35, 60.20, 60.14, 60.11, 58.76, 55.80, 55.78, 55.72, 55.46, 51.22, 50.65, 50.62, 50.37, 46.58, 43.20, 42.81.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{32}H_{35}N_5NaO_4$: 576.2587; found: 576.2584.

Minor pair of diastereomers

^{1}H NMR (500 MHz, CD_3OD): δ = 7.43–7.28 (m, 7 H, H_{Ar}), 7.23–7.18 (m, 2 H, H_{Ar}), 6.97–6.91 (m, 2 H, H_{Ar}), 6.87 (d, *J* = 8 Hz, 2 H, H_{Ar}), 6.82 (t, *J* = 7 Hz, 1 H, H_{Ar}), 5.04, 5.03 (2 s, 1 H, H1), 4.62, 4.63 (2 s, 1 H, H6), 4.41–4.28 (m, 2 H, $H5_{a,e}$), 3.85–3.75 (m, 4 H, OCH_3, H_pCH_2NC=O), 3.75–3.62 (m, 2 H, H_pCH_2NC=O), 3.61–3.56 (m, 1 H, H_pCH_2NC=O), 3.54, 3.36 (2 d, *J* = 11 Hz, 1 H, $H3_a$), 3.18–3.08 (m, 1 H, H_pCH_2NPh), 3.08–3.00 (m, 1 H, H_pCH_2NPh), 3.00–2.91 (m, 1.5 H, H_pCH_2NPh, 0.5 $H3_e$), 2.86, 2.80 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.74 (d, *J* = 11 Hz, 0.5 H, 0.5 $H3_e$), 2.66–2.56 (m, 1 H, H_pCH_2NPh), 2.44, 2.17 (2 t, *J* = 11 Hz, 1 H, H2), 2.37, 2.10 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$).

^{13}C NMR (125 MHz, CD_3OD): δ = 171.30, 171.29, 167.31, 167.23, 165.87, 165.83, 152.36, 152.35, 140.04, 140.01, 131.68, 131.65, 130.12, 129.95, 129.94, 129.61, 128.28, 128.25, 127.93, 121.51, 117.77, 115.41, 115.38, 79.48, 70.12, 60.26, 60.22, 57.79, 57.67, 55.81, 55.78, 55.68, 55.03, 51.15, 50.69, 50.44, 50.34, 46.62, 43.27, 42.60.

(9a*S*)-8-[2-Oxo-2-(4-phenylpiperazin-1-yl)-1-(2-thienyl)ethyl]-3-phenyltetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (51)

Major pair of diastereomers

IR: 3469, 3223, 3090, 3064, 2921, 2853, 2822, 1651, 1598, 1495, 1454, 1442, 1339, 1304, 1271, 1231, 1155, 1129, 1016, 759, 696 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.46 (d, *J* = 5 Hz, 1 H, H_{Ar}), 7.42–7.28 (m, 5 H, H_{Ar}), 7.22 (t, *J* = 8 Hz, 2 H, H_{Ar}), 7.13 (d, *J* = 3.5 Hz, 1 H, H_{Ar}), 7.03, 7.01 (2 d, *J* = 3.5 Hz, 1 H, H_{Ar}), 6.93 (d, *J* = 9 Hz, 2 H, H_{Ar}), 6.84 (t, *J* = 7.5 Hz, 1 H, H_{Ar}), 5.14, 5.13 (2 s, 1 H, H1), 5.04, 5.03 (2 s, 1 H, H6), 4.42–4.32 (m, 2 H, $H4_{a,e}$), 3.88–3.68 (m, 4 H, H_pCH_2NC=O), 3.53, 3.47 (2 d, *J* = 11 Hz, 2 H, $H3_a$), 3.19–3.07 (m, 2 H, H_pCH_2NPh), 3.07–3.01 (m, 1 H, H_pCH_2NPh), 2.96 (d, *J* = 11 Hz, 0.5 H, 0.5 $H3_e$), 2.91–2.78 (m, 2.5 H, H_pCH_2NPh, $H5_a$, 0.5 $H3_e$), 2.46, 2.20 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H5_e$).

^{13}C NMR (125 MHz, CD_3OD): δ = 170.24, 166.79, 165.50, 165.46, 140.05, 140.03, 137.99, 137.93, 130.14, 129.84, 129.77, 129.58, 128.61, 128.56, 128.50, 128.48, 127.50, 121.55, 117.83, 65.32, 60.22, 60.18, 60.15, 58.93, 58.91, 55.37, 54.71, 50.92, 50.83, 50.46, 49.91, 47.00, 43.41, 42.96, 42.92.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{29}H_{31}N_5NaO_3S$: 552.2045; found: 552.2061.

Minor pair of diastereomers

^{1}H NMR (500 MHz, CD_3OD): δ = 7.47–7.44 (m, 1 H, H_{Ar}), 7.39–7.29 (m, 5 H, H_{Ar}), 7.21 (t, *J* = 8 Hz, 2 H, H_{Ar}), 7.10, 7.12 (2 d, *J* = 3.5 Hz, 1 H, H_{Ar}), 7.04–7.00 (m, 1 H, H_{Ar}), 6.92 (d, *J* = 9 Hz, 2 H, H_{Ar}), 6.84 (t, *J* = 7.5 Hz, 1 H, H_{Ar}), 5.16, 5.14 (2 s, 1 H, H1), 5.05 (2 s, 1 H, H6), 4.37–4.28, 4.26–4.18 (2 m, 2 H, $H4_{a,e}$), 3.90–3.63 (m, 4 H, H_pCH_2NC=O), 3.56, 3.48 (2 d, *J* = 11 Hz, 1 H, $H3_a$), 3.20–3.10 (m, 2 H, H_pCH_2NPh), 3.10–3.04 (m, 1 H, H_pCH_2NPh), 2.97 (d, *J* = 11 Hz, 0.5 H, 0.5 $H3_e$), 2.94–2.76 (m, 2.5 H, H_pCH_2NPh, $H5_a$, 0.5 $H3_e$), 2.57 (t, *J* = 11 Hz, 0.5 H, 0.5 H2), 2.38–2.24 (m, *J* = 11 Hz, 1 H, 0.5 H2, 0.5 $H5_a$), 2.14 (dt, J_1 = 3 Hz, J_2 = 13 Hz, 0.5 H, 0.5 $H5_e$).

^{13}C NMR (125 MHz, CD_3OD): δ = 170.26, 167.25, 165.88, 152.44, 140.07, 140.06, 137.98, 137.95, 130.16, 129.97, 129.82, 29.77, 129.65, 128.49, 128.47, 128.33, 128.31, 127.56, 127.53, 121.59, 117.88, 65.48, 60.29, 60.26, 57.96, 57.91, 55.33, 54.39, 50.96, 50.74, 50.53, 47.04, 43.47, 42.77, 42.72;

(9a*S*)-8-[1-(2-Naphthyl)-2-oxo-2-(4-phenylpiperazin-1-yl)ethyl]-3-phenyltetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (52)

Major pair of diastereomers

IR: 3468, 3229, 3057, 2914, 2854, 2828, 1651, 1598, 1495, 1453, 1440, 1303, 1271, 1227, 1154, 1127, 1018, 753, 695 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.94–7.81 (m, 4 H, H_{Ar}), 7.63, 7.60 (2 d, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.52–7.48 (m, 2 H, H_{Ar}), 7.37–7.26 (m, 5 H, H_{Ar}), 7.17–7.12 (m, 2 H, H_{Ar}), 6.82–6.75 (m, 3 H, H_{Ar}), 5.04, 5.03 (2 s, 1 H, H1), 4.89, 4.88 (2 s, 1 H, H6), 4.31 (d, *J* = 13 Hz, 0.5 H, 0.5 $H5_a$), 4.28–4.20 (m, 1.5 H, $H5_{a,e}$), 3.86–3.67 (m, 3 H, 3 H_pCH_2NC=O), 3.58–3.49 (m, 1 H, H_pCH_2NC=O), 3.60, 3.38 (2 d, *J* = 11 Hz, 1 H, $H3_a$), 3.13–3.03 (m, 1 H, H_pCH_2NPh), 3.02–2.91 (m, 2.5 H, 2 H_pCH_2NPh, 0.5 $H3_e$), 2.88, 2.84 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.76 (d, *J* = 11 Hz, 0.5 H, $H3_a$), 2.67, 2.34 (2 t, *J* = 11 Hz, 1 H, H2), 2.63–2.55 (m, 1 H, H_pCH_2NPh), 2.39, 2.15 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$).

^{13}C NMR (125 MHz, CD_3OD): δ = 171.07, 171.00, 166.84, 166.78, 165.43, 165.37, 152.27, 152.26, 140.08, 140.03, 134.78, 134.74, 134.71, 134.68, 133.82, 130.07, 129.94, 129.88, 129.82, 129.80, 129.56, 129.08, 128.79, 128.63, 128.56, 127.75, 127.65, 127.57, 127.52, 121.47, 117.74, 60.22, 60.19, 60.13, 58.89, 55.71, 55.59, 51.11, 50.94, 50.65, 50.47, 46.69, 43.27, 42.92.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{35}H_{35}N_5NaO_3$: 596.2637; found: 596.2639.

Minor pair of diastereomers

^{1}H NMR (500 MHz, CD_3OD): δ = 7.95–7.82 (m, 4 H, H_{Ar}), 7.62 (t, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.53–7.46 (m, 2 H, H_{Ar}), 7.40–7.27 (m, 5 H, H_{Ar}), 7.17–7.12 (m, 2 H, H_{Ar}), 6.84–6.76 (m, 3 H, H_{Ar}), 5.04, 5.02 (2 s, 1 H, H1), 4.44–4.34 (m, 1.5 H, $H5_{a,e}$), 4.30 (d, *J* = 13 Hz, 0.5 H, 0.5 $H5_e$), 3.86–3.68 (m, 3 H, 3 H_pCH_2NC=O), 3.65–3.54 (m, 1.5 H, H_pCH_2NC=O, 0.5 $H3_a$), 3.38 (d, 0.5 H, 0.5 $H3_a$), 3.14–3.05 (m, 1 H, H_pCH_2NPh), 3.05–2.92 (m, 2.5 H, 2 H_pCH_2NPh, 0.5 $H3_e$), 2.88, 2.82 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.77 (d, *J* = 11 Hz, 0.5 H, $H3_a$), 2.66–2.58 (m, 1 H, H_pCH_2NPh), 2.54, 2.27 (2 t, *J* = 11 Hz, 1 H, H2), 2.47, 2.19 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$), the signal of H6 covered by the signal of MeOH at 4.87.

^{13}C NMR (125 MHz, CD_3OD): δ = 171.05, 171.03, 167.32, 167.21, 165.88, 165.85, 152.31, 140.03, 134.80, 134.78, 135.74, 134.74, 134.72, 133.81, 133.78, 130.09, 129.90, 129.63, 129.09, 128.81, 128.30, 128.27, 127.77, 127.69, 127.53, 127.50, 121.52, 117.78, 60.25, 57.84, 57.79, 55.56, 55.26, 51.06, 50.70, 50.62, 50.52, 46.72, 43.35, 42.68.

(9a*S*)-8-[1-(6-Methoxy-2-naphthyl)-2-oxo-2-(4-phenylpiperazin-1-yl)ethyl]-3-phenyltetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (53)

Major pair of diastereomers

IR: 3453, 3241, 3060, 2919, 2822, 1682, 1657, 1600, 1504, 1495, 1454, 1440, 1391, 1339, 1303, 1267, 1228, 1156, 1121, 1020, 757, 696 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.90–7.79 (m, 2 H, H_{Ar}), 7.77, 7.75 (2 d, *J* = 9 Hz, 1 H, H_{Ar}), 7.57, 7.55 (2 d, *J* = 8.5 Hz,1 H, H_{Ar}), 7.43–7.28 (m, 6 H, H_{Ar}), 7.26–7.20 (m, 1 H, H_{Ar}), 7.20–7.12 (m, 2 H, H_{Ar}), 6.89–6.76 (m, 3 H, H_{Ar}), 5.08, 5.06 (2 s, 1 H, H1), 4.85, 4.84 (2 s, 1 H, H6), 4.34 (d, *J* = 13 Hz, 0.5 H, $H5_e$), 4.32–4.22 (m, 1.5 H, $H5_{a,e}$), 3.91, 3.90 (2 s, 3 H, OCH_3), 3.86–3.70 (m, 3 H, $H_pCH_2NC{=}O$), 3.64–3.56 (m, 1.5 H, $H_pCH_2NC{=}O$, 0.5 $H3_a$), 3.38 (d, *J* = 11 Hz, 0.5 H, 0.5 $H3_a$), 3.18–3.07 (m, 1 H, H_pCH_2NPh), 3.07–2.94 (m, 2.5 H, 2 H_pCH_2NPh, 0.5 $H3_e$), 2.92, 2.87 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H5_a$), 2.79 (d, *J* = 11 Hz, 0.5 H, $H3_e$), 2.64–2.56 (m, 1 H, H_pCH_2NPh), 2.66, 2.32 (2 t, *J* = 11 Hz, 1 H, H2), 2.39, 2.18 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, H4).

^{13}C NMR (125 MHz, CD_3OD): δ = 171.27, 171.19, 166.91, 166.85, 165.55, 165.49, 159.88, 159.89, 152.37, 152.36, 140.12, 136.23, 136.18, 131.24, 130.54, 130.20, 130.16, 130.09, 129.86, 129.84, 129.74, 129.61, 129.59, 128.91, 128.85, 128.67, 128.60, 128.03, 127.97, 121.55, 120.50, 117.83, 117.81, 106.73, 79.51, 70.69, 60.27, 60.21, 58.89, 55.85, 55.73, 51.36, 50.94, 50.74, 50.60, 46.76, 43.35, 42.92.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{36}H_{37}N_5O_4$: 604.2924; found: 604.2954.

Minor pair of diastereomers

^1H NMR (500 MHz, CD_3OD): δ = 7.90–7.80 (m, 2 H, H_{Ar}), 7.76 (d, *J* = 9 Hz, 1 H, H_{Ar}), 7.56 (t, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.44–7.29 (m, 6 H, H_{Ar}), 7.25 (m, 1 H, H_{Ar}), 7.20–7.12 (m, 2 H, H_{Ar}), 6.90–6.76 (m, 3 H, H_{Ar}), 5.06, 5.04 (2 s, 1 H, H1), 4.84 (s, 1 H, H6), 4.46–4.36 (m, 1.5 H, $H5_{a,e}$), 4.33 (d, *J* = 13 Hz, 0.5 H, $H5_e$), 3.91, 3.90 (2 s, 3 H, OCH_3), 3.86–3.70 (m, 3 H, $H_pCH_2NC{=}O$), 3.67–3.56 (m, 1.5 H, $H_pCH_2NC{=}O$, 0.5 $H3_a$), 3.37 (d, *J* = 11 Hz, 0.5 H, 0.5 $H3_a$), 3.18–3.09 (m, 1 H, H_pCH_2NPh), 3.09–2.95 (m, 2.5 H, 2 H_pCH_2NPh, 0.5 $H3_e$), 2.92, 2.85 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H5_a$), 2.79 (d, *J* = 11 Hz, 0.5 H, $H3_e$), 2.68–2.58 (m, 1 H, H_pCH_2NPh), 2.54, 2.27 (2 t, *J* = 11 Hz, 1 H, H2), 2.48, 2.21 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, H4).

^{13}C NMR (125 MHz, CD_3OD): δ = 171.30, 171.15, 167.34, 167.22, 165.94, 165.90, 159.89, 159.87, 152.37, 152.35, 140.05, 136.24, 136.20, 131.21, 130.54, 130.20, 130.15, 130.10, 129.99, 129.97, 129.74, 129.66, 129.55, 128.93, 128.87, 128.31, 128.29, 128.01, 127.93, 121.57, 120.53, 117.83, 117.81, 106.73, 79.50, 70.87, 60.23, 57.81, 55.85, 55.69, 55.21, 51.29, 50.75, 50.61, 46.75, 43.34, 42.63.

(3*R*,9a*S*)-3-Methyl-8-[2-oxo-1-phenyl-2-(4-phenylpiperazin-1-yl)ethyl]tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (54)

IR: 3460, 3243, 3061, 2923, 2855, 2821, 1684, 1650, 1599, 1495, 1450, 1322, 1273, 1228, 1153, 1020, 758, 697 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.52–7.44 (m, 2 H, H_{Ar}), 7.44–7.30 (m, 3 H, H_{Ar}), 7.19 (t, *J* = 8 Hz, 2 H, H_{Ar}), 6.88 (d, *J* = 8 Hz, 2 H, H_{Ar}), 6.82 (t, *J* = 7 Hz, 1 H, H_{Ar}), 4.68, 4.67 (2 s, 1 H, H6), 4.40, 4.36 (2 d, *J* = 13 Hz, 1 H, $H5_a$), 4.22, 4.16 (2 d, *J* = 13 Hz, 1 H, $H5_e$), 4.01 (quintet, *J* = 7 Hz, 1 H, H1), 3.87–3.78 (m, 1 H, $H_pCH_2NC{=}O$), 3.78–3.71 (m, 1 H, $H_pCH_2NC{=}O$), 3.71–3.64 (m, 1 H, $H_pCH_2NC{=}O$), 3.64–3.55 (m, 1 H, $H_pCH_2NC{=}O$), 3.46, 3.25 (2 d, *J* = 11 Hz, 1 H, $H3_a$), 3.19–3.09 (m, 1 H, H_pCH_2NPh), 3.08–2.99 (m, 1 H, H_pCH_2NPh), 2.99–2.92 (m, 1.5 H, H_pCH_2NPh, 0.5 $H3_e$), 2.88, 2.83 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_a$), 2.75 (d, *J* = 11 Hz, 0.5 H, 0.5 $H3_e$), 2.64–2.53 (m, 1 H, H_pCH_2NPh), 2.39, 2.13 (2 t, *J* = 11 Hz, 1 H, H2), 2.37, 2.10 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$), 1.43, 1.41 (2 d, *J* = 7 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, CD_3OD): δ = 171.05, 167.88, 167.85, 166.92, 166.86, 152.38, 136.26, 130.49, 130.46, 130.11, 130.08, 129.83, 121.57, 117.81, 70.83, 70.80, 57.91, 57.80, 55.42, 54.88, 51.82, 51.78, 51.17, 50.71, 50.49, 46.66, 43.33, 42.51, 42.48, 21.29, 21.26.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{31}N_5O_3$: 462.2427; found: 462.2485.

(3*R*,9a*S*)-3-Benzyl-8-[2-oxo-1-phenyl-2-(4-phenylpiperazin-1-yl)ethyl]tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (55)

IR: 3457, 3243, 3061, 3028, 2921, 2858, 2820, 1685, 1656, 1599, 1495, 1453, 1439, 1335, 1321, 1272, 1228, 1154, 1017, 758, 701 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.40–7.24 (m, 8 H, H_{Ar}), 7.22–7.14 (m, 2 H, H_{Ar}), 7.12–7.04 (m, 2 H, H_{Ar}), 6.88–6.78 (m, 3 H, H_{Ar}), 4.56, 4.50 (2 s, 1 H, H6), 4.32–4.18 (m, 2 H, $H5_a$, H1), 3.80–3.44 (m, 5 H, 4 $H_pCH_2NC{=}O$, $H5_e$), 3.26–3.20 (m, 1 H, $PhCH_2CH$), 3.12–3.02, 3.02–2.80, 2.70–2.48 (m, 7 H, 4 H_pCH_2NPh, $PhCH_2CH$, $H3_a$, 0.5 $H5_a$, 0.5 $H3_e$), 2.48–2.36 (m, 1 H, 0.5 $H4_a$, 0.5 $H3_e$), 2.25 (dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$), 2.10 (t, *J* = 11 Hz, 0.5 H, H2), 1.97–1.86 (m, 1 H, 0.5 $H4_e$, 0.5 H2).

^{13}C NMR (125 MHz, CD_3OD): δ = 170.80, 170.73, 167.72, 167.66, 166.93, 166.90, 152.28, 136.02, 135.96, 131.38, 130.41, 130.39, 130.08, 130.07, 129.96, 129.93, 129.71, 129.68, 129.60, 129.58, 128.71, 128.68, 121.47, 117.72, 117.70, 79.47, 70.85, 70.49, 57.05, 56.75, 56.59, 55.13, 54.37, 50.61, 50.52, 50.29, 50.07, 46.59, 46.52, 43.23, 43.16, 42.12, 41.97, 41.66.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{32}H_{35}N_5NaO_3$: 560.2637; found: 560.2665.

(3*R*,9a*S*)-3-(4-Hydroxybenzyl)-8-[2-oxo-1-phenyl-2-(4-phenylpiperazin-1-yl)ethyl]tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (56)

IR: 3251, 3024, 2922, 2821, 1645, 1598, 1515, 1495, 1441, 1333, 1272, 1228, 1175, 1154, 1017, 757, 697 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.42–7.28 (m, 5 H, H_{Ar}), 7.22–7.12 (m, 2 H, H_{Ar}), 6.94–6.78 (m, 5 H, H_{Ar}), 6.76–6.63 (m, 2 H, H_{Ar}), 4.57, 4.51 (2 s, 1 H, H6), 4.32–4.22 (m, 1 H, $H4_a$), 4.20, 4.19 (2 s, 1 H, H1), 3.92–3.46 (m, 5 H, 4 $H_pCH_2NC{=}O$, $H5_e$), 3.27, 3.05 (2 d, 1 H, $H3_a$), 3.21–3.07 (m, 2 H, H_pCH_2NPh, $PhCH_2CH$), 3.04–2.85 (m, 2.5 H, 2 H_pCH_2NPh, 0.5 $H3_e$), 2.85–2.76 (m, 1 H, $PhCH_2CH$), 2.72–2.51 (m, 1.5 H, H_pCH_2NPh, 0.5 $H3_e$), 2.51–2.39 (m, 1 H, $H4_a$), 2.27, 1.96 (2 dt, J_1 = 3 Hz, J_2 = 13 Hz, 1 H, $H4_e$), 2.10, 1.92 (2 t, *J* = 11 Hz, 1 H, H2).

^{13}C NMR (125 MHz, CD_3OD): δ = 170.94, 170.80, 168.00, 167.94, 167.37, 167.28, 158.38, 158.34, 152.36, 136.21, 136.10, 132.49, 130.42, 130.40, 130.10, 130.04, 130.02, 129.77, 126.22, 126.20; 121.54, 117.80, 116.45, 116.41, 71.03, 70.64, 57.32, 57.29, 56.76, 56.54, 55.18, 54.57, 50.65, 50.42, 50.14, 46.64, 46.59, 43.35, 43.27, 42.11, 41.92, 40.97.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{32}H_{35}N_5O_4$: 554.2767; found: 554.2785.

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