Facile synthesis of structurally diverse 5-oxopiperazine-2-carboxylates as dipeptide mimics and templates†‡

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A sequence of Michael addition of a primary amine onto methyl 2-chloro-2-cyclopropylidene-acetate (**1**), acylation of the adduct with α-bromo acid chlorides under modified Schotten-Baumann conditions and ring-closing twofold nucleophilic substitution on the thus formed bishalides **3a–e** with aliphatic or aromatic amines according to a very simple protocol with final acid/base extraction or filtration over silica gel for purification leads to the 3-spirocyclopropanated 5-oxopiperazine-2-carboxylates **2** or in two cases, after intermolecular transesterification of **2**, to bicyclic oxopiperazines **6**, with a remarkable variability of the substituents R^1–R^3 in 39–99% yields (20 examples). Starting with α-bromophenylacetic acid chloride, the *trans*-configured 6-phenyl-5-oxopiperazine-2-carboxylates are formed preferentially.

Introduction

Modern medicinal chemistry requires diverse compounds with rigid backbones bearing pharmacophoric functionalities, since rigidity helps with the understanding of the conformational requirements for biological activity. Thus, the piperazine and piperazinone moieties as present in the 5-oxopiperazine-2-carboxylates **2** are frequently encountered in a large variety of bioactive compounds,[1] such as metalloproteinase-inhibiting antitumor agents,[2] antiarthritics,[3] factor Xa[4] and Xa/IIa inhibitors,[5] as well as inhibitors of $\alpha_1\beta_2$ integrin-mediated cell adhesion and osteoporosis.[6] Compounds with a skeleton of type **2** can therefore be used in the treatment of inflammatory diseases like asthma, thrombosis, arteriosclerosis and rheumatoid arthritis. Although a multitude of synthesis approaches to such compounds have been reported,[7] there are only a few reasonably general accesses to this structural motif, especially few for a combinatorial synthesis.[8]

As has previously been demonstrated, the multifunctional building block methyl 2-chloro-2-cyclopropylideneacetate (**1**),[9] for which a second-generation synthesis has recently been developed,[10] provides an easy access to a large variety of heterocycles[11] including octahydro[2*H*]pyrazino[1,2-*a*]-pyrazines[12] with an incorporated piperazine-2,5-dione moiety in a heterobicyclic system. Being an extremely good Michael acceptor, **1** is known to rapidly undergo addition of nucleophiles including secondary and primary amines, and the products can further react by nucleophilic substitution of the chlorine substituent adjacent to the cyclopropyl group. Relying on exactly these reactivities of **1**, a new access to a library of spirocyclopropanated 5-oxopiperazinecarboxylates **2** has been developed and is reported here.

Results and discussion

Five different primary amines including methyl glycinate and two *p*-substituted benzylamines were added to methyl 2-chloro-2-cyclopropylideneacetate (**1**) smoothly at 0 to 20 °C.

Since the adducts of primary amines are intrinsically unstable and undergo rearrangement,[13] they were not isolated in pure form, but directly acylated with α-bromoacetic and α-bromophenylacetic acid chloride, respectively, under modified Schotten-Baumann conditions to yield the stable acyclic bishaloesteramides **3**.

Unfortunately, several attempts to condense the initial Michael adducts obtained here with *N*-Boc-protected amino acids by activation with standard carbodiimide (DCC, EDC) or even more potent (PyBOP, HATU) peptide coupling reagents as reported previously for certain such adducts of **1**,[12] were not successful.

To avoid hydrolysis of the α-bromo acid chlorides under the usual biphasic Schotten-Baumann conditions, 2 –3 equivalents of the acid chloride and solid sodium bicarbonate were added to a solution of the respective amine adduct of **2** in 1,2-dichloroethane, and water was added very slowly drop by drop under vigorous stirring, to furnish **3a–e** in high yields (Table 1). In this way, the liberated hydrogen chloride was trapped by sodium bicarbonate in a very small volume of an aqueous phase without the danger of letting the acid chloride in the organic phase be quenched by a large excess of water. Even with the sterically more encumbered α-bromophenacetyl chloride, this method furnished respectable yields (80–86%) of the acylation products **3c** and **3e**.

An intermolecular nucleophilic substitution of the bromide in **3a–e** with a second set of nitrogen nucleophiles and a subsequent ring-closing intramolecular nucleophilic substitution of the chloride adjacent to the methoxycarbonyl group (Scheme 2, reaction mode **A**) yielded the substituted oxopiperazincarboxylates **2**. From

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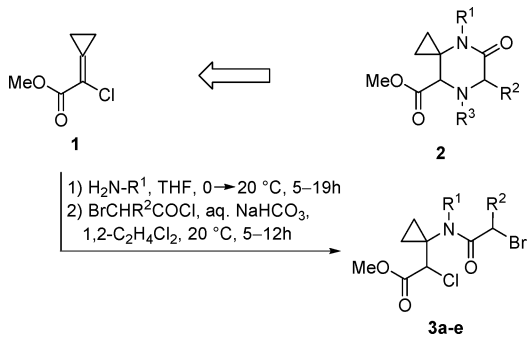
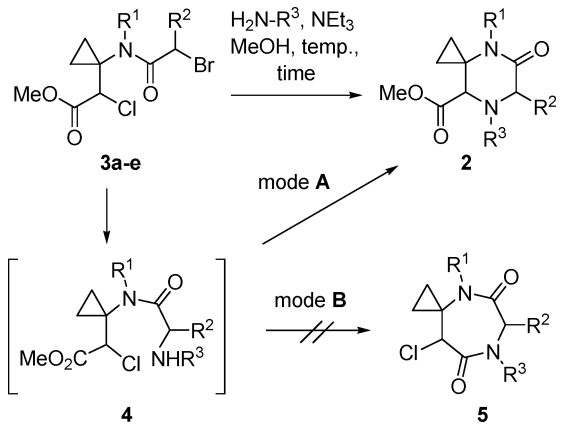
Table 1 Michael addition of primary amines to methyl 2-chloro-2-cyclopropylideneacetate (**1**) and direct acylation of the adducts with α-bromo acid chlorides (see Scheme 1)

R^1	R^2	Product	Yield (%)[a]
$BnO(CH_2)_3$	H	**3a**	91
$MeO(CH_2)_2$	H	**3b**	66
MeO_2CCH_2	Ph	**3c**	86
$4\text{-}ClC_6H_4CH_2$	H	**3d**	72
$4\text{-}F_3CC_6H_4CH_2$	Ph	**3e**	80

[a] Yield of isolated product over two steps.



Scheme 1 Michael addition of primary amines to methyl 2-chloro-2-cyclopropylideneacetate (**1**) and direct acylation of the adducts with α-bromo acid chlorides. For details see Table 1.



Scheme 2 Ring-closing twofold nucleophilic substitution on compounds **3a–e** to yield methyl 5-oxo-4,7-diazaspiro[2.5]octane-8-carboxylates **2**. For details see Table 2.

precursors with R^2 = Ph, the *trans*-configured products **2cj**-Ph and **2ej**-Ph were formed diastereoselectively.

This intramolecular substitution is apparently particularly efficient because of the 1,1-disubstituted cyclopropane motif in the precursors **3a–e** which, due to its Thorpe-Ingold effect,[14] favors the ring closure. The yields strongly depended on the nucleophilicity of the amine. While alkyl- and benzylamines cleanly gave the correspondingly substituted oxopiperazinecarboxylates **2** (see Table 2) at ambient temperature, the less nucleophilic anilines in some cases required higher temperatures (up to 120 °C) and longer reaction times (up to 120 h). While donor-substituted anilines such as *p*-toluidine and 3,4-dimethylaniline reacted smoothly at 40 °C, *p*-chloroaniline only reacted under more drastic conditions

Table 2 Ring-closing twofold nucleophilic substitution on dihaloamidoesters **3** with various nitrogen nucleophiles (see Scheme 2)

R^1	R^2	R^3	Product	T/°C	Time/h	Yield (%)
$BnO(CH_2)_3$	H	Bn	**2af**	20	48	75
$MeO(CH_2)_2$	H	Bn	**2bf**	20	24	81
$MeO(CH_2)_2$	H	$3\text{-}MeC_6H_4$	**2bg**	120	48	80
$MeO(CH_2)_2$	H	$4\text{-}PhC_6H_4$	**2bh**	50	36	87
$MeO(CH_2)_2$	H	$2\text{-}MeC_6H_4$	**2bi**	120	48	76
MeO_2CCH_2	Ph	$4\text{-}MeOC_6H_4$	**2cj**-Ph	20	120	68
$4\text{-}ClC_6H_4CH_2$	H	$4\text{-}MeC_6H_4$	**2dk**	50	16	73
$4\text{-}ClC_6H_4CH_2$	H	$2\text{-}F_3CC_6H_4CH_2$	**2dl**	20	72	87
$4\text{-}ClC_6H_4CH_2$	H	Me_2CHCH_2	**2dm**	20	72	90
$4\text{-}ClC_6H_4CH_2$	H	MeO_2CCH_2	**2dd**	50	48	64
$4\text{-}ClC_6H_4CH_2$	H	(*S*)-$PhCHCO_2Me$	**2dn**	80	24	70[a]
$4\text{-}ClC_6H_4CH_2$	H	(*S*)-$iPrCHCO_2Me$	**2do**	80	24	70[a]
$4\text{-}ClC_6H_4CH_2$	H	(*R*)-$HOCH_2CHPh$	**6dp**	40	36	70[a,b]
$4\text{-}ClC_6H_4CH_2$	H	(*S*)-$HOCH_2CHPh$	**6dq**	40	36	65[a,b]
$4\text{-}ClC_6H_4CH_2$	H	$4\text{-}O_2NC_6H_4CH_2$	**2dr**	20	48	84
$4\text{-}ClC_6H_4CH_2$	H	$2\text{-}NaphthCH_2$	**2ds**	20	48	85
$4\text{-}ClC_6H_4CH_2$	H	$3,4\text{-}Me_2C_6H_3$	**2dt**	20	48	72
$4\text{-}ClC_6H_4CH_2$	H	$4\text{-}ClC_6H_4$	**2du**	80	72	39
$4\text{-}ClC_6H_4CH_2$	H	3-indolyl-$(CH_2)_2$	**2dv**	40	16	99
$4\text{-}F_3CC_6H_4$	Ph	$4\text{-}MeOC_6H_4$	**2ej**-Ph	50	12	62

[a] Total yield of isolated diastereomers, which were separated. [b] The product of subsequent intramolecular transesterification of initially formed **2**.

(80 °C) and gave a poor yield (39%) of **2du** with a number of by-products.

Surprisingly, in no case was the seven-membered chlorolactam **5** formed by an intramolecular attack of the terminal amino group in the intermediate **4** on the ester moiety (Scheme 2, reaction mode **B**), as evidenced by LC-MS of the crude products. Chlorolactams of type **5**, however, have previously been obtained as the main products, when free aminoacyl derivatives of type **4** were cyclized under biphasic basic conditions.[15]

To demonstrate the possible diversity of substituents R^3 in the 5-oxopiperazinecarboxylates **2**, the substitution of the bromide in **3** was performed with methyl glycinate as well as with enantiomerically pure α-amino acid esters and enantiomerically pure β-amino alcohols, to yield the oxopiperazinecarboxylates **2dn**, **2do** and bicyclic oxopiperazines **6dp**, **6dq**, respectively, as 1:1 mixtures of diastereomers, which could be separated by column chromatography. Apparently, the latter two products (Fig. 1) were obtained by intramolecular transesterification of initially formed products of type **2**.

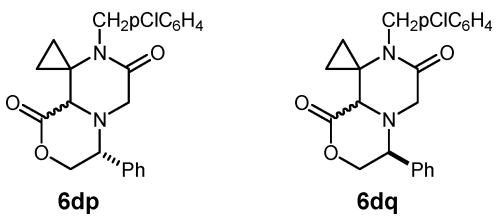
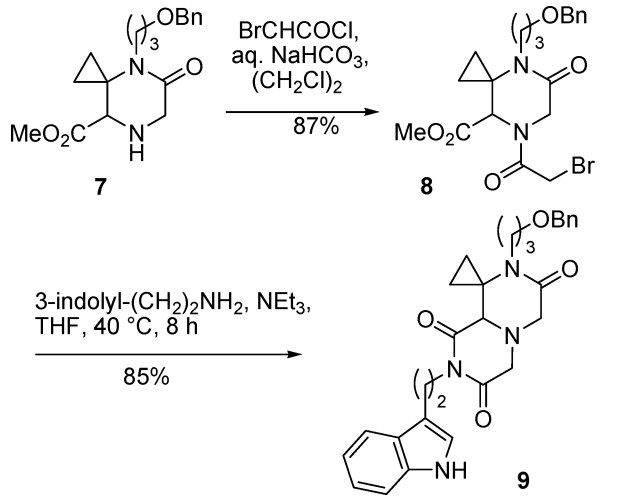


Fig. 1 Bicyclic oxopiperazines **6dp**, **6dq**, obtained from **3d** and (*R*)- or (*S*)-phenylglycinol, respectively.

The achievable substitution pattern on this scaffold was extended by acylation of the free secondary amino group in the previously reported[15] 4-(3-benzyloxypropyl)-5-oxopiperazinecarboxylate **7**, and subsequent cyclization following the



Scheme 3 Synthesis of the bicyclic tripeptide mimic **9**.

protocol described above for the preparation of oxopiperazinecarboxylates **2**.

Reaction of **7** with bromoacetyl chloride under the established conditions, subsequent nucleophilic substitution of the bromine in the bromoacetyl moiety on the dipeptide scaffold **8** with tryptamine and thermally induced ring closure gave the bicyclic tripeptide mimic **9** with further potentially addressable variation points (the benzyloxy group, two C,H-acidic methylene groups α to carbonyls, one NH in the indol moiety) for increased diversity and the possible build-up of tetrapeptide isosteres.

Experimental section

General remarks

All reagents were used as purchased from commercial suppliers without further purification. Solvents were purified and dried according to conventional methods prior to use. ^{1}H- and ^{13}C-NMR spectra were recorded at ambient temperature with a Bruker AM 250 (250 MHz for ^{1}H and 62.9 MHz for ^{13}C) or a Varian UNITY-300 (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) instrument. Chemical shifts δ are presented in ppm relative to residual resonances of solvents (^{1}H: 7.26 ppm for $CHCl_3$; ^{13}C: 77.0 ppm for $CDCl_3$), coupling constants *J* are given in Hertz. Characterization of the multiplicities of signals: s = singlet, br s = broad singlet, d = doublet, t = triplet, m = multiplet. The multiplicities of ^{13}C signals were determined by the DEPT or the APT technique: DEPT: + = primary or tertiary (positive DEPT signal), − = secondary (negative DEPT signal), C_{quat} = quaternary C-atom; APT: + = primary or tertiary (positive APT signal), − = secondary or quaternary C-atom (negative APT signal). IR: Bruker IFS 66. EI-MS: Finnigan MAT 95, 70 eV; ESI-MS: Finnigan LCQ. High resolution mass spectrometry (HRMS): APEX IV 7T FTICR, Bruker Daltonic. Chromatography: Separations were carried out on Merck Silica 60 (0.063–0.200 mm, 70–230 mesh ASTM). The dimensions of the columns are given as "diameter × height of the silica gel column". TLC: Macherey-Nagel, TLC plates Alugram® Sil G/UV_{254}. Detection under UV light at 254 nm, development with MOPS reagent (10% molybdophosphoric acid, solution in ethanol). Melting points: apparatus according to Dr Tottoli (Büchi); values are uncorrected. Elemental analyses: Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Universität Göttingen.

Methyl 2-(1-(*N*-(3-(benzyloxy)propyl)-2-bromoacetamido)-cyclopropyl)-2-chloroacetate (3a). To a solution of methyl 2-chloro-2-cyclopropylideneacetate (**1**) (2.00 g, 13.7 mmol) in THF (100 mL) was added 3-benzyloxypropylamine (2.48 g, 15.0 mmol) at 0 °C, and the solution was stirred at this temperature for 8 h. (Michael adduct, ninhydrine, hexane/EtOAc 2 : 1, R_f = 0.37). Volatiles were removed under reduced pressure, the residue was taken up in 1,2-dichloroethane (100 mL), bromoacetyl chloride (6.45 g, 41.0 mmol) and solid $NaHCO_3$ (3.44 g, 41.0 mmol) were added with stirring at 20 °C and slowly water (10 mL). The suspension was vigorously stirred for 5 h, a saturated $NaHCO_3$ solution (10 mL) was added, the phases were separated, the aqueous phase was extracted with CH_2Cl_2 (1 × 50 mL), the combined organic phases were dried over Na_2SO_4, and the solvent was removed under reduced pressure. Chromatographic purification of the residue on silica (50 g, 4 × 40 cm, pentane/Et_2O 1 : 1, ninhydrine, R_f = 0.41) yielded 5.39 g (91%) of **3a** as a colorless solid, m.p. 60 – 61 °C. IR (film): $\tilde{\nu}$ = 2953, 2860, 1752 (C=O), 1662 (C=O), 1453, 1435, 1404, 1369, 1290, 1203, 1167, 1102, 911, 734 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of two rotamers): δ = 1.04–1.12 (m, 1 H, Cpr-*H*), 1.24–1.46 (m, 2 H, Cpr-*H*), 1.52–1.64 (m, 1 H, Cpr-*H*), 1.78–2.08 (m, 2 H, CH_2), 3.43–3.50 (m, 3 H, CH_2, CH), 3.57–3.71 (m, 2 H), 3.76 (s, 1 H, CH_3), 3.77 (s, 2 H, CH_3), 3.85–3.98 (m, 1 H, CH_2), 4.20–4.36 (m, 1 H, CH_2), 4.49 (dd, *J* = 5.6, 5.6 Hz, 2 H, CH_2), 7.28–7.36 (m, 5 H, aryl-*H*). ^{13}C NMR ($CDCl_3$, 75.5 MHz, APT): δ = 13.2 (–, Cpr-*C*), 13.6 (–, Cpr-*C*), 17.0 (–, Cpr-*C*), 19.2 (–, Cpr-*C*), 26.9 (–, CH_2), 27.0 (–, CH_2), 27.2 (–, CH_2), 28.3 (–, CH_2), 43.3 (C_{quat}, Cpr-*C*), 43.6 (C_{quat}, Cpr-*C*), 47.8 (–, NCH_2), 48.1 (–, NCH_2), 53.1 (+, *C*H), 53.3 (+, *C*H), 61.1 (+, OCH_3), 63.7 (OCH_3), 67.0 (–, CH_2), 67.8 (–, CH_2), 72.8 (–, CH_2), 73.1 (–, CH_2), 127.4 (+, aryl-*C*), 127.5 (+, aryl-*C*), 127.6 (+, aryl-*C*), 127.7 (+, aryl-*C*), 128.3 (+, aryl-*C*), 128.4 (+, aryl-*C*), 137.9 (C_{quat}, aryl-*C*), 138.2 (C_{quat}, aryl-*C*), 167.4 (C_{quat}), 167.5 (C_{quat}), 169.3 (C_{quat}), 169.4 (C_{quat}). MS (ESI), *m/z* (%): 456.1/458.1 (76/100) $[M + Na]^+$, 888.6/886.6 (66/78) $[2M + Na]^+$.–$C_{18}H_{23}BrClNO_4$ (432.7): calcd. C 49.96, H 5.36, N 3.24; found C 50.21, H 5.08, N 3.11.

General procedure for the preparation of di- and trisubstituted methyl 4,7-diazaspiro[2.5]octane-8-carboxylates (2). To a solution of the respective bishalo ester amide **3a–e** (1.00 g, 2.44 mmol) in MeOH (20 mL) was added at 20 °C the respective amine (288 mg, 2.69 mmol) as well as triethylamine (764 mg, 5.91 mmol), and the solution was stirred at the stated temperature for the stated time. The solvent was removed under reduced pressure, the residue taken up in CH_2Cl_2 (100 mL), the solution extracted with aq. 1 N HCl (20 mL), the organic phase dried over $MgSO_4$, and the solvent removed under reduced pressure. Chromatographic purification of the residue on silica gel or recrystallization from the stated solvent yielded the respective compound.

Methyl 7-benzyl-4-(3-benzyloxypropyl)-5-oxo-4,7-diazaspiro-[2.5]octane-8-carboxylate (2af). The crude product from **3a** (4.11 g, 9.80 mmol) in MeOH (50 mL), benzylamine (1.16 g, 10.8 mmol), triethylamine (2.98 mL, 29.4 mmol) at 20 °C within

48 h was purified by chromatography on 50 g of silica gel (3 × 20 cm, MOPS, pentane/Et_2O 1 : 3; R_f = 0.43 [Et_2O]) to yield 2.98 g (75%) of **2af** as a colorless oil. IR (film): $\tilde{\nu}$ = 3448 cm^{-1}, 3005, 2953, 1749 (C=O), 1684 (C=O), 1436, 1365, 1336, 1277, 1198, 1167, 1014, 947, 876, 807, 762, 691, 657. ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.67–0.96 (m, 4 H, Cpr-*H*), 1.36–1.43 (m, 1 H, CH_2), 1.69–1.74 (m, 2 H, CH_2), 2.54–2.59 (m, 1 H, CH_2), 2.72 (s, 1 H, C*H*), 3.41–3.50 (m, 2 H, CH_2), 3.59–3.84 (m, 7 H, 2 CH_2, CH_3), 4.47 (s, 2 H, CH_2), 7.23–7.38 (m, 10 H, aryl-*H*).–^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.5 (–, Cpr-*C*), 12.8 (–, Cpr-*C*), 37.4 (–, CH_2), 41.2 (C_{quat}, Cpr-*C*), 41.4 (–, NCH_2), 51.5 (+, OCH_3), 53.8 (–, NCH_2Ph), 59.0 (–, CH_2), 66.2 (+, CHN), 68.0 (–, OCH_2Ph), 73.1 (–, OCH_2), 127.5 (+, 2 C, aryl-*C*), 127.6 (+, 2 C, aryl-*C*), 128.3 (+, 2 C, aryl-*C*), 128.5 (+, 2 C, aryl-*C*), 128.9 (+, 2 C, aryl-*C*), 137.0 (C_{ipso}, aryl-*C*), 138.1 (C_{ipso}, aryl-*C*), 169.6 (C_{quat}, CN=O), 171.0 (C_{quat}, C=O). MS (ESI), *m/z*: 445.2 (100) $[M + Na]^+$, 867.4 (95) $[2M + Na]^+$. $C_{25}H_{30}N_2O_4$ (422.5): calcd. C 71.07, H 7.16, N 6.63; found C 71.38, H 6.95, N 6.76.

Methyl 4-(4-chlorobenzyl)-7-(methoxyphenylmethyl)-5-oxo-4,7-diazaspiro[2.5]octane-8-carboxylate (6dp). The crude product obtained from **3d** (1.12 g, 2.73 mmol) in MeOH (20 mL), (*R*)-α-phenylglycinol (412 mg, 3.00 mmol) and triethylamine (1.50 mL, 10.9 mmol) at 20 °C in 24 h, was purified by chromatography on 50 g of silica gel (3 × 20 cm, MOPS, Et_2O; R_f = 0.32) to yield 707 mg (70%) of **6dp** as a colorless oil (1:1 mixture of diastereomers, which were separated by column chromatography on silica gel). *Diastereomer 1*: IR (KBr): $\tilde{\nu}$ = 3319, 3213, 3090, 3068, 2961, 2928, 1682 (C=O), 1495, 1462, 1443, 1325, 1229, 1092, 1016, 819, 813, 804, 735, 604, 553, 433 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.26–0.35 (m, 1 H, Cpr-H), 0.55–0.64 (m, 1 H, Cpr-H), 0.95–1.04 (m, 1 H, Cpr-H), 1.12–1.23 (m, 1 H, Cpr-H), 2.38–2.61 (br s, 1 H, OH), 3.08 (s, 1 H, CH), 3.54 (s, 3 H, OCH_3), 3.68–3.81 (m, 4 H, 2 × CH, CH_2), 3.83–3.91 (m, 1 H, CH), 3.92 (d, ^3J = 7.90 Hz, 1 H, A-part of an AB-system), 4.68 (d, ^3J = 7.90 Hz, 1 H, B-part of an AB-system), 7.06 (d, ^3J = 4.16 Hz, 2 H, aryl-H), 7.22–7.41 (m, 7 H, aryl-H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.67 (–, Cpr-C), 12.6 (–, Cpr-C), 42.6 (C_{quat}, Cpr-C), 44.3 (–, CH_2), 52.0 (+, OCH_3), 53.1 (–, CH_2), 62.8 (–, CH_2), 63.7 (+, CH), 67.9 (+, CH), 128.1 (+, 2 C, aryl-C), 128.3 (+, aryl-C), 128.4 (+, 2 C, aryl-C), 128.6 (+, 2 C, aryl-C), 128.8 (+, 2 C, aryl-C), 128.9 (+, 2 C, aryl-C), 132.9 (C_{quat}, C_{ipso}), 136.4 (C_{quat}, C_{ipso}), 136.8 (C_{quat}, C_{ipso}), 170.5 (C_{quat}, C=O), 172.4 (C_{quat}, C=O). MS (EI, 70 eV), *m/z* (%): 397 (100) $[M]^+$, 369 (19), 236 (15), 125 (50). $C_{22}H_{21}ClN_2O_3$ (396.9): calcd. C 66.58, H 5.33, N 7.06; found C 66.72, H 5.55, N 7.16. *Diastereomer 2*: IR (KBr): $\tilde{\nu}$ = 3304, 3055, 2950, 1736 (C=O), 1659 (C=O), 1457, 1436, 1419, 1341, 1213, 745 cm^{-1}.–^1H NMR ($CDCl_3$, 250 MHz): δ = 0.44–0.48 (m, 1 H, Cpr-H), 0.63–0.67 (m, 1 H, Cpr-H), 0.86–0.93 (m, 1 H, Cpr-H), 1.12–1.25 (m, 1 H, Cpr-H), 2.76 (s, 1 H, OH), 3.08 (s, 1 H, CH), 3.52 (s, 3 H, OCH_3), 3.69–4.02 (m, 6 H, 2 × CH, 2 × CH_2), 4.72 (d, ^3J = 7.85 Hz, 1 H, A-part of an AB-system), 7.05 (d, ^3J = 4.13 Hz, 2 H, aryl-H), 7.21–7.36 (m, 7 H, aryl-H).–^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.53 (–, Cpr-C), 13.3 (–, Cpr-C), 41.3 (C_{quat}, Cpr-C), 44.4 (–, CH_2), 50.0 (+, CH), 52.0 (+, OCH_3), 62.0 (–, CH_2), 65.6 (–, CH_2), 67.8 (+, CH), 128.45 (+, 2 C, aryl-C), 128.52 (+, 3 C, aryl-C), 128.6 (+, 2 C, aryl-C), 128.9 (+, 2 C, aryl-C), 132.9 (C_{quat}, C_{ipso}), 136.3 (C_{quat}, C_{ipso}), 136.6 (C_{quat}, C_{ipso}), 170.4 (C_{quat}, C=O), 171.6 (C_{quat}, C=O). MS (EI, 70 eV), *m/z* (%): 399/397 (32/100) $[M]^+$, 369 (21), 249 (16), 236 (24), 139 (19), 125 (100), 105 (100), 77 (62).–$C_{22}H_{21}ClN_2O_3$ (396.9): calcd. C 66.58, H 5.33, N 7.06; found C 66.73, H 5.55, N 7.26.

Methyl 4-(3-benzyloxypropyl)-7-(2-bromacetyl)-5-oxo-4,7-diazaspiro[2.5]octane-8-carboxylate (8). To a solution of **7**[15] (3.76 g, 11.3 mmol) in 1,2-dichloroethane (100 mL) was added at 20 °C bromoacetyl chloride (2.13 g, 13.6 mmol), solid $NaHCO_3$ (1.14 g, 13.6 mmol), and then water (5 mL) was slowly added dropwise with vigorous stirring. The mixture was extracted with $NaHCO_3$ solution (50 mL) and the organic phase dried over Na_2SO_4. Purification of the residue after concentration, by chromatography on 100 g silica gel (3 × 35 cm, CH_2Cl_2/MeOH 40 : 1, R_f = 0.21, MOPS) gave 3.57 g (87%) of **8** as a colorless oil. IR (film): $\tilde{\nu}$ = 3489, 2954, 2861, 2248, 1748 (C=O), 1661 (C=O), 1409, 1347, 1209, 1102, 1028, 910, 733 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.79–0.87 (m, 1 H, Cpr-*H*), 0.94–1.01 (m, 1 H, Cpr-*H*), 1.32–1.41 (m, 1 H, Cpr-*H*), 1.47–1.55 (m, 1 H, Cpr-*H*), 1.55–1.77 (m, 2 H, CH_2), 2.88–2.98 (m, 1 H, CH_2), 3.37–3.46 (m, 2 H, CH_2), 3.61–3.68 (m, 1 H, CH_2), 3.72 (s, 3 H, CH_3), 3.91 (dd, *J* = 31.3, 11.3 Hz, 2 H, CH_2), 4.09 (s, 1 H, CH), 4.38 (dd, *J* = 27.5, 15.5 Hz, 2 H, CH_2), 4.46 (s, 2 H, CH_2), 7.27–7.36 (m, 5 H, aryl-*H*). ^{13}C NMR ($CDCl_3$, 75.5 MHz, APT): δ = 9.6 (–, Cpr-*C*), 13.1 (–, Cpr-*C*), 25.4 (–, CH_2), 28.5 (–, C_{quat}, Cpr-*C*), 39.3 (–, CH_2), 39.4 (–, CH_2), 49.0 (–, CH_2), 52.4 (+, CH), 61.4 (+, CH_3), 67.2 (–, CH_2), 72.7 (–, CH_2), 125.2 (+, aryl-*C*), 127.3 (+, 2C, aryl-*C*), 128.1 (+, 2C, aryl-*C*), 138.0 (C_{quat}, aryl-*C*), 165.7 (–, C_{quat}), 166.4 (–, C_{quat}), 168.8 (–, C_{quat}). MS (ESI), *m/z* (%): 475.1/477.1 (100) $[M + Na]^+$, 927.2/929.2 (73) $[M + Na]^+$–HRMS (ESI): calcd. for $C_{20}H_{25}BrN_2O_5Na$ $[M + Na^+]$ 475.0839; found 475.0846.

7′-Indolylmethyl-1′,3′,4′,6′,7′,8′,9′,9a′-octahydro-2′-(3-benzyloxypropyl)spiro(cyclopropane-1,1′-[2*H*]pyrazino[1, 2-a]-pyrazin)-3′,6′,9′-trione (9). To a solution of **7** (1.50 g, 3.31 mmol) in MeOH (30 mL) were added tryptamine (583 mg, 3.64 mmol) and triethylamine (402 mg, 3.97 mmol), and the mixture was stirred at 20 °C for 12 h. The volatile material was removed under reduced pressure, the residue taken up in THF (50 mL), triethylamine (402 mg, 3.97 mmol) was added again and the mixture heated under reflux for 18 h. The solvents were removed under reduced pressure, the residue taken up in CH_2Cl_2 (100 mL), the solution washed with 1 N HCl (30 mL), and the organic phase dried ($MgSO_4$). Chromatographic purification of the residue after evaporation of the solvent, on 50 g of silica gel (3 × 40 cm, CH_2Cl_2/MeOH 40 : 1 → 20 : 1, R_f = 0.37 (CH_2Cl_2/MeOH 20 : 1), MOPS) gave 1.40 g (85%) of **9** as a colorless foam. IR (KBr): ν = 3330 (NH), 3033, 2929, 1692 (C=O), 1662 (C=O), 1646 (C=O), 1456, 1399, 1363, 1325, 1288, 1228, 1190, 987, 813, 738 cm^{-1}. H NMR (250 MHz, $CDCl_3$): δ = 0.89–1.11 (m, 3 H, Cpr-H), 1.32–1.38 (m, 1 H, Cpr-H), 2.80 (dd, ^3J = 9.6, ^2J = 17.5 Hz, 1 H, CH at C-7′), 3.07 (dd, ^3J = 2.8, ^2J = 17.5 Hz, 1 H, CH at C-7′), 4.01 (d, ^2J = 17.1 Hz, 1 H), 4.05 (s, 1 H, CH at 9a′-H), 4.22 (d, ^2J = 15.9 Hz, 1 H), 4.39 (dt, ^3J = 2.8, ^2J = 9.6 Hz, 1 H, 7′-H), 4.85 (d, ^2J = 15.9 Hz, 1 H), 5.02 (d, ^2J = 17.1 Hz, 1 H), 5.15 (s, 2 H, OCH_2), 6.58 (d, ^3J = 2.7 Hz, 1 H, NH), 7.12 (d, ^3J = 8.5 Hz, 2 H, Ar-H), 7.28 (d, ^3J = 8.5 Hz, 2 H, Ar-H), 7.25–7.41 (m, 5 H, Ar-H). ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ = 8.8 (–, Cpr-C), 12.0 (–, Cpr-C), 37.4 (–, CH_2 at C-7′), 41.2 (C_{quat}, Cpr-C), 46.2 (–, C-4′ and NCH_2), 52.2 (+, C-7′), 61.1 (+, C-9a′), 67.3 (–, OCH_2), 128.1 (+, 2 Ar-C), 128.4 (+, 2 Ar-C), 128.7 (+, Ar-C), 128.8 (+, 2 Ar-C), 128.9 (+, 2 Ar-C), 133.2 (C_{quat}, Ar-C), 134.8 (C_{quat}, Ar-C),

135.9 (C_{quat}, Ar-C), 163.4 (C_{quat}, C=O), 167.9 (C_{quat}, C=O), 169.9 (C_{quat}, C=O).–MS (EI, 70 eV), *m/z* (%): 483/481 (14/42) [M^+], 392/390 (25/72), 330 (10), 288 (19), 281 (11), 127/125 (14/45), 91 (76). $C_{35}H_{36}N_4O_4$ (576.7): calcd. C 72.90, H 6.29, N 9.72; found C 72.68, H 6.32, N 9.56.

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