



# Convenient two-step synthesis of highly functionalized benzo-fused 1,4-diazepin-3-ones and 1,5-diazocin-4-ones by sequential Ugi and intramolecular $S_NAr$ reactions

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## ABSTRACT

Benzodiazepinones are an important family of heterocycles with very attractive pharmacological properties and peptidomimetic abilities. We report herein a rapid and efficient two-step synthesis of polysubstituted 1,4-benzodiazepin-3-ones and 1,5-benzodiazocin-4-ones using a multicomponent condensation/cyclization strategy. The approach uses an Ugi four-component reaction to condense readily available *N*<sup>ε</sup>-Fmoc-amino acids, amines and isocyanides with a 2-fluorobenzaldehyde derivative followed by a one-pot Fmoc-group removal, intramolecular aromatic nucleophilic substitution for ring closure and side chain deprotection. The described method gives access to benzo-fused 7- and 8-membered rings bearing a wide variety of functionalized substituents and was applied to efficiently prepare tri- and tetrasubstituted 1,4-benzodiazepin-3-ones and 1,5-benzodiazocin-4-ones in high yields in two straightforward steps.

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## 1. Introduction

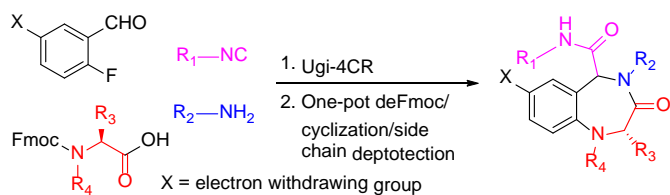
Benzodiazepines are very useful scaffolds in medicinal chemistry and they have been successfully exploited in the discovery and optimization of several bioactive compounds.<sup>1, 2</sup> With their good druglike properties and ability to provide potent and selective ligands for different biological targets, benzodiazepines are considered privileged structures.<sup>1-3</sup> In addition to their well known anxiolytic, sedative and anticonvulsant activities,<sup>4-7</sup> 1,4-benzodiazepine scaffolds can be found in a wide variety of bioactive molecules such as antitumor,<sup>8-11</sup> antithrombotic,<sup>12, 13</sup> anti-HIV,<sup>14, 15</sup> and antimalarial agents.<sup>16, 17</sup> The capacity of 1,4-benzodiazepinones to mimic different peptide secondary structures such as  $\beta$ - and  $\gamma$ -turns offers attractive opportunities for the development of small molecule protein-ligands and protein-protein interaction inhibitors.<sup>3, 16, 18-24</sup> For this reason, the development of new synthetic methodologies to access highly diversified benzodiazepinones and prepare libraries is of continuous interest.

Over the years, a great number of 1,4-benzodiazepinone syntheses have been reported.<sup>3, 25-27</sup> While most of these methods give access to 1,4-benzodiazepin-2-ones and 2,5-diones,<sup>3, 4, 9, 10, 12, 15, 16, 18-21, 25-29</sup> very few describe the preparation of 1,4-benzodiazepin-3-ones.<sup>13, 22, 30-34</sup> Interested in their peptidomimetic potential and use in combinatorial library, we were looking for a straightforward and efficient approach to generate

polysubstituted 1,4-benzodiazepin-3-ones with a high degree of functional diversity. Among the different reported methods to prepare benzodiazepinones, the Ugi four-component reaction (Ugi-4CR) is very attractive as it offers a great inputs diversity to access scaffolds with elaborate substitution patterns.<sup>35-38</sup> This isocyanide-based multicomponent reaction involves the reaction of isocyanide, carboxylic acid, amine and carbonyl compounds to afford a  $\alpha$ -acylamino amide in a single step.<sup>39, 40</sup> With this method, benzo-fused heterocyclic compounds can be obtained by using a bifunctional building block in a Ugi-3CR or by performing a postcondensation transformation for ring closure.<sup>41, 42</sup> As reviewed by Huang and Domling<sup>43</sup> and more recently by Banfi *et al.*,<sup>44</sup> several synthetic routes to prepare benzodiazepines by the Ugi multicomponent reaction have been described.<sup>45-48, 49-66</sup> Among them, the Ugi-deprotection-cyclization (UDC) strategy is the most commonly used and was shown to be very powerful to prepare benzodiazepinone derivatives.<sup>35-38, 41-44, 49-66</sup> To perform the cyclization step, several strategies including ester or amide aminolysis,<sup>9, 10, 49-58</sup> imine formation,<sup>55, 59</sup> aromatic nucleophilic substitution ( $S_NAr$ ),<sup>60, 61</sup> Staudinger/aza-Wittig<sup>62-65</sup> aza-Michael,<sup>33</sup> and Mitsunobu<sup>66</sup> reactions have been used. However, because they often involve modified or hardly accessible building blocks and/or Boc protecting group removal prior to cyclization, most reported UDC methodologies generate limited functional diversity on benzodiazepinone scaffolds. This limitation can be an important drawback in the design and generation of

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combinatorial libraries as well as for the introduction of relevant functional groups in structure-activity relationship studies and lead compound optimization.



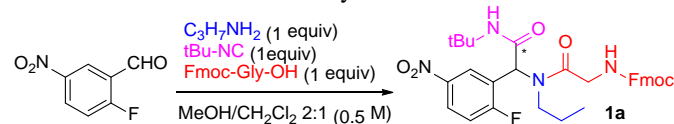
**Figure 1.** Synthesis of polysubstituted 1,4-benzodiazepin-3-ones from readily available building blocks by a Ugi-deprotection-cyclization approach.

For this reason, our strategy to prepare highly functionalized 1,4-benzodiazepin-3-ones was to use readily available *N*-Fmoc-amino acids in the Ugi-4CR with a 2-fluorobenzaldehyde derivative to allow a postcondensation one-pot deprotection/ $S_NAr$  cyclization (Figure 1). Taking advantage of the orthogonality with acid labile side chain protecting groups and the wide variety of commercially available amino acids compatible with the Fmoc/*t*Bu strategy, this approach allows the incorporation of functionalized side chains on the benzodiazepinone scaffold and significantly increases the accessible molecular complexity and diversity. Moreover, the use of  $\beta$ -amino acids can give access to a benzodiazocinone scaffold. Here we report our results concerning the use of an Ugi/deFmoc/cyclization approach to prepare 1,4-benzodiazepin-3-ones and 1,5-benzodiazocin-4-ones in two straightforward steps.

## 2. Results and discussion

The UDC strategy is a very attractive alternative to traditional multistep 1,4-benzodiazepin-3-one syntheses and, to our knowledge, has never been applied to prepare these heterocycles. Moreover, compared to the numerous reported UDC methods with Boc removal prior to cyclization, very few studies describe the use of the Fmoc group in the UDC.<sup>67</sup> To evaluate the efficiency of the Ugi-4CR with our building blocks and identify the best conditions, the reaction was first performed with 2-fluoro-5-nitrobenzaldehyde, 1-propylamine, *tert*-butyl isocyanide and Fmoc-Gly-OH in MeOH/ $CH_2Cl_2$  (2:1) at room temperature or under microwave (MW) heating in a sealed vial at 60°C (Table 1). The best result was observed when the Ugi-4CR was performed at room temperature for 72 h where compound **1a** has been obtained in 96 % yield after purification by HPLC (entry 3).

**Table 1.** Selection of optimal conditions for the Ugi-4CR with 2-fluoro-5-nitrobenzaldehyde



Entry	Temperature	Reaction time (h)	Yield [%] <sup>a</sup>
1	rt	24	39
2	rt	48	72
3	rt	72	96
4	Microwave 60°C	1	66
5	Microwave 60°C	2	68

<sup>a</sup> Isolated yields after purification.

Lower conversion rates and yields were observed with shorter reaction times (entries 1 and 2). MW irradiations have been shown to accelerate and improve Ugi-4CR<sup>33, 51, 52, 67, 68</sup> but in our

case no significant improvement was observed after 1 or 2 h of MW heating at 60°C (entries 4 and 5). For this reason and based on the possibility to perform parallel synthesis more efficiently, the room temperature condition was selected to conduct the next experiments.

To determine the extents and limitations of the cyclization step, 2-fluorobenzaldehyde derivatives bearing different electron withdrawing groups were used in the Ugi-4CR and the linear product submitted to the one-pot deprotection- $S_NAr$  reaction in presence of  $Na_2CO_3$  in DMF for 16 h (Table 2). The  $S_NAr$  cyclization at room temperature has been previously reported<sup>60, 61</sup> but in our case, no Fmoc cleavage was observed at this temperature. However, further experiments showed that heating at 85°C was required for complete Fmoc group removal with  $Na_2CO_3$  in DMF and to perform the one-pot deFmoc/cyclize. At 85°C, Ugi products containing a 5-nitro and 5-cyano substituted 2-fluorobenzyl were successfully converted into 1,4-benzodiazepin-3-ones (entries 5 and 6).

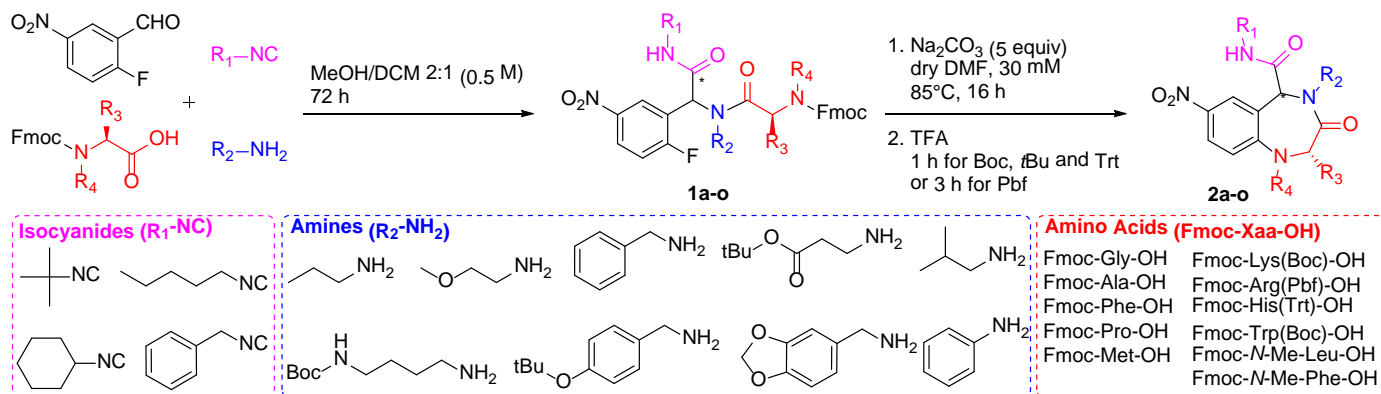
Other tested 2-fluorobenzaldehyde derivatives showed no trace of cyclized product under these conditions (entries 1-4). As expected, these results confirmed the importance of the substituent's electron withdrawing effect in the  $S_NAr$ . On the other hand, the linear product containing a Fmoc-sarcosine was also successfully converted into its cyclic counterpart (entry 7). This result demonstrated that *N*-Fmoc-*N*-alkylated amino acids can also be used in our Ugi/deFmoc/ $S_NAr$  cyclization method for the preparation of 1,4-benzodiazepin-3-ones. MW irradiations were also evaluated for the one-pot deprotection/cyclization steps from **1a**. The study showed that MW heating at 85°C for 2 h was needed to achieve a conversion rate equivalent to conventional heating for 16 h. Longer MW exposure led to product degradation.

**Table 2.** Substitution scope for the cyclization by  $S_NAr$

Entry	X	Y	R <sup>1</sup>	Conversion [%] <sup>a</sup>
1	H	H	H	0
2	H	Cl	H	0
3	Cl	H	H	0
4	Br	Cl	H	0
5	CN	H	H	99
6	NO <sub>2</sub>	H	H	99
7	NO <sub>2</sub>	H	CH <sub>3</sub>	99

<sup>a</sup> Conversion rates of linear precursor into 1,4-benzodiazepin-3-one were determined by HPLC.

To demonstrate the chemical diversity that could be generated with this approach, a first series of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted 1,4-benzodiazepin-3-ones was prepared (Figure 2). Different *N*-Fmoc-protected-amino acids, amines and isocyanides were used in the Ugi-4CR with 2-fluoro-5-nitrobenzaldehyde in MeOH/ $CH_2Cl_2$  at room temperature for 72 h (Figure 2). After removal of the solvent under reduced pressure, the Ugi products **1a-o** were purified by HPLC and isolated as a mixture of two diastereoisomers in 61-96% yields (Table 3).



**Figure 2.** Two-step synthesis of 1,4-benzodiazepin-3-ones by sequential Ugi-4CR and one-pot deFmoc/intramolecular  $S_NAr$ /side chain deprotection

**Table 3.** Prepared 1,4-benzodiazepin-3-ones **2a-o** by sequential Ugi-4CR and one-pot deFmoc/ $S_NAr$ /side chain deprotection

	$R^1$	$R^2$	$R^3$	$R^4$	Ugi-4CR yield [%] <sup>a</sup>	deFmoc/ $S_NAr$ /deprotection yield [%] <sup>a</sup>	dr <sup>b</sup>	Overall yield [%] <sup>a</sup>
<b>2a</b>			H	H	96	68		66
<b>2b</b>				H	77	87	>19:1	67
<b>2c</b>				H	84	81	16:1	68
<b>2d</b>				H	75	82	>19:1	61
<b>2e</b>			$-CH_3$	H	94	29 ( <b>2e'</b> ) 43 ( <b>2e''</b> )	1:3.5 ( <b>2e'</b> ) >19:1 ( <b>2e''</b> )	68 <sup>b</sup>
<b>2f</b>				H	80	68	2.3:1	54
<b>2g</b>				H	76	76	2.1:1	58
<b>2h</b>				H	67	84	10.1:1	57
<b>2i</b>				H	73	66	2.3:1	48
<b>2j</b>				H	70	68	2.2:1	48
<b>2k</b>				H	77	72	6.1:1	56
<b>2l</b>					87	29 ( <b>2l'</b> ) 38 ( <b>2l''</b> )	1:10 ( <b>2l'</b> ) >19:1 ( <b>2l''</b> )	58 <sup>c</sup>
<b>2m</b>					80	26 ( <b>2m'</b> ) 40 ( <b>2m''</b> )	1:13.3 ( <b>2m'</b> ) >19:1 ( <b>2m''</b> )	53 <sup>b</sup>
<b>2n</b>				$CH_3$	69	76	13.3:1	47
<b>2o</b>				$CH_3$	61	77	7.3:1	53

<sup>a</sup> Isolated yields after purification.

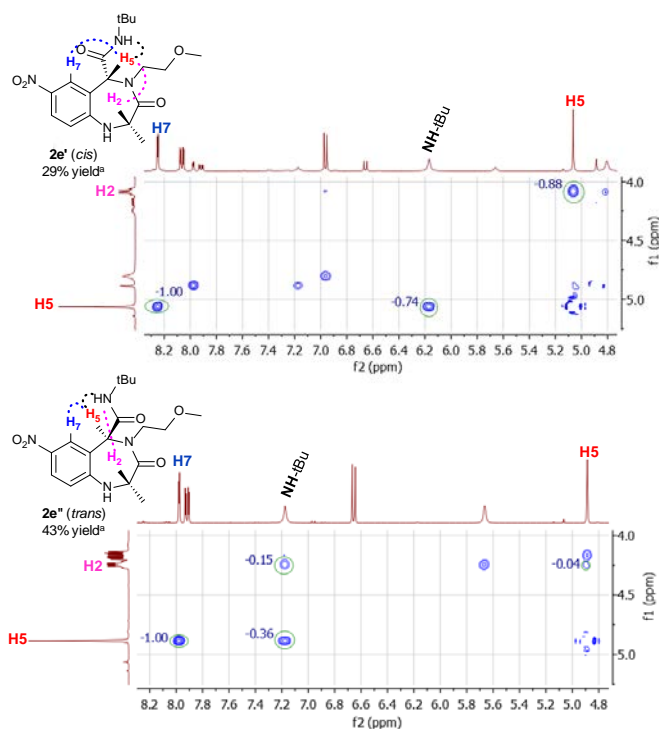
<sup>b</sup> Determined by <sup>1</sup>H NMR integration and reported as 2*S*,5*S* versus 2*S*,5*R* diastereoisomer as determined from NOESY spectra.

<sup>c</sup> Combined yields of the separated diastereoisomers.

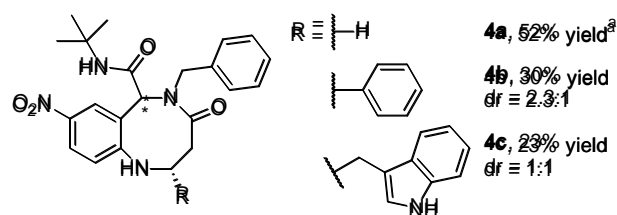
The results showed that a wide variety of isocyanides, amino acids and amines, including arylamines can be used in the Ugi-4CR. The lowest yields were observed for products containing *N*-methylated amino acids **1n** and **1o** with 61% and 69% yields, respectively. Then, the linear compounds were submitted to the one-pot deFmoc/cyclization/side chain deprotection. To do so, the Fmoc cleavage and  $S_NAr$  steps were performed simultaneously in presence of  $Na_2CO_3$  in DMF at 85°C for 16 h followed by DMF removal under reduced pressure and side chain deprotection with a TFA cocktail containing water and triisopropylsilane (TIS) for 1 h or 3 h for compound **2j** to remove the 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf) group. After their purification by HPLC, the cyclized compounds **2a-o** were isolated in yields ranging from 66% to 87% (Table 3). In addition to amino acids primary amines, the results demonstrated that the  $S_NAr$  can also be efficiently achieved with secondary amines to yield *N*-alkylated (**2n**, **2o**) and tricyclic (**2l**, **2m**) compounds. For this first series of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted 1,4-benzodiazepin-3-ones prepared by parallel synthesis, the desired compounds were obtained in 47–68% overall yields (Table 3). These very encouraging results showed that the approach is compatible with Boc, *tert*-butyl, Pbf and trityl protected side chains and allows an efficient and simple incorporation of functional groups on the 1,4-benzodiazepin-3-one scaffold.

While most synthesized 1,4-benzodiazepin-3-ones were isolated as a mixture of two diastereoisomers, both diastereoisomers of compounds **2e**, **2l** and **2m** have been successfully separated during HPLC purification and named **2e'**, **2e''**, **2l'**, **2l''**, **2m'** and **2m''** for their characterization and configuration determination. Analysis of the NOESY spectra of these compounds by looking at the H2/H5 and H2/NH-*t*Bu NOE interactions showed that the first peak in the HPLC chromatogram contained the 2*S*,5*R* diastereoisomer (*cis* isomer) while the 2*S*,5*S* diastereoisomer (*trans* isomer) was found in the second one (Figure 3 and Figure S7). For compounds **2e**, **2l** and **2m**, the 2*S*,5*S* (*trans*) diastereoisomers **2e''**, **2l''** and **2m''** have been isolated as the major product in 43%, 38% and 40% yields, respectively (Table 3). In comparison, the 2*S*,5*R* (*cis*) diastereoisomers **2e'**, **2m'** and **2l'** have been obtained in 29%, 29% and 26% isolated yields, respectively.

These results led us to investigate the diastereoisomeric composition of the isolated products **2b-o**. Since products obtained by UDC are generally considered as racemic mixtures, the diastereoisomeric composition of the final product has been rarely evaluated.<sup>59</sup> Diastereoisomeric ratios of compounds **2b-2o** were determined by  $^1H$  NMR (Table 3). The results showed a wide range of diastereoisomeric ratios with at the best >19:1 ratios for compounds **2b** and **2d** and at worst 2.1–2.3:1 ratios for compounds **2f**, **2g**, **2i** and **2j**. In the case of compounds **2c**, **2h**, **2k**, **2n** and **2o**, the determined ratios were 16:1, 10:1, 6:1, 13:1 and 7:1, respectively. Unfortunately, these results did not allow us to observe a relationship between substituents nature and diastereoisomeric ratios. As observed with **2e**, **2l** and **2m**, analysis of the H2/H5 and H2/NH-*t*Bu NOE interaction in the NOESY spectra showed that the 2*S*,5*S* (*trans*) diastereoisomer is predominant over the 2*S*,5*R* (*cis*) diastereoisomer for compounds **2b-o** of this series (Figure S7). Moreover, it is important to highlight that in some cases, the observed diastereoisomeric predominance was significantly high with >85% (**2k**, **2o**), >90% (**2c**, **2h** and **2n**) and even >95% (**2b**, **2d**) of the 2*S*,5*S* (*trans*) diastereoisomer in the isolated product. The observed difference in diastereoisomers content in the final products should be seriously considered during library screening, evaluation of the activity in bioassays and selection of hit compounds.



**Figure 3.** Expanded H2 and H5 region of the 2D  $^1H$ - $^1H$  NOESY spectra of isolated diastereoisomers **2e'** and **2e''**. <sup>a</sup>Isolated yields



**Figure 4.** Synthesized 1,5-benzodiazocin-4-ones. <sup>a</sup>Overall isolated yields

To expand the ring size, Fmoc- $\beta$ -Ala-OH, Fmoc- $\beta$ -Phe-OH and Fmoc- $\beta$ -homoTrp-OH were used with benzylamine, *tert*-butyl isocyanide and 2-fluoro-5-nitrobenzaldehyde in the Ugi-4CR/deFmoc/ $S_NAr$  cyclization to generate 1,5-benzodiazocin-4-ones (Figure 4). Here again, the first step worked and Ugi products **3a**, **3b** and **3c** were isolated in 76%, 69% and 81% yields, respectively (Table S1). As expected, since eight-membered ring formation is slower than seven, lower cyclization yields were observed. After one-pot deFmoc/ $S_NAr$  cyclization on **3a-c**, compounds **4a**, **4b** and **4c** were isolated in 69%, 44% and 29% yields, respectively (Table S1). The effects of microwave irradiations, temperature and reaction time on the formation of the eight-membered ring are currently under investigation. Nevertheless, 1,5-benzodiazocin-4-ones **4a**, **4b** and **4c** were obtained in 52%, 30% and 23% overall yields, respectively. Compared to 7-membered compounds **2a-o**, lower diastereoisomeric ratios were observed for diazocinone derivatives **4b** and **4c** with ratios of 2.3:1 (2*R*,6*S* versus 2*R*,6*R*) and 1:1 (2*S*,6*S* versus 2*S*,6*R*), respectively (Figure 4).

### 3. Conclusions

In summary, we report the use of a Ugi-4CR/deprotection/cyclization strategy to efficiently prepare polysubstituted 1,4-benzodiazepin-3-ones and 1,5-benzodiazocin-4-ones from readily available *N*-Fmoc-amino acids, amine derivatives and isocyanides. The study showed that a nitro or cyano substituent at the para position was necessary to

efficiently displace the fluorine and allow cyclization by  $S_NAr$ . We also demonstrated that the Fmoc-group removal and cyclization steps can be performed in one-pot in presence of  $Na_2CO_3$  with heating at  $85^\circ C$ . Structural analysis of the products showed that the *2S,5S* (*trans*) diastereoisomer was the major isomer obtained in the described conditions. Additional chemical modifications such as alkylation or acylation of the reduced nitro group, use of peptoid monomers and incorporation of convertible isocyanide are currently under investigation to expand the applicability of the approach and increase the accessible diversity. Simple and affordable, the described approach allows the introduction of a wide variety of functionalized substituents on the 1,4-benzodiazepin-3-one and 1,5-benzodiazocin-4-one scaffolds from readily available building blocks and is likely to become a useful method for the preparation benzodiazepinone and benzodiazocinone libraries.

## 4. Experimental section

### 4.1 General methods

All the chemical reagents and solvents from commercial sources were used without further purification. Amino acid derivatives were purchased from Matrix Innovation (Quebec, QC, Canada) or Chem-Impex International (Wood Dale, IL, USA). *tert*-Butyl (4-aminobutyl)carbamate and 4-*tert*-butoxybenzylamine building blocks were prepared as previously described.<sup>69-71</sup> All other reagents and solvents were purchased from Sigma-Aldrich (St. Louis, MO, USA). Microwave experiments were conducted on a Biotage Initiator microwave instrument (Charlotte, NC, USA) with 0.5-2 mL sealed microwave vials. Intermediates and final products were purified by RP-HPLC on a Shimadzu Prominence instrument (Columbian, MD, USA) using a Phenomenex Kinetex® EVO C18 column ( $250 \times 21.2$  mm, 300 Å, 5  $\mu$ m) and water (0.1% TFA) (A) and  $CH_3CN$  (0.1% TFA) (B) as mobile phase, with a linear gradient of 10% to 100% (B) for 15 min at 14 mL min<sup>-1</sup> and UV detection at 220 nm and 254 nm. LC-MS analyses were conducted on a Shimadzu Prominence instrument using a Phenomenex Kinetex column (4.6 mm x 100 mm, 2.6  $\mu$ m XB-C18, 100 Å, 1.8 mL/min) with a 10.5 min gradient from water (0.1% HCOOH) and  $CH_3CN$  (0.1% HCOOH) ( $CH_3CN$  10-100%), UV detection at 220 nm and 254 nm and mass spectrometry on a Shimadzu Prominence LCMS-2020 equipped with an ESI and APCI ion source. 1D <sup>1</sup>H NMR, <sup>13</sup>C NMR (APT) and 2D <sup>1</sup>H-<sup>1</sup>H COSY, <sup>1</sup>H-<sup>13</sup>C HSQC, <sup>1</sup>H-<sup>1</sup>H TOCSY and <sup>1</sup>H-<sup>1</sup>H NOESY spectra were obtained on a Bruker AVANCE 400 spectrometer (Billerica, MA, USA). NMR spectra were processed with TopSpin 2.0 software (Bruker) and analyzed with MestRenova software (MestreLab Research, Santiago de Compostela, Spain). Chemical shifts ( $\delta$ ) are reported in parts per million, coupling constants (*J*) in hertz (Hz) and signal patterns indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; br, broad. High-resolution mass spectrometry was performed on a Waters Synapt G2-Si (Quadrupole/TOF) with a Waters UPLC binary pump and FTN injector. The mass spectrometer was operated in High resolution mode and calibration performed with a sodium formate solution (Sigma) and lock-mass correction using a Leucine-enkephaline solution (Waters).

### 4.2 General procedure for the synthesis of the UGI intermediates 1a-o and 3a-c

2-Fluorobenzaldehyde (42.3 mg, 0.25 mmol) was first dissolved in a 15 mL conical centrifuge tube with MeOH (330  $\mu$ L) and the amine (0.25 mmol) was added. The resulting mixture

was agitated with an orbital mixer for 30 min and the Fmoc-protected amino acid (0.25 mmol) added to the reaction with  $CH_2Cl_2$  (170  $\mu$ L). After stirring for 15 min, the isocyanide (0.25 mmol) was added and the mixture agitated for 72 h. Finally, the solvent was removed under reduced pressure and the crude product dissolved in DMF to be purified by RP-HPLC. The fractions containing the desired product in >95% purity were pooled and freeze dried.

(1a). White powder (154 mg, 0.24 mmol, 96%); RP-HPLC  $t_R$  = 10.67 min; MS (APCI+): calcd for  $C_{36}H_{36}FN_4O_6$   $[M+H]^+$  = 639.26, found: 639.30.

(1b). White powder (159 mg, 0.19 mmol, 77%); RP- HPLC  $t_R$  = 11.46 min; MS (APCI-): calcd for  $C_{46}H_{54}FN_5O_8$   $M^-$  = 823.40, found: 823.40.

(1c). White powder (175 mg, 0.21 mmol, 84%); RP-HPLC  $t_R$  = 11.52 min; MS (APCI-): calcd for  $C_{47}H_{54}FN_5O_8$   $M^-$  = 835.40, found: 835.40.

(1d). White powder (158 mg, 0.19 mmol, 75%); RP-HPLC  $t_R$  = 13.42 min; MS (APCI-): calcd for  $C_{48}H_{50}FN_5O_8$   $M^-$  = 843.36, found: 843.35.

(1e). White powder (147 mg, 0.24 mmol, 95%); RP-HPLC  $t_R$  = 10.38/10.46 min; MS (APCI+): calcd for  $C_{33}H_{38}FN_4O_7$   $[M+H]^+$  = 621.28, found: 621.30.

(1f). White powder (151 mg, 0.20 mmol, 80%); RP-HPLC  $t_R$  = 10.79 min; MS (APCI+): calcd for  $C_{40}H_{42}FN_4O_8S$   $[M+H]^+$  = 757.27, found: 757.35.

(1g). White powder (130 mg, 0.19 mmol, 76%); RP-HPLC  $t_R$  = 11.31/11.37 min; MS (APCI+): calcd for  $C_{39}H_{42}FN_4O_6$   $[M+H]^+$  = 681.30, found: 681.30.

(1h). Yellow powder (174 mg, 0.17 mmol, 67%); RP-HPLC  $t_R$  = 8.29 min; MS (APCI+): calcd for  $C_{63}H_{62}FN_6O_7$   $[M+H]^+$  = 1033.47, found: 791.40  $[M-Trt+H]^+$  ( $C_{44}H_{47}FN_6O_7$ ).

(1i). White powder (173 mg, 0.18 mmol, 73%); RP-HPLC  $t_R$  = 12.02/12.11 min; MS (APCI+): calcd for  $C_{52}H_{62}FN_6O_{10}$   $[M+H]^+$  = 949.45, found: 949.55.

(1j). White powder (181 mg, 0.18 mmol, 70%); RP-HPLC  $t_R$  = 11.41/11.45 min; MS (APCI+): calcd for  $C_{53}H_{67}FN_7O_{11}S$   $[M+H]^+$  = 1028.45, found: 1028.50.

(1k). Brown powder (160 mg, 0.19 mmol, 77%); RP-HPLC  $t_R$  = 11.11/11.19 min; MS (APCI+): calcd for  $C_{47}H_{49}FN_5O_8$   $[M+H]^+$  = 830.36, found: 830.30.

(1l). White powder (137 mg, 0.22 mmol, 87%); RP-HPLC  $t_R$  = 11.01 min; MS (APCI+): calcd for  $C_{35}H_{40}FN_4O_6$   $[M+H]^+$  = 631.29, found: 631.45.

(1m). White powder (137 mg, 0.20 mmol, 80%); RP-HPLC  $t_R$  = 11.19 min; MS (APCI-): calcd for  $C_{39}H_{39}FN_4O_6$   $M^-$  = 678.28, found: 678.30.

(1n). White powder (121 mg, 0.15 mmol, 61%); RP-HPLC  $t_R$  = 12.87 min; MS (APCI+): calcd for  $C_{43}H_{57}FN_5O_8$   $[M+H]^+$  = 790.41, found: 790.55.

(1o). White powder (142 mg, 0.17 mmol, 69%); RP-HPLC  $t_R$  = 12.75/12.81 min; MS (APCI+): calcd for  $C_{46}H_{55}FN_5O_8$   $[M+H]^+$  = 824.40, found: 824.45.

(3a). White powder (123 mg, 0.19 mmol, 76%); RP-HPLC  $t_R$  = 10.61 min; MS (APCI-): calcd for  $C_{37}H_{37}FN_4O_6$   $M^-$  = 652.27, found: 652.35.

(3b). White powder (125 mg, 0.19 mmol, 69%); RP-HPLC  $t_R = 11.46$  min; MS (APCI+): calcd for  $C_{43}H_{42}FN_4O_6$   $[M+H]^+ = 729.30$ , found: 729.40.

(3c). Yellow powder (158 mg, 0.20 mmol, 81%); RP-HPLC  $t_R = 11.44$  min; MS (APCI+): calcd for  $C_{46}H_{45}FN_5O_6$   $[M+H]^+ = 782.33$ , found: 782.40.

### 4.3 General procedure for the synthesis of compounds 2a-o and 4a-c by one-pot deprotection-cyclization

The Ugi product (0.08 mmol) and  $Na_2CO_3$  (42.4 mg, 0.4 mmol) were dissolved in a 20 mL glass vial with dry DMF (2.66 mL) and the mixture was heated at 85°C overnight under magnetic agitation. Afterwards, the solvent was removed under reduced pressure and the side chains deprotected by treatment with a mixture of TFA/water/TIS (95:2.5:2.5) (1 mL) for 1 h for compounds with Boc, tBu, Trt protecting groups or 3 h for compounds containing a Pbf protecting group. After solvent removal under reduced pressure, the crude product was dissolved in MeOH and purified by RP-HPLC. The fractions containing the desired product were pooled and freeze dried.

4.3.1 (5*R,S*)-4-benzyl-*N*-(*tert*-butyl)-7-nitro-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-5-carboxamide (2a). Yellow powder (22 mg, 0.055 mmol, 68%); RP-HPLC  $t_R = 8.71$  min;  $^1H$  NMR (400 MHz,  $CD_3CN$ ):  $\delta$  7.89 (dd,  $J = 9.1, 2.7$  Hz, 1*H*, *H9*), 7.82 (d,  $J = 2.6$  Hz, 1*H*, *H7*), 7.38–7.21 (m, 5*H*, *Ph'*), 6.63 (d,  $J = 9.1$  Hz, 1*H*, *H10*), 6.16 (d,  $J = 6.2$  Hz, 1*H*, *NHtBu*), 5.52 (s, 1*H*, *NH1*), 4.88 (s, 1*H*, *H5*), 4.75 (d,  $J = 14.7$  Hz, 1*H*, *H1'*), 4.62 (d,  $J = 14.7$  Hz, 1*H*, *H1''*), 4.18 (dd,  $J = 15.3, 1.7$  Hz, 1*H*, *H2*), 3.71 (dd,  $J = 15.4, 7.6$  Hz, 1*H*, *H2*), 1.16 (s, 9*H*, *tBu*);  $^{13}C$  NMR (101 MHz,  $CD_3CN$ ):  $\delta$  152.5 (C), 138.4 (C), 138.0 (C), 129.9 (CH), 129.7 (CH), 129.6 (CH), 128.7 (CH), 126.1 (CH), 117.7 (C), 116.7 (CH), 66.6 (CH), 52.6 (CH<sub>2</sub>), 52.4 (C), 48.9 (CH<sub>2</sub>), 28.4 (CH<sub>3</sub>); HRMS (ESI-TOF): calcd for  $C_{21}H_{25}N_4O_4$   $[M+H]^+ = 397.1871$ , found: 397.1864.

4.3.2 (2*S,5S*)-2-(4-aminobutyl)-4-benzyl-7-nitro-3-oxo-*N*-pentyl-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-5-carboxamide (2b). Red oil (41 mg, 0.069 mmol, 87%); RP-HPLC  $t_R = 6.94$  min;  $^1H$  NMR (400 MHz,  $CD_3CN$ ):  $\delta$  7.84 (dd,  $J = 9.1, 2.6$  Hz, 1*H*, *H9*), 7.70 (d,  $J = 2.6$  Hz, 1*H*, *H7*), 7.57 (br s, 3*H*,  $NH_3^+$ ), 7.22–7.11 (m, 5*H*, *Ph'*), 6.72 (d,  $J = 9.1$  Hz, 1*H*, *H10*), 6.56 (t,  $J = 5.9$  Hz, 1*H*, *NH*-pentyl), 6.22 (d,  $J = 2.8$  Hz, 1*H*, *NH1*), 5.18 (d,  $J = 14.9$  Hz, 1*H*, *H1'*), 4.95 (s, 1*H*, *H5*), 4.29 (d,  $J = 14.9$  Hz, 1*H*, *H1''*), 4.11–3.93 (m, 1*H*, *H2*), 3.12 (ddt,  $J = 15.7, 13.3, 6.3$  Hz, 2*H*,  $NHCH_2CH_2CH_2CH_2CH_3$ ), 2.97 (t,  $J = 7.1$  Hz, 2*H*, *Hε*), 1.97 (m, 1*H*, *Hβ*), 1.67 (m, 3*H*, *Hδ*, *Hβ*), 1.60–1.33 (m, 4*H*, *Hγ*,  $CH_2CH_2CH_2CH_2CH_3$ ), 1.34–1.08 (m, 4*H*,  $CH_2CH_2CH_2CH_2CH_3$ ), 0.86 (t,  $J = 7.2$  Hz, 3*H*, pentyl-*CH*<sub>3</sub>);  $^{13}C$  NMR (101 MHz,  $CD_3CN$ ):  $\delta$  170.7 (C), 170.6 (C), 152.6 (C), 138.2 (C), 137.9 (C), 130.1 (CH), 129.3 (CH), 129.1 (CH), 128.3 (CH), 125.9 (CH), 117.5 (C), 116.8 (CH), 66.3 (CH), 55.1 (CH), 53.1 (CH<sub>2</sub>), 40.6 (CH<sub>2</sub>), 40.1 (CH<sub>2</sub>), 29.9 (CH<sub>2</sub>), 29.6 (2 CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 23.4 (CH<sub>2</sub>), 23.0 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>); HRMS (ESI-TOF): calcd for  $C_{26}H_{36}N_5O_4$   $[M+H]^+ = 482.2762$ , found: 482.2805.

4.3.3 (2*S,5S*)-2-(4-aminobutyl)-4-benzyl-*N*-cyclohexyl-7-nitro-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-5-carboxamide (2c). Orange powder (39 mg, 0.064 mmol, 81%); RP-HPLC  $t_R = 6.96$  min;  $^1H$  NMR (400 MHz,  $CD_3CN$ ):  $\delta$  7.84 (dd,  $J = 9.1, 2.6$  Hz, 1*H*, *H9*), 7.72 (d,  $J = 2.5$  Hz, 1*H*, *H7*), 7.58 (br s, 3*H*,  $Lys-NH_3^+$ ), 7.27–7.14 (m, 5*H*, *Ph'*), 6.71 (d,  $J = 9.1$  Hz, 1*H*, *H10*), 6.22 (d,  $J = 2.9$  Hz, 1*H*, *NH1*), 6.13 (d,  $J = 8.2$  Hz, 1*H*, *NHCy*), 4.98 (d,  $J = 14.7$  Hz, 1*H*, *H1'*), 4.93 (s, 1*H*, *H5*), 4.46 (d,  $J = 14.7$  Hz, 1*H*, *H1''*), 4.03 (q,  $J = 6.3$  Hz, 1*H*, *H2*), 3.57 (m, 1*H*,

*Cy-CH*), 2.96 (t,  $J = 7.1$  Hz, 2*H*, *Hε*), 1.89–0.96 (m, 16*H*, *Hβ*, *Hγ*, *Hδ*, *Cy-CH*<sub>2</sub>);  $^{13}C$  NMR (101 MHz,  $CD_3CN$ ):  $\delta$  170.6 (C), 169.7 (C), 152.5 (C), 138.3 (C), 137.9 (C), 130.1 (CH), 129.5 (CH), 129.3 (CH), 128.5 (CH), 125.9 (CH), 117.5 (C), 116.8 (CH), 66.3 (CH), 55.1 (CH), 52.9 (CH<sub>2</sub>), 50.1 (CH), 40.1 (CH<sub>2</sub>), 33.0 (CH<sub>2</sub>), 30.0 (CH<sub>2</sub>), 27.5 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 25.7 (CH<sub>2</sub>), 23.44 (CH<sub>2</sub>); HRMS (ESI-TOF): calcd for  $C_{27}H_{36}N_5O_4$   $[M+H]^+ = 494.2762$ , found: 494.2775.

4.3.4 (2*S,5S*)-2-(4-aminobutyl)-*N,4*-dibenzyl-7-nitro-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-5-carboxamide (2d). Orange powder (40 mg, 0.066 mmol, 82%); RP-HPLC  $t_R = 9.87$  min;  $^1H$  NMR (400 MHz,  $CD_3CN$ ):  $\delta$  7.86 (dd,  $J = 9.1, 2.6$  Hz, 1*H*, *H9*), 7.73 (d,  $J = 2.5$  Hz, 1*H*, *H7*), 7.59 (br s, 3*H*,  $NH_3^+$ ), 7.38–7.10 (m, 11*H*, *Ph*, *Ph'*,  $NHCH_2Ph$ ), 6.74 (d,  $J = 9.1$  Hz, 1*H*, *H10*), 6.29–6.16 (m, 1*H*, *NH1*), 5.25 (d,  $J = 14.9$  Hz, 1*H*, *H1'*), 5.05 (s, 1*H*, *H5*), 4.41–4.23 (m, 3*H*, *H1''*,  $NHCH_2Ph$ ), 3.90–3.80 (m, 1*H*, *H2*), 3.05–2.83 (m, 2*H*, *Hε*), 1.84 (m, 1*H*, *Hβ*), 1.62 (m, 3*H*, *Hβ*, *Hδ*), 1.33–1.18 (m, 1*H*, *Hγ*), 1.18–1.04 (m, 1*H*, *Hγ*);  $^{13}C$  NMR (101 MHz,  $CD_3CN$ ):  $\delta$  170.8 (C), 170.6 (C), 152.5 (C), 139.9 (C), 138.2 (C), 137.9 (C), 130.1 (CH), 129.4 (CH), 129.2 (CH), 129.1 (CH), 128.7 (CH), 128.3 (CH), 128.1 (CH), 126.0 (CH), 117.4 (C), 116.8 (CH), 66.2 (CH), 55.1 (CH), 53.0 (CH<sub>2</sub>), 44.1 (CH<sub>2</sub>), 40.1 (CH<sub>2</sub>), 29.9 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 23.1 (CH<sub>2</sub>); HRMS (ESI-TOF): calcd for  $C_{28}H_{32}N_5O_4$   $[M+H]^+ = 502.2449$ , found: 502.2464.

4.3.5 (2*S,5R,S*)-*N*-(*tert*-butyl)-4-(2-methoxyethyl)-2-methyl-7-nitro-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-5-carboxamide (2e'). Yellow powder (9 mg, 0.024 mmol, 29%); RP-HPLC  $t_R = 7.91$  min;  $^1H$  NMR (400 MHz,  $CD_3CN$ ):  $\delta$  (major, 78%) 8.25 (d,  $J = 2.6$  Hz, *H7*), 8.06 (dd,  $J = 8.8, 2.6$  Hz, *H9*), 6.96 (d,  $J = 8.8$  Hz, 1*H*, *H10*), 6.17 (br s, 1*H*, *NHtBu*), 5.06 (s, 1*H*, *H5*), 4.80 (br s, 1*H*, *NH1*), 4.08 (q,  $J = 6.7$  Hz, 1*H*, *H2*), 3.83 (ddd,  $J = 14.1, 7.2, 5.2$  Hz, 1*H*, *H1'*), 3.70–3.58 (m, 1*H*, *H1''*), 3.56–3.46 (m, 2*H*, *H2'*), 3.27 (s, 3*H*,  $OCH_3$ ), 1.49 (d,  $J = 6.8$  Hz, 3*H*, *Hβ*), 1.27 (s, 9*H*, *tBu*); (minor, 22%) 7.98 (d,  $J = 2.6$  Hz, 1*H*, *H7*), 7.92 (dd,  $J = 9.1, 2.7$  Hz, 1*H*, *H9*), 7.17 (br s, 1*H*, *NHtBu*), 6.66 (d,  $J = 9.1$  Hz, 1*H*, *H10*), 5.66 (br s, 1*H*, *NH1*), 4.89 (s, 1*H*, *H5*), 4.25 (qd,  $J = 6.5, 2.9$  Hz, 1*H*, *H2*), 4.17 (ddd,  $J = 14.5, 7.0, 3.7$  Hz, 1*H*, *H1'*), 3.70–3.58 (m, 2*H*, *H2'*), 3.34 (s, 3*H*,  $OCH_3$ ), 3.24–3.15 (m, 1*H*, *H1''*), 1.32 (m, 12*H*, *Hβ*, *tBu*);  $^{13}C$  NMR (101 MHz,  $CD_3CN$ ): (major and minor)  $\delta$  168.3 (C), 154.5 (C), 130.3 (C), 130.1 (CH), 127.2 (CH), 126.2 (CH), 125.9 (CH), 120.3 (CH), 116.3 (CH), 71.0 (CH<sub>2</sub>), 70.2 (CH<sub>2</sub>), 67.0 (CH), 65.3 (CH), 59.2 (CH), 58.8 (CH<sub>3</sub>), 58.7 (CH<sub>3</sub>), 52.0 (C), 50.5 (CH), 49.3 (CH<sub>2</sub>), 48.2 (CH<sub>2</sub>), 28.6 (CH<sub>3</sub>), 28.5 (CH<sub>3</sub>), 20.8 (CH<sub>3</sub>); HRMS (ESI-TOF):  $m/z$  calcd for  $C_{18}H_{27}N_4O_5$   $[M+H]^+ = 379.1976$ , found: 379.1982.

4.3.6 (2*S,5S*)-*N*-(*tert*-butyl)-4-(2-methoxyethyl)-2-methyl-7-nitro-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-5-carboxamide (2e''). Yellow powder (13 mg, 0.035 mmol, 43%); RP-HPLC  $t_R = 8.19$  min;  $^1H$  NMR (400 MHz,  $CD_3CN$ ):  $\delta$  7.98 (d,  $J = 2.6$  Hz, 1*H*, *H7*), 7.92 (dd,  $J = 9.1, 2.7$  Hz, 1*H*, *H9*), 7.18 (br s, 1*H*, *NHtBu*), 6.66 (d,  $J = 9.1$  Hz, 1*H*, *H10*), 5.66 (br s, 1*H*, *NH1*), 4.89 (s, 1*H*, *H5*), 4.31–4.21 (m, 1*H*, *H2*), 4.21–4.11 (m, 1*H*, *H1'*), 3.64 (m, 2*H*, *H2'*), 3.34 (s, 3*H*,  $OCH_3$ ), 3.24–3.14 (m, 1*H*, *H1''*), 1.36–1.29 (m, 12*H*, *Hβ*, *tBu*);  $^{13}C$  NMR (101 MHz,  $CD_3CN$ ):  $\delta$  170.6 (C), 170.5 (C), 152.5 (C), 137.9 (C), 130.1 (CH), 125.9 (CH), 116.3 (CH), 70.2 (CH<sub>2</sub>), 67.0 (CH), 58.7 (CH<sub>3</sub>), 51.8 (C), 50.5 (CH), 48.3 (CH<sub>2</sub>), 28.5 (CH<sub>3</sub>), 15.9 (CH<sub>3</sub>); HRMS (ESI-TOF): calcd for  $C_{18}H_{27}N_4O_5$   $[M+H]^+ = 379.1976$ , found: 379.1982.

4.3.7 (2*S,5R,S*)-4-(benzo[d][1,3]dioxol-5-ylmethyl)-*N*-(*tert*-butyl)-2-(2-(methylthio)ethyl)-7-nitro-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine-5-carboxamide (2f). Yellow powder

(28 mg, 0.054 mmol, 68%); RP-HPLC  $t_R$  = 9.47 min;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ ):  $\delta$  (major, 77%) 7.88 (dd,  $J$  = 9.1, 2.6 Hz, 1H,  $H_9$ ), 7.82 (d,  $J$  = 2.5 Hz, 1H,  $H_7$ ), 6.87–6.71 (m, 3H,  $\text{Pip}'_{\text{Ar}}$ ), 6.67 (d,  $J$  = 9.1 Hz, 1H,  $H_{10}$ ), 5.88 (m, 2H,  $\text{OCH}_2\text{O}$ ), 5.80–5.69 (m, 1H,  $\text{NH}_1$ ), 5.60 (s, 1H,  $\text{NHtBu}$ ), 4.89 (s, 1H,  $H_5$ ), 4.69–4.50 (m, 2H,  $H_{1'}$ ), 4.19 (m, 1H,  $H_2$ ), 2.63–2.52 (m, 2H,  $H_\gamma$ ), 2.36–2.11 (m, 1H,  $H_\beta$ ), 2.08 (s, 3H,  $\text{SCH}_3$ ), 1.93 (m, 1H,  $H_\beta$ ), 1.19 (s, 9H,  $t\text{Bu}$ ); (minor, 33%) 7.99 (dd,  $J$  = 8.8, 2.6 Hz, 1H,  $H_9$ ), 7.94 (d,  $J$  = 2.5 Hz, 1H,  $H_7$ ), 6.90 (d,  $J$  = 8.8 Hz, 1H,  $H_{10}$ ), 6.87–6.71 (m, 3H,  $\text{Pip}'_{\text{Ar}}$ ), 5.88 (m, 2H,  $\text{OCH}_2\text{O}$ ), 5.80–5.69 (m, 1H,  $\text{NH}_1$ ), 5.14 (s, 1H,  $H_5$ ), 4.96 (d,  $J$  = 14.8 Hz, 1H,  $H_{1'}$ ), 4.40 (d,  $J$  = 14.8 Hz, 1H,  $H_{1'}$ ), 4.35–4.28 (m, 1H,  $H_2$ ), 2.68 (m, 2H,  $H_\gamma$ ), 2.36–2.11 (m, 2H,  $H_\beta$ ), 2.10 (s, 3H,  $\text{SCH}_3$ ), 1.18 (s, 9H,  $t\text{Bu}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_3\text{CN}$ ): (major and minor)  $\delta$  171.6 (C), 170.1 (C), 169.5 (C), 167.5 (C), 153.7 (C), 152.2 (C), 148.9 (C), 148.3 (C), 138.1 (C), 132.5 (C), 132.3 (C), 130.2 (CH), 127.1 (CH), 126.4 (C), 126.1 (CH), 125.8 (CH), 123.4 (CH), 122.7 (CH), 119.9 (CH), 117.9 (C), 116.8 (CH), 109.8 (CH), 109.6 (CH), 109.1 (CH), 108.8 (CH), 102.4 ( $\text{CH}_2$ ), 102.2 ( $\text{CH}_2$ ), 66.6 (CH), 63.4 (CH), 61.2 (CH), 54.2 (CH), 52.3 ( $\text{CH}_2$ ), 52.2 (C), 51.9 ( $\text{CH}_2$ ), 33.9 ( $\text{CH}_2$ ), 31.1 ( $\text{CH}_2$ ), 30.9 ( $\text{CH}_2$ ), 30.7 ( $\text{CH}_2$ ), 28.6 ( $\text{CH}_3$ ), 28.5 ( $\text{CH}_3$ ), 15.4 ( $\text{CH}_3$ ), 15.2 ( $\text{CH}_3$ ); HRMS (ESI-TOF): calcd for  $\text{C}_{25}\text{H}_{31}\text{N}_4\text{O}_6\text{S}$   $[\text{M}+\text{H}]^+$  = 515.1959, found: 515.1965.

4.3.8 (2*S*,5*R*/*S*)-2-benzyl-*N*-(*tert*-butyl)-7-nitro-3-oxo-4-propyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine-5-carboxamide (**2g**): Yellow powder (27 mg, 0.062 mmol, 76%); RP-HPLC  $t_R$  = 9.51/9.64 min;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (major, 68%) 8.00 (d,  $J$  = 2.5 Hz, 1H,  $H_7$ ), 7.98–7.93 (m, 1H,  $H_9$ ), 7.42–7.20 (m, 5H,  $\text{Phe}_{\text{Ar}}$ ), 6.47 (d,  $J$  = 9.0 Hz, 1H,  $H_{10}$ ), 5.51 (s, 1H,  $\text{NHtBu}$ ), 4.64 (s, 1H,  $H_5$ ), 4.56 (br s, 1H,  $\text{NH}_1$ ), 4.35 (dd,  $J$  = 7.9, 6.0 Hz, 1H,  $H_2$ ), 3.81–3.69 (m, 1H,  $H_{1'}$ ), 3.52–3.37 (m, 2H,  $H_\beta$ ,  $H_{1'}$ ), 2.97–2.86 (m, 1H,  $H_\beta$ ), 1.78–1.49 (m, 2H,  $H_2'$ ), 1.26 (s, 9H,  $t\text{Bu}$ ), 0.86 (t,  $J$  = 7.4 Hz, 3H,  $H_3'$ ); (minor, 32%) 8.19 (d,  $J$  = 2.5 Hz, 1H,  $H_7$ ), 8.08 (dd,  $J$  = 8.6, 2.5 Hz, 1H,  $H_9$ ), 7.42–7.20 (m, 5H,  $\text{Phe}_{\text{Ar}}$ ), 6.67 (d,  $J$  = 8.6 Hz, 1H,  $H_{10}$ ), 5.34 (s, 1H,  $\text{NH}_1$ ), 4.71 (s, 1H,  $\text{NHtBu}$ ), 4.09 (dd,  $J$  = 11.5, 2.7 Hz, 1H,  $H_2$ ), 3.94 (ddd,  $J$  = 13.5, 9.3, 6.4 Hz, 1H,  $H_{1'}$ ), 3.65 (dd,  $J$  = 13.5, 2.5 Hz, 1H,  $H_\beta$ ), 3.32 (ddd,  $J$  = 13.5, 9.2, 5.8 Hz, 1H,  $H_{1'}$ ), 3.09–3.01 (m, 1H,  $H_\beta$ ), 1.78–1.49 (m, 2H,  $H_2'$ ), 1.35 (s, 9H,  $t\text{Bu}$ ), 0.95 (t,  $J$  = 7.4 Hz, 3H,  $H_3'$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ): (major and minor)  $\delta$  170.3 (C), 168.7 (C), 168.2 (C), 167.2 (C), 151.9 (C), 150.1 (C), 142.6 (C), 138.1 (C), 137.3 (C), 136.2 (C), 131.0 (C), 129.3 (CH), 129.2 (CH), 129.0 (CH), 128.8 (CH), 127.5 (CH), 127.3 (CH), 126.1 (CH), 125.8 (CH), 125.6 (CH), 121.0 (CH), 116.6 (CH), 116.5 (C), 66.9 (CH), 65.9 (CH), 65.1 (CH), 55.3 (CH), 53.1 ( $\text{CH}_2$ ), 52.2 (C), 52.0 (C), 51.5 ( $\text{CH}_2$ ), 40.8 ( $\text{CH}_2$ ), 36.6 ( $\text{CH}_2$ ), 28.6 ( $\text{CH}_3$ ), 28.4 ( $\text{CH}_3$ ), 21.7 ( $\text{CH}_2$ ), 21.1 ( $\text{CH}_2$ ), 11.4 ( $\text{CH}_3$ ), 11.1 ( $\text{CH}_3$ ); HRMS (ESI-TOF): calcd for  $\text{C}_{24}\text{H}_{31}\text{N}_4\text{O}_4$   $[\text{M}+\text{H}]^+$  = 439.2340, found: 439.2351.

4.3.9 (2*S*,5*S*)-2-((1*H*-imidazol-5-yl)methyl)-*N*-(*tert*-butyl)-4-(4-hydroxybenzyl)-7-nitro-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine-5-carboxamide (**2h**): Yellow oil (33 mg, 0.067 mmol, 84%); RP-HPLC  $t_R$  = 6.09 min;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ ):  $\delta$  8.43 (d,  $J$  = 1.3 Hz, 1H,  $H_\pi$ ), 7.92–7.82 (m, 2H,  $H_7$ ,  $H_9$ ), 7.25–7.15 (m, 3H,  $H_\delta$ ,  $\text{Ph}'$ ), 6.76–6.68 (m, 3H,  $\text{Ph}'$ ,  $H_{10}$ ), 6.38 (br s, 1H,  $\text{NH}_1$ ), 5.43 (s, 1H,  $\text{NHtBu}$ ), 4.93 (s, 1H,  $H_5$ ), 4.71 (d,  $J$  = 14.4 Hz, 1H,  $H_{1'}$ ), 4.52 (d,  $J$  = 14.4 Hz, 1H,  $H_{1'}$ ), 4.30 (br m, 1H,  $H_2$ ), 3.44 (dd,  $J$  = 15.0, 7.8 Hz, 1H,  $H_\beta$ ), 3.13 (dd,  $J$  = 15.0, 5.4 Hz, 1H,  $H_\beta$ ), 1.02 (s, 9H,  $t\text{Bu}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_3\text{CN}$ ):  $\delta$  170.0 (C), 169.6 (C), 157.9 (C), 152.0 (C), 138.5 (C), 131.2 (CH), 130.9 (C), 130.0 (CH), 129.1 (C), 125.8 (CH), 118.6 (CH), 118.0 (C), 117.2 (CH), 116.5 (CH), 66.4 (CH), 55.8 (CH), 52.3 ( $\text{CH}_2$ ), 52.2 (C), 28.3 ( $\text{CH}_3$ ), 26.0 ( $\text{CH}_2$ ); HRMS (ESI-TOF): calcd for  $\text{C}_{25}\text{H}_{29}\text{N}_6\text{O}_5$   $[\text{M}+\text{H}]^+$  = 493.2194, found: 493.2192

4.3.10 (2*S*,5*R*/*S*)-2-((1*H*-indol-3-yl)methyl)-4-(4-aminobutyl)-*N*-(*tert*-butyl)-7-nitro-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine-5-carboxamide (**2i**): Yellow powder (33 mg, 0.053 mmol, 66%); RP-HPLC  $t_R$  = 6.86 min;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ ):  $\delta$  (major, 68%) 9.47 (s, 1H,  $\text{Trp-NH}_{\text{Ar}}$ ), 8.09 (d,  $J$  = 2.5 Hz, 1H,  $H_7$ ), 7.92 (m, 1H,  $H_9$ ), 7.73–6.95 (m, 8H,  $\text{NH}_3^+$ ,  $\text{Trp}_{\text{Ar}}$ ), 6.72–6.62 (m, 1H,  $H_{10}$ ), 6.02 (d,  $J$  = 3.0 Hz, 1H,  $\text{NH}_1$ ), 5.83 (s, 1H,  $\text{NHtBu}$ ), 4.96 (s, 1H,  $H_5$ ), 4.42 (td,  $J$  = 6.7, 3.1 Hz, 1H,  $H_2$ ), 3.69 (m, 1H,  $H_{1'}$ ), 3.60–3.35 (m, 2H,  $H_{1'}$ ,  $H_\beta$ ), 3.04 (dd,  $J$  = 14.9, 6.8 Hz, 1H,  $H_\beta$ ), 2.98–2.75 (m, 2H,  $H_4'$ ), 1.69–1.41 (m, 4H,  $H_2'$ ,  $H_3'$ ), 1.11 (s, 9H,  $t\text{Bu}$ ); (minor, 32%) 9.47 (s, 1H,  $\text{Trp-NH}_{\text{Ar}}$ ), 8.32 (d,  $J$  = 2.6 Hz, 1H,  $H_7$ ), 7.92 (m, 1H,  $H_9$ ), 7.73–6.95 (m, 8H,  $\text{NH}_3^+$ ,  $\text{Trp}_{\text{Ar}}$ ), 6.72–6.62 (m, 1H,  $H_{10}$ ), 5.98 (s, 1H,  $\text{NHtBu}$ ), 5.30 (s, 1H,  $H_5$ ), 4.91–4.84 (m, 1H,  $\text{NH}_1$ ), 4.55–4.47 (m, 1H,  $H_2$ ), 3.69 (m, 1H,  $H_{1'}$ ), 3.60–3.35 (m, 2H,  $H_{1'}$ ,  $H_\beta$ ), 3.20 (dd,  $J$  = 14.5, 10.0 Hz, 1H,  $H_\beta$ ), 2.98–2.75 (m, 2H,  $H_4'$ ), 1.69–1.41 (m, 4H,  $H_2'$ ,  $H_3'$ ), 1.29 (s, 9H,  $t\text{Bu}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_3\text{CN}$ ): (major and minor)  $\delta$  171.8 (C), 170.6 (C), 169.8 (C), 167.9 (C), 153.5 (C), 152.4 (C), 140.9 (C), 138.4 (C), 137.7 (C), 137.3 (C), 130.0 (CH), 128.2 (C), 126.8 (CH), 126.6 (C), 126.3 (CH), 125.2 (CH), 124.6 (CH), 122.5 (CH), 119.9 (CH), 119.4 (CH), 117.5 (C), 117.2 (CH), 112.4 (CH), 112.2 (CH), 111.3 (C), 66.7 (CH), 63.2 (CH), 61.9 (CH), 55.3 (CH), 52.7 (C), 52.4 (C), 48.6 ( $\text{CH}_2$ ), 47.9 ( $\text{CH}_2$ ), 40.1 ( $\text{CH}_2$ ), 40.0 ( $\text{CH}_2$ ), 30.5 ( $\text{CH}_2$ ), 28.6 ( $\text{CH}_3$ ), 28.5 ( $\text{CH}_3$ ), 26.4 ( $\text{CH}_2$ ), 25.7 ( $\text{CH}_2$ ), 25.6 ( $\text{CH}_2$ ), 25.0 ( $\text{CH}_2$ ), 24.9 ( $\text{CH}_2$ ); HRMS (ESI-TOF): calcd for  $\text{C}_{27}\text{H}_{35}\text{N}_6\text{O}_4$   $[\text{M}+\text{H}]^+$  = 507.2715, found: 507.2728.

4.3.11 3-((2*S*,5*R*/*S*)-5-(*tert*-butylcarbamoyl)-2-(3-guanidinopropyl)-7-nitro-3-oxo-1,2,3,5-tetrahydro-4*H*-benzo[*e*][1,4]diazepin-4-yl)propanoic acid (**2j**): Yellow semi-solid (32 mg, 0.054 mmol, 68%); RP-HPLC  $t_R$  = 5.75 min;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ ):  $\delta$  (major, 69%) 8.11–7.99 (m, 1H,  $H_7$ ), 7.93 (dd,  $J$  = 9.1, 2.6 Hz, 2H,  $H_9$ ,  $\text{NH}$ ), 7.74 (m, 1H,  $\text{NH}$ ), 7.22–6.43 (m, 5H,  $\text{NH}_3^+$ ,  $H_{10}$ ,  $\text{NHtBu}$ ), 6.16 (br s, 1H,  $\text{NH}_1$ ), 5.01 (s, 1H,  $H_5$ ), 4.13–3.91 (m, 2H,  $H_2$ ,  $H_{1'}$ ), 3.54–3.39 (m, 1H,  $H_{1'}$ ), 3.25–3.06 (m, 2H,  $H_\delta$ ), 2.64–2.42 (m, 2H,  $H_2'$ ), 1.84–1.47 (m, 2H,  $H_\gamma$ ), 1.30 (s, 9H,  $t\text{Bu}$ ); (minor, 31%) 8.29 (d,  $J$  = 2.6 Hz, 1H,  $H_7$ ), 8.11–7.99 (m, 1H,  $H_9$ ), 7.22–6.43 (m, 6H,  $\text{NH}_3^+$ ,  $H_{10}$ ,  $\text{NH}$ ), 5.97 (s, 1H,  $\text{NHtBu}$ ), 5.29 (s, 2H,  $H_5$ ,  $\text{NH}_1$ ), 4.13–3.91 (m, 2H,  $H_2$ ,  $H_{1'}$ ), 3.73–3.59 (m, 1H,  $H_{1'}$ ), 3.54–3.39 (m, 1H,  $H_\beta$ ), 3.25–3.06 (m, 3H,  $H_\beta$ ,  $H_\delta$ ), 2.64–2.42 (m, 2H,  $H_2'$ ), 1.84–1.47 (m, 2H,  $H_\gamma$ ), 1.24 (s, 9H,  $t\text{Bu}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_3\text{CN}$ ): (major and minor)  $\delta$  174.2, 174.0, 172.0, 170.4, 168.9, 158.4, 154.2, 152.3, 141.4, 138.2, 130.4, 127.4, 127.2, 126.6, 120.4, 119.2, 118.3, 117.1, 116.3, 67.3, 65.0, 61.8, 55.0, 52.9, 52.5, 46.5, 45.8, 41.9, 34.0, 33.8, 31.6, 28.5, 27.6, 26.0, 25.6; HRMS (ESI-TOF): calcd for  $\text{C}_{21}\text{H}_{32}\text{N}_7\text{O}_6$   $[\text{M}+\text{H}]^+$  = 478.2409, found: 478.2442.

4.3.12 (2*S*,5*R*/*S*)-2-(4-aminobutyl)-*N*-benzyl-7-nitro-3-oxo-4-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine-5-carboxamide (**2k**): Yellow oil (35 mg, 0.058 mmol, 72%); RP-HPLC  $t_R$  = 6.66 min;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  (major, 86%): 8.04 (d,  $J$  = 2.5 Hz, 1H,  $H_7$ ), 7.97 (dd,  $J$  = 9.1, 2.6 Hz, 1H,  $H_9$ ), 7.65–7.07 (m, 14H,  $\text{Ph}$ ,  $\text{Ph}'$ ,  $\text{NH}_3^+$ ,  $\text{NHCH}_2\text{Ph}$ ), 6.83 (d,  $J$  = 9.2 Hz, 1H,  $H_{10}$ ), 6.29 (d,  $J$  = 2.9 Hz, 1H,  $\text{NH}_1$ ), 5.34 (s, 1H,  $H_5$ ), 4.51–4.20 (m, 2H,  $\text{CH}_2\text{Ph}$ ), 3.98–3.89 (m, 1H,  $H_2$ ), 2.87 (t,  $J$  = 6.9 Hz, 2H,  $\text{He}$ ), 1.87–1.73 (m, 1H,  $H_\beta$ ), 1.65–1.41 (m, 3H,  $H_\beta$ ,  $H_\delta$ ), 1.33–1.00 (m, 2H,  $H_\gamma$ ); (minor, 14%) 7.83 (dd,  $J$  = 9.1, 2.6 Hz, 1H,  $H_9$ ), 7.70 (d,  $J$  = 2.5 Hz, 1H,  $H_7$ ), 7.65–7.07 (m, 14H,  $\text{Ph}$ ,  $\text{Ph}'$ ,  $\text{NH}_3^+$ ,  $\text{NHCH}_2\text{Ph}$ ), 6.68 (d,  $J$  = 9.1 Hz, 1H,  $H_{10}$ ), 6.15 (d,  $J$  = 2.6 Hz, 1H,  $\text{NH}_1$ ), 5.21 (d,  $J$  = 14.9 Hz, 1H,  $\text{CH}_2\text{Ph}$ ), 5.01 (s, 1H,  $H_5$ ), 4.51–4.20 (m, 1H,  $\text{CH}_2\text{Ph}$ ), 3.86–3.78 (m, 1H,  $H_2$ ), 2.52 (m, 2H,  $\text{He}$ ), 1.87–1.73 (m, 1H,  $H_\beta$ ), 1.65–1.41 (m, 3H,  $H_\beta$ ,  $H_\delta$ ), 1.33–1.00 (m, 2H,  $H_\gamma$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_3\text{CN}$ ): (major and minor)  $\delta$  170.8 (C), 170.1 (C), 152.7 (C), 144.7 (C),

140.1 (C), 138.5 (C), 130.3 (CH), 130.1 (CH), 129.5 (CH), 129.3 (CH), 129.1 (CH), 128.7 (CH), 128.3 (CH), 126.6 (CH), 117.3 (CH), 116.7 (C), 69.5 (CH), 66.2 (CH), 55.6 (CH), 55.2 (CH), 53.1 (CH<sub>2</sub>), 44.5 (CH<sub>2</sub>), 40.2 (CH<sub>2</sub>), 30.0 (CH<sub>2</sub>), 27.5 (CH<sub>2</sub>), 23.2 (CH<sub>2</sub>); HRMS (ESI-TOF): calcd for C<sub>27</sub>H<sub>30</sub>N<sub>5</sub>O<sub>4</sub> [M+H]<sup>+</sup> = 488.2293, found: 488.2292.

**4.3.13** (3*aS*,6*R*)-*N*-(*tert*-butyl)-8-nitro-4-oxo-5-propyl-2,3,3*a*,4,5,6-hexahydro-1*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepine-6-carboxamide (**2l'**). Orange powder (9 mg, 0.023 mmol, 29%); RP-HPLC *t*<sub>R</sub> = 8.78 min; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): δ 8.34 (d, *J* = 2.7 Hz, 1H, *H7*), 8.18 (dd, *J* = 8.9, 2.7 Hz, 1H, *H9*), 6.98 (d, *J* = 8.9 Hz, 1H, *H10*), 5.52 (br s, 1H, *NHtBu*), 5.06 (s, 1H, *H5*), 3.84 (t, *J* = 8.5 Hz, 1H, *H2*), 3.73 (m, 1H, *H1'*), 3.37–3.16 (m, 3H, *H1'*, *Hδ*), 2.34–2.23 (m, 2H, *Hβ*), 1.92–1.73 (m, 2H, *Hγ*), 1.68–1.41 (m, 2H, *H2'*), 1.20 (s, 9H, *tBu*), 0.84 (t, *J* = 7.4 Hz, 3H, *H3'*); <sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>CN): δ 130.6 (C), 126.6 (CH), 126.5 (CH), 117.6 (CH), 67.6 (CH), 64.4 (CH), 52.1 (C), 50.9 (CH<sub>2</sub>), 50.9 (CH<sub>2</sub>), 30.9 (CH<sub>2</sub>), 28.5 (CH<sub>3</sub>), 22.0 (CH<sub>2</sub>), 21.4 (CH<sub>2</sub>), 11.5 (CH<sub>3</sub>); HRMS (ESI-TOF): calcd for C<sub>20</sub>H<sub>29</sub>N<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup> = 389.2184, found: 389.2192.

**4.3.14** (3*aS*,6*S*)-*N*-(*tert*-butyl)-8-nitro-4-oxo-5-propyl-2,3,3*a*,4,5,6-hexahydro-1*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepine-6-carboxamide (**2l''**). Orange powder (12 mg, 0.031 mmol, 38%); RP-HPLC *t*<sub>R</sub> = 9.07 min; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): δ 8.11–7.99 (m, 2H, *H7*, *H9*), 6.62 (d, *J* = 9.0 Hz, 1H, *H10*), 5.84 (br s, 1H, *NHtBu*), 4.93 (s, 1H, *H5*), 4.49–4.36 (m, 1H, *H2*), 3.78–3.66 (m, 1H, *H1'*), 3.51–3.34 (m, 2H, *Hδ*), 3.30–3.17 (m, 1H, *H1'*), 2.60–2.47 (m, 1H, *Hβ*), 1.97 (m, 3H, *Hβ*, *Hγ*), 1.57–1.36 (m, 2H, *H2'*), 1.29 (s, 9H, *tBu*), 0.75 (t, *J* = 7.4 Hz, 3H, *H3'*); <sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>CN): δ 170.0 (C), 151.3 (C), 129.5 (CH), 126.6 (CH), 119.3 (C), 114.5 (CH), 67.4 (CH), 60.1 (CH), 52.6 (C), 51.4 (CH<sub>2</sub>), 51.3 (CH<sub>2</sub>), 28.5 (CH<sub>3</sub>), 28.2 (CH<sub>2</sub>), 24.4 (CH<sub>2</sub>), 22.4 (CH<sub>2</sub>), 11.4 (CH<sub>3</sub>); HRMS (ESI-TOF): calcd for C<sub>20</sub>H<sub>29</sub>N<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup> = 389.2184, found: 389.2192.

**4.3.15** (3*aS*,6*R*)-5-benzyl-*N*-(*tert*-butyl)-8-nitro-4-oxo-2,3,3*a*,4,5,6-hexahydro-1*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepine-6-carboxamide (**2m'**). Brown oil (9 mg, 0.021 mmol, 26%); RP-HPLC *t*<sub>R</sub> = 9.32 min; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.21 (dd, *J* = 8.8, 2.6 Hz, 1H, *H9*), 7.69 (d, *J* = 2.6 Hz, 1H, *H7*), 7.43–7.28 (m, 5H, *Ph'*), 7.02 (d, *J* = 8.8 Hz, 1H, *H10*), 5.28 (d, *J* = 14.7 Hz, 1H, *H1'*), 4.90 (s, 1H, *NHtBu*), 4.68 (s, 1H, *H5*), 4.46 (d, *J* = 14.6 Hz, 1H, *H1'*), 3.75 (dd, *J* = 9.9, 8.0 Hz, 1H, *H2*), 3.32 (q, *J* = 9.1 Hz, 1H, *Hδ*), 3.21 (td, *J* = 9.4, 8.8, 2.4 Hz, 1H, *Hδ*), 2.63–2.47 (m, 1H, *Hβ*), 2.46–2.32 (m, 1H, *Hβ*), 2.09–1.69 (m, 2H, *Hγ*), 1.13 (s, 9H, *tBu*); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 170.6 (C), 153.3 (C), 152.9 (C), 136.1 (C), 131.1 (C), 129.1 (CH), 128.9 (CH), 128.4 (CH), 126.1 (CH), 125.5 (CH), 117.4 (CH), 68.3 (CH), 64.5 (CH), 52.8 (CH<sub>2</sub>), 51.5 (C), 49.8 (CH<sub>2</sub>), 30.7 (CH<sub>2</sub>), 28.3 (CH<sub>3</sub>), 20.6 (CH<sub>2</sub>); HRMS (ESI-TOF): calcd for C<sub>24</sub>H<sub>29</sub>N<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup> = 437.2184, found: 437.2181.

**4.3.16** (3*aS*,6*S*)-5-benzyl-*N*-(*tert*-butyl)-8-nitro-4-oxo-2,3,3*a*,4,5,6-hexahydro-1*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepine-6-carboxamide (**2m''**). Brown oil (14 mg, 0.032 mmol, 40%); RP-HPLC *t*<sub>R</sub> = 9.63 min; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.08 (dd, *J* = 9.2, 2.6 Hz, 1H, *H9*), 7.83 (d, *J* = 2.6 Hz, 1H, *H7*), 7.45–7.33 (m, 5H, *Ph'*), 6.55 (d, *J* = 9.3 Hz, 1H, *H10*), 5.24 (d, *J* = 14.3 Hz, 1H, *H1'*), 5.11 (s, 1H, *NHtBu*), 4.65 (s, 1H, *H5*), 4.48–4.41 (m, 1H, *H2*), 4.18 (d, *J* = 14.3 Hz, 1H, *H1'*), 3.55–3.47 (m, 1H, *Hδ*), 3.47–3.38 (m, 1H, *Hδ*), 2.80–2.69 (m, 1H, *Hβ*), 2.22–1.94 (m, 3H, *Hβ*, *Hγ*), 1.08 (s, 9H, *tBu*); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 168.6 (C), 168.4 (C), 149.9 (C), 136.6 (C), 129.6 (CH), 129.2 (CH), 128.8 (CH), 128.7 (CH), 126.1 (CH), 116.8 (C), 113.5 (CH), 66.6 (CH), 59.2 (CH), 51.8 (CH<sub>2</sub>), 51.7

(C), 50.6 (CH<sub>2</sub>), 28.2 (CH<sub>3</sub>), 27.7 (CH<sub>2</sub>), 23.8 (CH<sub>2</sub>); HRMS (ESI-TOF): calcd for C<sub>24</sub>H<sub>29</sub>N<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup> = 437.2184, found: 437.2181.

**4.3.17** (2*S*,5*S*)-4-(4-aminobutyl)-*N*-(*tert*-butyl)-2-isobutyl-1-methyl-7-nitro-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine-5-carboxamide (**2n**). Yellow powder (34 mg, 0.061 mmol, 76%); RP-HPLC *t*<sub>R</sub> = 7.27 min; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): δ 8.14 (d, *J* = 2.4 Hz, 1H, *H7*), 8.06 (dd, *J* = 9.1, 2.8 Hz, 1H, *H9*), 7.46–6.93 (m, 4H, *NH<sub>3</sub><sup>+</sup>*, *H10*), 5.99 (s, 1H, *NHtBu*), 5.03 (s, 1H, *H5*), 4.06 (t, *J* = 6.6 Hz, 1H, *H2*), 3.78 (m, 1H, *H1'*) 3.30–3.16 (m, 1H, *H1'*), 2.92 (m, 5H, *NCH<sub>3</sub>*, *H4'*), 1.75 (m, 1H, *Hβ*), 1.66–1.37 (m, 6H, *Hγ*, *Hβ*, *H2'*, *H3'*), 1.29 (s, 9H, *tBu*), 0.96–0.87 (m, 3H, *Hδ*), 0.87–0.77 (m, 3H, *Hδ*); <sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>CN): δ 169.7 (C), 156.4 (C), 139.6 (C), 129.5 (CH), 125.5 (CH), 122.8 (C), 119.9 (CH), 67.8 (CH), 58.2 (CH), 52.9 (C), 48.3 (CH<sub>2</sub>), 40.2 (CH<sub>2</sub>), 37.4 (CH<sub>2</sub>), 36.0 (CH<sub>3</sub>), 28.7 (CH<sub>3</sub>), 25.8 (CH<sub>2</sub>), 25.7 (CH), 24.9 (CH<sub>2</sub>), 23.4 (CH<sub>3</sub>), 22.6 (CH<sub>3</sub>); HRMS (ESI-TOF): calcd for C<sub>23</sub>H<sub>38</sub>N<sub>5</sub>O<sub>4</sub> [M+H]<sup>+</sup> = 448.2919, found: 448.2928.

**4.3.18** (2*S*,5*S*)-4-(4-aminobutyl)-2-benzyl-*N*-(*tert*-butyl)-1-methyl-7-nitro-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine-5-carboxamide (**2o**): Yellow powder (36.5 mg, 0.061 mmol, 77%); RP-HPLC *t*<sub>R</sub> = 7.29 min; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): δ 8.12 (d, *J* = 2.6 Hz, 1H, *H7*), 8.02 (dd, *J* = 9.2, 2.5 Hz, 1H, *H9*), 7.42–7.10 (m, 8H, *Ph<sub>Ar</sub>*, *NH<sub>3</sub><sup>+</sup>*), 6.90 (d, *J* = 9.2 Hz, 1H, *H10*), 5.90 (s, 1H, *NHtBu*), 5.03 (s, 1H, *H5*), 4.39 (t, *J* = 7.0 Hz, 1H, *H2*), 3.83 (m, 1H, *H1'*), 3.23 (m, 2H, *H1'*, *Hβ*), 3.13–3.01 (m, 1H, *Hβ*), 2.95 (s, 3H, *NCH<sub>3</sub>*), 2.91–2.81 (m, 2H, *H4'*), 1.58–1.41 (m, 4H, *H2'*, *H3'*), 1.17 (s, 9H, *tBu*); <sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>CN): δ 170.5 (C), 169.4 (C), 156.0 (C), 139.9 (C), 138.6 (C), 130.1 (CH), 129.3 (CH), 127.4 (CH), 125.5 (CH), 123.5 (C), 120.0 (CH), 67.5 (CH), 62.0 (CH), 52.7 (C), 48.6 (CH<sub>2</sub>), 40.1 (CH<sub>2</sub>), 36.7 (CH<sub>3</sub>), 35.0 (CH<sub>2</sub>), 28.5 (CH<sub>3</sub>), 25.7 (CH<sub>2</sub>), 24.9 (CH<sub>2</sub>); HRMS (ESI-TOF): calcd for C<sub>26</sub>H<sub>36</sub>N<sub>5</sub>O<sub>4</sub> [M+H]<sup>+</sup> = 482.2762, found: 482.2805.

**4.3.19** (6*R*/*S*)-5-benzyl-*N*-(*tert*-butyl)-8-nitro-4-oxo-1,2,3,4,5,6-hexahydrobenzo[*b*][1,5]diazocine-6-carboxamide (**4a**). Yellow powder (23 mg, 0.056 mmol, 69%); RP-HPLC *t*<sub>R</sub> = 8.81 min; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): δ 8.07 (d, *J* = 2.6 Hz, 1H, *H8*), 7.86 (dd, *J* = 9.0, 2.6 Hz, 1H, *H10*), 7.22–7.07 (m, 5H, *Ph'*), 6.71 (d, *J* = 9.0 Hz, 1H, *H11*), 6.36 (br s, 1H, *NHtBu*), 5.73 (br s, 1H, *NH1*), 5.60 (s, 1H, *H6*), 4.53–4.34 (m, 2H, *H1'*), 3.72–3.45 (m, 2H, *H2*), 3.23–3.11 (m, 1H, *H3*), 2.81 (ddd, *J* = 15.7, 7.6, 5.8 Hz, 1H, *H3*), 1.27 (s, 9H, *tBu*); <sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>CN): δ 174.4 (C), 168.1 (C), 156.4 (C), 139.8 (C), 139.7 (C), 129.8 (CH), 128.9 (CH), 128.3 (CH), 127.4 (CH), 125.4 (CH), 121.5 (C), 119.1 (CH), 63.8 (CH), 52.5 (C), 50.4 (CH<sub>2</sub>), 42.4 (CH<sub>2</sub>), 39.1 (CH<sub>2</sub>), 28.5 (CH<sub>3</sub>); HRMS (ESI-TOF): calcd for C<sub>22</sub>H<sub>27</sub>N<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup> = 411.2027, found: 411.2024.

**4.3.20** (2*R*,6*R*/*S*)-5-benzyl-*N*-(*tert*-butyl)-8-nitro-4-oxo-2-phenyl-1,2,3,4,5,6-hexahydrobenzo[*b*][1,5]diazocine-6-carboxamide (**4b**). Yellow powder (17 mg, 0.035 mmol, 44%); RP-HPLC *t*<sub>R</sub> = 10.19 min; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): δ (major, 70%) 8.02 (d, *J* = 2.6 Hz, 1H, *H8*), 7.87 (m, 1H, *H10*), 7.46–7.31 (m, 5H, *β-Ph<sub>Ar</sub>*), 7.26–7.08 (m, 5H, *Ph'*), 6.85 (d, *J* = 8.9 Hz, 1H, *H11*), 6.13 (br s, 1H, *NHtBu*), 5.43 (s, 1H, *H6*), 5.38–5.21 (m, 1H, *NH1*), 4.76 (dd, *J* = 11.7, 4.4 Hz, 1H, *H2*), 4.61 (m, 2H, *H1'*), 3.38 (dd, *J* = 15.8, 11.7 Hz, 1H, *H3*), 3.12–2.98 (m, 1H, *H3*), 1.26 (s, 9H, *tBu*); (minor, 30%) 8.30 (d, *J* = 2.6 Hz, 1H, *H8*), 7.87 (m, 1H, *H10*), 7.46–7.31 (m, 5H, *β-Ph<sub>Ar</sub>*), 7.26–7.08 (m, 5H, *Ph'*), 6.75–6.67 (m, 2H, *H-11*, *NHtBu*), 6.04 (s, 1H, *H6*), 5.38–5.21 (m, 1H, *NH1*), 5.15 (t, *J* = 8.4 Hz, 1H, *H2*), 4.39 (m, 2H, *H1'*), 3.74 (dd, *J* = 15.1, 7.9 Hz, 1H, *H3*), 3.12–2.98 (m, 1H, *H3*), 1.31 (s, 9H, *tBu*); <sup>13</sup>C NMR (101 MHz,



CD<sub>3</sub>CN): (major and minor)  $\delta$  173.0 (C), 169.1 (C), 155.4 (C), 143.4 (C), 138.8 (C), 131.2 (CH), 130.1 (CH), 129.2 (CH), 128.9 (CH), 128.7 (CH), 128.0 (CH), 127.8 (CH), 127.5 (CH), 127.0 (CH), 125.2 (CH), 125.1 (CH), 120.8 (CH), 120.4 (CH), 66.9 (CH), 61.3 (CH), 59.8 (CH), 58.6 (CH), 52.6 (C), 52.4 (CH<sub>2</sub>), 48.4 (CH<sub>2</sub>), 47.7 (CH<sub>2</sub>), 45.3 (CH<sub>2</sub>), 28.5 (CH<sub>3</sub>); HRMS (ESI-TOF): calcd for C<sub>28</sub>H<sub>31</sub>N<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup> = 487.2340, found: 487.2353.

4.3.21 (2*S*,6*R*/*S*)-2-((1*H*-indol-3-yl)methyl)-5-benzyl-*N*-(*tert*-butyl)-8-nitro-4-oxo-1,2,3,4,5,6-hexahydrobenzo[*b*][1,5]diazocine-6-carboxamide (**4c**). Yellow powder (13 mg, 0.024 mmol, 29%); RP-HPLC  $t_R$  = 10.09/10.20; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): (major and minor)  $\delta$  9.22 (s, 1H, indole-NH), 9.16 (s, 1H, indole-NH), 8.25 (d,  $J$  = 2.6 Hz, 1H, *H*8), 7.85–7.73 (m, 3H, *H*8, *H*10), 7.63 (d,  $J$  = 8.0 Hz, 1H, indole-*H*<sub>Ar</sub>), 7.52 (d,  $J$  = 8.0 Hz, 1H, indole-*H*<sub>Ar</sub>), 7.43–7.33 (m, 2H, indole-*H*<sub>Ar</sub>), 7.25–7.01 (m, 16H, *Ph*’, *H*11, indole-*H*<sub>Ar</sub>), 6.73 (s, 1H, *NH*tBu), 6.55 (d,  $J$  = 9.0 Hz, 2H, *H*11), 5.96 (s, 1H, *H*6), 5.87 (s, 1H, *NH*tBu), 5.35–5.09 (m, 3H, *H*6, *NH*1), 4.67–4.42 (m, 2H, *H*1’), 4.39–4.24 (m, 3H, *H*1’, *H*2), 4.10–3.99 (m, 1H, *H*2), 3.71–3.66 (dd,  $J$  = 15.2, 7.6 Hz, 1H, *H*3), 3.17–2.84 (m, 6H, *H*3, *H*γ), 2.71 (dd,  $J$  = 15.2, 8.5 Hz, 1H, *H*3), 1.28 (s, 9H, *t*Bu), 1.14 (s, 9H, *t*Bu); <sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>CN): (major and minor)  $\delta$  174.6, 166.8, 155.7, 155.3, 140.6, 138.7, 137.4, 129.3, 129.1, 128.6, 128.3, 128.1, 127.8, 127.5, 126.8, 125.2, 124.6, 124.3, 122.6, 122.00, 119.9, 119.4, 119.3, 118.3, 112.4 (CH), 112.3 (CH), 111.6 (C), 60.4 (CH), 55.2 (CH), 54.1 (CH), 53.1 (CH<sub>2</sub>), 52.5 (CH<sub>2</sub>), 52.4 (C), 47.9 (CH<sub>2</sub>), 47.4 (CH<sub>2</sub>), 44.8 (CH<sub>2</sub>), 34.5 (CH<sub>2</sub>), 33.5 (CH<sub>2</sub>), 28.5 (CH<sub>3</sub>), 28.4 (CH<sub>3</sub>); HRMS (ESI-TOF): calcd for C<sub>31</sub>H<sub>34</sub>N<sub>5</sub>O<sub>4</sub> [M+H]<sup>+</sup> = 540.2606, found: 540.2601.

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## Supplementary Material

Supplementary data (spectroscopic and chromatographic data) associated with this article can be found, in the online version, at

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