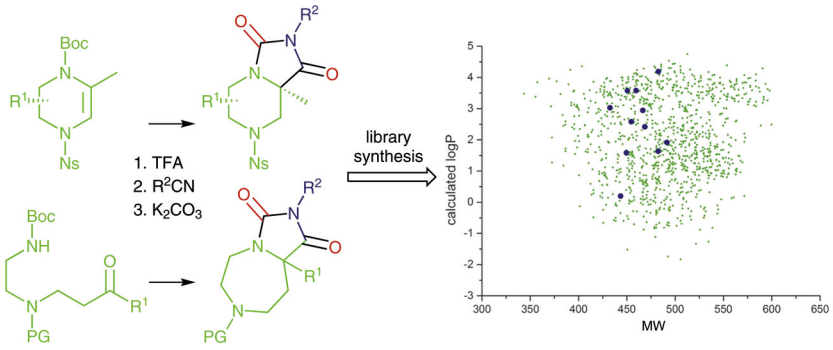
Synthesis J. D. Firth et al. Special Topic

Exploitation of the Ugi–Joullié Reaction in the Synthesis of Libraries of Drug-Like Bicyclic Hydantoins

James D. Firth[a]
Rong Zhang[a]
Rémy Morgentin[b]
Rachel Guilleux[b]
Tuomo Kalliokoski[c]
Stuart Warriner[a,d]
Richard Foster[a,d]
Stephen P. Marsden[a]
Adam Nelson*[a,d]

[a] School of Chemistry, University of Leeds, Leeds LS2 9JT, UK
[b] Edelris, 115 Avenue Lacassagne, 69003 Lyon, France
[c] Lead Discovery Center GmbH, Otto-Hahn-Straße 15, 44227 Dortmund, Germany
[d] Astbury Centre for Structural Molecular Biology, University of Leeds, Leeds LS2 9JT, UK
a.s.nelson@leeds.ac.uk



Received: 30.03.2015
Accepted: 16.04.2015
Published online: 19.06.2015
DOI: 10.1055/s-0034-1378704; Art ID: ss-2015-c0208-st

Abstract A general and efficient method for the synthesis of drug-like fused bicyclic hydantoins is reported. An Ugi–Joullié reaction/cyclisation sequence was exploited as the key complexity-generating process in which trifluoroacetic acid was employed as synthetic equivalent for chloroformic acid. Exemplar diversification of the bicyclic scaffolds was performed to enable subsequent translation to the synthesis of large small molecule libraries, leading to the production of >1000 compounds for addition to the screening collection of the European Lead Factory.

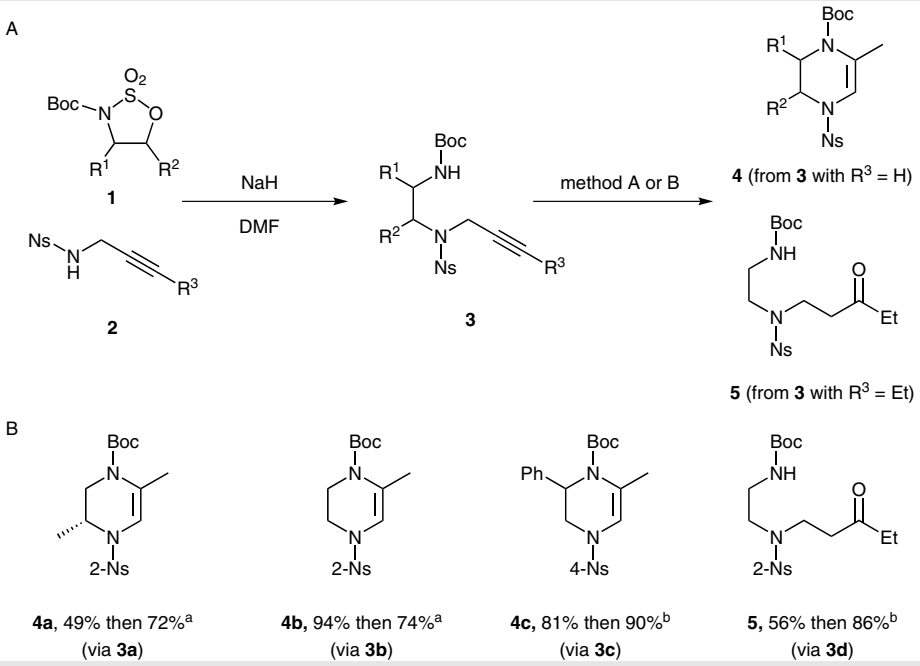
Key words multicomponent reactions, scaffolds, libraries, Ugi reaction, hydantoin

Controlling molecular properties is crucial in drug discovery, and guidelines have been developed to direct medicinal chemists towards drug-like chemical space.[1] Key properties, such as molecular weight,[2] lipophilicity[2,3] and the fraction of sp^3-hybridised carbons[4] correlate strongly with the successful translation of clinical candidates. Multicomponent reactions (MCRs),[5] especially the Ugi reaction, have been widely exploited in the synthesis of small molecule libraries.[6] However, many products of four-component (4-CR) Ugi reactions are linear and peptidic, and can suffer from poor drug-likeness.[7] In contrast, the use of cyclic imines in the three-component (3-CR) Ugi–Joullié reaction[8] leads to the formation of more drug-like nitrogen heterocycles.[9,10d] Here, we describe the exploitation of trifluoroacetic acid as a synthetic equivalent for chloroformic acid,[11] which can facilitate subsequent cyclisation to yield hydantoins that are fused to either a six- or seven-membered heterocycle. Furthermore, we demonstrate the value of two bicyclic scaffolds in the synthesis of diverse drug-like screening compounds.

The synthesis of four substrates for Ugi–Joullié reactions was achieved using our previously reported method.[12] Thus, the required *N*-Boc-appended propargylic sulfonamides **3** were prepared by treatment of propargylic sulfonamides **2** with sodium hydride, and reaction with cyclic sulfamidates **1**[13] (Scheme 1). Treatment of terminal alkyne products **3** (R^3 = H) with either 5 mol% $Au(PPh_3)Cl$ and 5 mol% $AgSbF_6$, or 1 mol% of the N-heterocyclic carbene complex Au(IPr)Cl[14] and 1 mol% $AgSbF_6$, in 1,4-dioxane at 100 °C yielded the tetrahydropyrazines **4a**–**c** in 35–76% yield over the two steps. In contrast, with an intermediate 1,2-disubstituted alkyne **3d** (in which R^3 = Et), hydration occurred distal to the *N*-nitrophenylsulfonyl group to give, without subsequent cyclisation, the ketone **5** in 48% overall yield.[12]

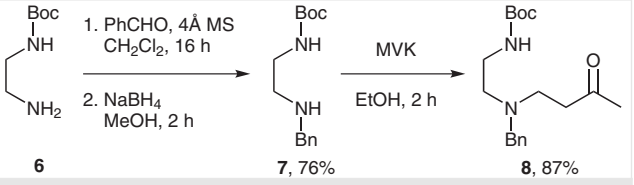
In order to assess the effect of a basic amine on the Ugi–Joullié reaction, the benzyl-protected amino ketone **8** (Scheme 2) was also prepared. Reductive amination of benzaldehyde with the amine **6**, to give **7**, was followed by aza-Michael reaction with methyl vinyl ketone to give the β-amino ketone **8** in 66% overall yield.

An initial investigation into the deprotection/3-CR[8,12] was performed by treating **5** with TFA in dichloromethane to generate, presumably, the cyclic iminium ion **9**; subsequent treatment with 1-isocyano-2-methoxyethane in ethanol gave the 3-CR product **10a** in 71% yield (Scheme 3). It was envisaged that decoration of **10a** might enable the synthesis of a library of diverse 1,4-diazepanes. However, treatment of **10a** with K_2CO_3 in MeOH–H_2O[15] did not result in the removal of the trifluoroacetamide; instead, the bicyclic hydantoin **11a** was obtained in 86% yield. Presumably, base-catalysed attack of the secondary amide onto the trifluoroacetamide was followed by expulsion of the trifluoromethyl anion to yield the observed hydantoin.[10] In this sequence, TFA serves as a reagent for the deprotection of the Boc

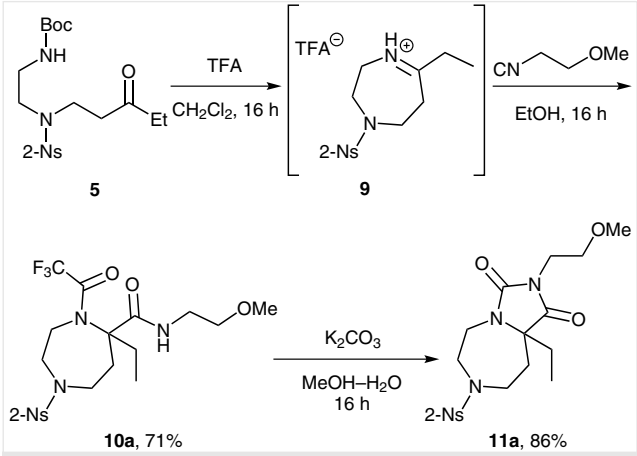


Scheme 1 Synthesis of substrates for the Ugi–Joullié reactions. Panel A: Synthetic scheme. Panel B: Specific substrates prepared. [a] Method A: $Au(PPh_3)Cl$ (5 mol%), $AgSbF_6$ (5 mol%), 1,4-dioxane, 100 °C. [b] Method B: Au(IPr)Cl (1 mol%), $AgSbF_6$ (1 mol%), 1,4-dioxane, 100 °C. 2-Ns: 2-nitrophenylsulfonyl; 4-Ns: 4-nitrophenylsulfonyl.

group; is the acidic component in the 3-CR; and provides the necessary leaving group for hydantoin formation. Importantly, hydantoins have a privileged place within medicinal chemistry,[16] hence skeletally novel variants of these molecules would be valuable for populating lead-generation libraries.



Scheme 2 Synthesis of β-amino ketone **8**



Scheme 3 Synthesis of bicyclic hydantoin **11a**

The method was exploited in the efficient synthesis of a wide range of bicyclic scaffolds in which a hydantoin is fused to a six- or seven-membered heterocycle. The results are summarised in Table 1. With the ketone **5**, the deprotection/3-CR proceeded smoothly, and gave the trifluoroacetamide **10b** in 80% yield; subsequent base-mediated cyclisation gave the required bicyclic hydantoin **11b** in 36% yield (Table 1, entry 1). It was anticipated that the bicyclic hydantoins might be obtained without purification of the intermediate trifluoroacetamides. To this end, the benzyl-protected β-amino ketone **8** was treated with TFA in dichloromethane, followed by treatment with an isonitrile in EtOH, before finally being subjected to K_2CO_3 in EtOH at 70 °C; the hydantoins **11c–e** were isolated in 75–95% overall yield over three steps (entries 2–4). Both 2-nitrophenylsulfonyl- and benzyl-protected substrates (**5** and **8**, respectively) may thus be exploited in the synthesis of bicyclic hydantoins.

Table 1 Scope of the Synthesis of Bicyclic Hydantoins

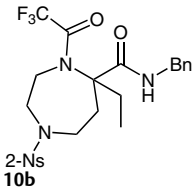
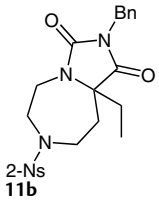
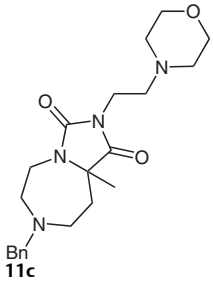
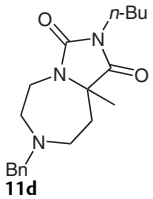
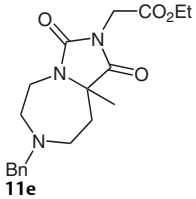
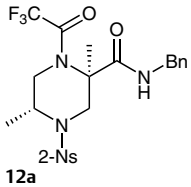
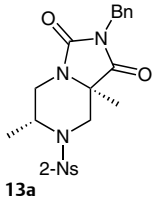
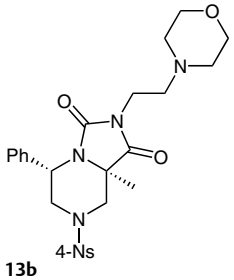
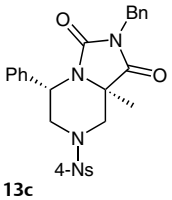
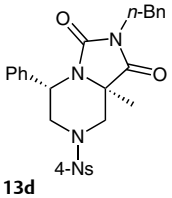
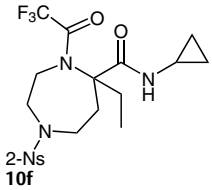
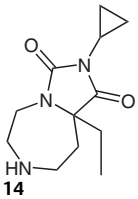
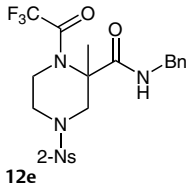
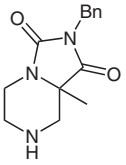
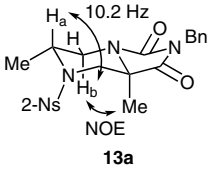
Entry	Substrate	Method[a,b]	Trifluoroacetamide	Hydantoin	Ugi yield (%),[c] cyclisation yield (%)[c]
1	**5**	A1, B1	 **10b**	 **11b**	80, 36
2	**8**	A1, B2	–	 **11c**	75[d]
3	**8**	A1, B2	–	 **11d**	95[d]
4	**8**	A1, B2	–	 **11e**	81[d]
5	**4a**	A1, B2	 **12a**	 **13a**	77, 41
6	**4c**	A2, B2	–	 **13b**	91[d]

Table 1 (continued)

Entry	Substrate	Method[a,b]	Trifluoroacetamide	Hydantoin	Ugi yield (%),[c] cyclisation yield (%)[c]
7	**4c**	A2, B2	–	 **13c**	72[d]
8	**4c**	A2, B2	–	 **13d**	52[d]
9	**5**	A1, B3	 **10f**	 **14**	66, 73
10	**4b**	A1, B3	 **12e**	 **15**	86, 87

[a] Method A1: TFA then isonitrile (2.0 equiv), EtOH, r.t.; Method A2: TFA then isonitrile (2.0 equiv), CH_2Cl_2, r.t., 1 h, then Et_3N (5.0 equiv), 2 h.
[b] Method B1: K_2CO_3 (10 equiv), MeOH–H_2O, r.t., 16 h; Method B2: K_2CO_3 (5.0 equiv), EtOH, 70 °C; Method B3: PhSH (1.2 equiv) K_2CO_3 (3.0 equiv), DMF, r.t.
[c] Product isolated by flash column chromatography.
[d] Yield over 2 steps.

Pleasingly, treatment of the enantiomerically enriched tetrahydropyrazine **4a** with TFA, and then benzyl isocyanide, gave the trifluoroacetamide **12a** as a single diastereomer, in 77% yield (entry 5). Subsequent base-mediated cyclisation gave the hydantoin **13a** in 41% yield. The relative configuration of **13a** was determined by analysis of the NMR spectra: an axial–axial coupling of 10.2 Hz between H_a and H_b and a strong NOESY cross peak between H_b and the methyl group on the ring junction were both observed (Figure 1).

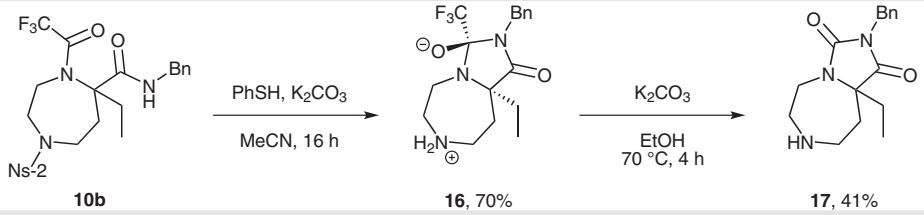


13a **13b**

Figure 1 Determination of the relative configuration of **13a** and **13b**

Modified conditions for the 3-CR were required with the phenyl-substituted tetrahydropyrazine **4c** as substrate.[17] Use of non-nucleophilic dichloromethane as a solvent, followed by addition of Et_3N to neutralize excess TFA and expedite Mumm rearrangement, led to formation of the intermediate trifluoroacetamides (which were not isolated); hydantoin formation then occurred readily to yield, as single diastereoisomers, the substituted hydantoins **13b–d** in 52 to 91% yields (entries 6–8). The relative configuration of **13b** was determined by observation of a strong NOESY cross peak indicating the close proximity of the methyl and phenyl substituents on the piperazine ring (Figure 1).

Finally, treatment of the intermediate 2-nitrophenylsulfonyl-protected trifluoroacetamides **10f** and **12e** (prepared from **5** and **4b** respectively) with PhSH and an excess of K_2CO_3 resulted in both hydantoin formation and N-deprotection to give **14** and **15** in 73% and 87% yield, respectively (entries 9 and 10).



10b **16**, 70% **17**, 41%

Scheme 4 Formation and reaction of the stable zwitterion **16**

An investigation into the selective removal of the 2-nitrophenylsulfonyl protecting group of **10b** without concomitant hydantoin formation was undertaken. Treatment of **10b** with 1.5 equivalents of PhSH and K_2CO_3 led to the unexpected isolation of stable zwitterion **16** in 70% yield (Scheme 4). The structure of **16** was determined unambiguously by X-ray crystallography and shows a hydrogen bond between the oxy and ammonium ions (Figure 2). Subsequent treatment of **16** with excess K_2CO_3 led to formation of the fused bicyclic hydantoin **17** in 41% yield, proving the intermediacy of **16** in base-mediated hydantoin formation.

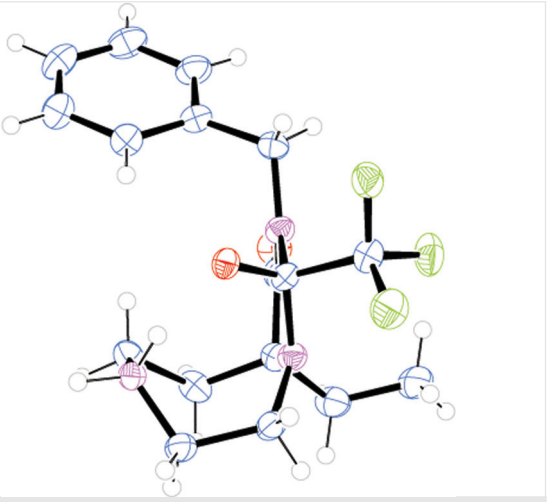


Figure 2 X-ray crystal structure of the stable zwitterion **16**[18]

Due to their molecular properties, the substituted bicyclic hydantoins **11c–e** and **13b–d** were considered to be ideal scaffolds for the synthesis of drug-like compounds. Removal of the benzyl group from **11c–e** proceeded smoothly under transfer hydrogenation conditions using Pearlman's catalyst; the secondary amines **18–20** were obtained in 86–97% yield (Scheme 5). Deprotection of the 4-nitrophenylsulfonyl protected scaffolds **13b–d** was accomplished using PhSH and K_2CO_3, giving secondary amines **21–23** in 57–78% yield. The deprotected scaffolds fulfilled drug-like criteria, having low molecular weight and logP values.

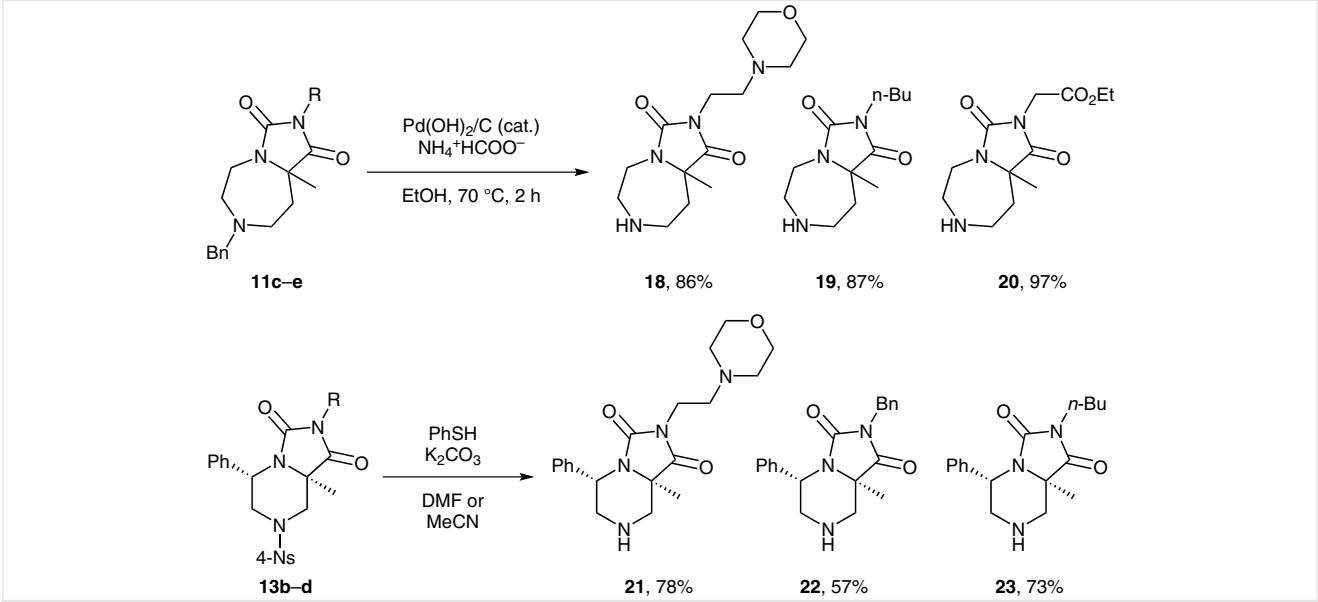
Rapid construction of the scaffolds was followed by decoration (see Figure 3 for examples). The secondary amines **18–23** were shown to be amenable to sulfonylation (e.g., **19** → **24** and **23** → **27**), reductive amination (e.g., **19** → **25** and **22** → **28**), urea formation (e.g., **18** → **26** and **23** → **29**) and amidation (e.g., **21** → **30**). These exemplar compounds were purified by mass-directed HPLC, an approach which would facilitate the subsequent production of large numbers of screening compounds.

Use of ethyl isocyanoacetate in the key deprotection/Ugi/cyclisation sequence to form **11e** led to the introduction of an ester group that could be exploited as a site for further scaffold decoration. After functionalisation of secondary amine **20** to give the sulfonamide **31**, saponification of the ethyl ester group was performed prior to TBTU-mediated amidation. For example, amide **32** was synthesised and purified by mass-directed HPLC (Scheme 6).

The use of a three-component Ugi–Joullié reaction/cyclisation as a key complexity-generating procedure allowed rapid construction of the bicyclic core of the hydantoin scaffolds **11** and **13** and defined the scope and limitations of the methods for use in library synthesis. In both cases, a library was subsequently nominated for production and subsequent incorporation into the European Lead Factory compound collection.[19] The nominated libraries were selected to target drug-like space in accordance with the overall objectives of the European Lead Factory consortium (see Figure 4 for the molecular properties of exemplar compounds and the nominated libraries). Notably, a large proportion of the nominated library compounds fall within drug-like space.[1] Additionally, the nominated compounds had a high proportion of sp^3-hybridised carbons, which can be an attractive feature in clinical candidates.[4]

In this paper, the development of methods for the synthesis of bicyclic fused hydantoins via an Ugi–Joullié reaction has been described. This led to the successful synthesis of >1000 novel compounds that will be added to the European Lead Factory screening collection (the Joint European Compound Library, JECL).

All nonaqueous reactions were performed under an atmosphere of N_2 unless otherwise stated. THF, CH_2Cl_2, toluene and MeCN were dried and purified by means of a Pure Solv MD solvent purification system (Innovative Technology Inc.). Anhydrous DMF and 1,4-dioxane were obtained in SureSeal bottles from Sigma-Aldrich. All other solvents used were of chromatography or analytical grade. PE refers to petroleum spirit (bp 40–60 °C). Commercially available starting materials



Scheme 5 Deprotection of the molecular scaffolds

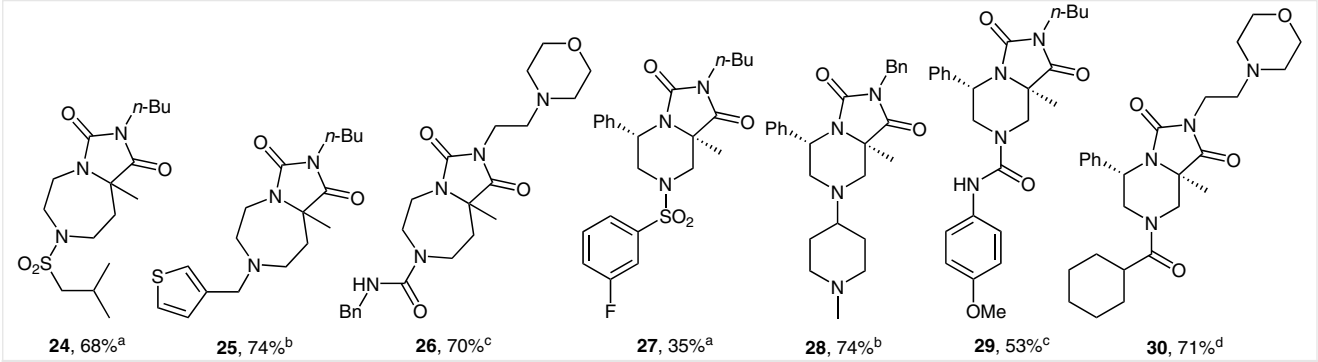
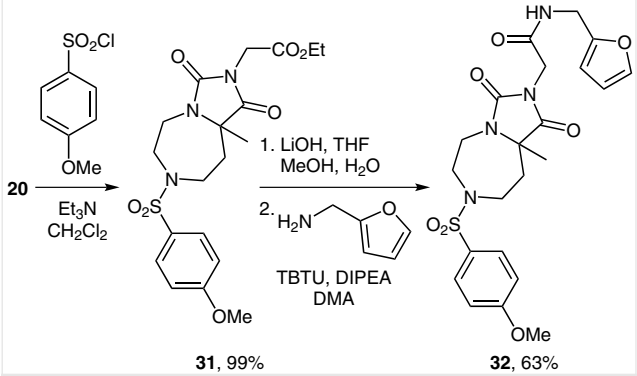


Figure 3 Exemplar decorated scaffolds. [a] Method: Sulfonyl chloride, *i*-Pr_2NEt, DMA, r.t., 16 h. [b] Method: Aldehyde/ketone, $NaBH(OAc)_3$, AcOH, DMA, 60 °C, 16 h. [c] Method: Isocyanate, *i*-Pr_2NEt, DMA, r.t., 16 h. [d] Method: Carboxylic acid, TBTU, *i*-Pr_2NEt, DMA, r.t., 16 h. DMA: Dimethylacetamide; TBTU: *O*-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate.

were obtained from Sigma-Aldrich, Fluka, Acros or Alfa-Aesar and were used without purification unless stated. TLC was carried out on aluminum backed silica gel (Merck silica gel 60 F_{254}) plates supplied by Merck. Flash chromatography was carried out using silica gel 60 (60–63 μm particles) supplied by Merck. Mass-directed HPLC purification was carried out using an Agilent 1260 Infinity HPLC system comprising an Agilent 6120 Quadrupole LC/MS and Agilent G1968D active splitter.

Optical rotation measurements were carried out at the sodium D-line (589 nm) on a Schmidt + Haensch Polatronic H532 polarimeter instrument. IR spectra were recorded on a PerkinElmer One FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on a Bruker MaXis Impact spectrometer with electrospray ionisation (ESI) source. ^{1}H, ^{13}C and ^{19}F NMR spectral data were collected on a Bruker



Scheme 6 Diversification of **20**

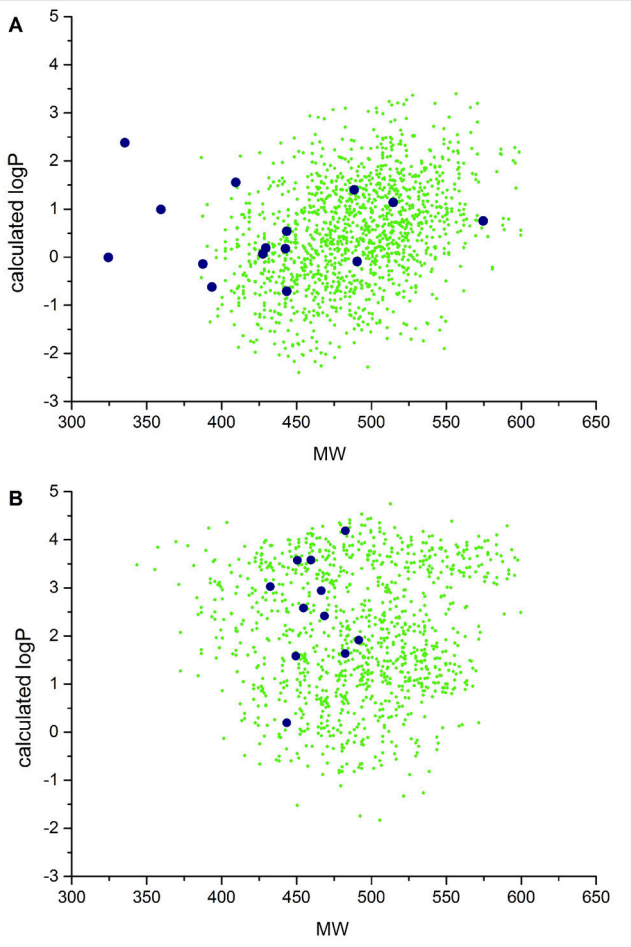


Figure 4 Molecular properties of exemplar screening compounds synthesised during validation work (blue, enlarged for clarity) and compounds nominated for library production (green). Panel A: Library based on hydantoins with a fused seven-membered heterocycle. Panel B: Library based on hydantoins with a fused six-membered heterocycle.

Advance500 or DPX300 spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to the residual solvent peak.

Opening of Cyclic Sulfamidates 1 with Propargylic Sulfonamides 2; General Procedure

NaH (60% suspension in mineral oil, 1.1 equiv) was added in one portion to nitrobenzenesulfonamide **2** (1.1 equiv) in DMF (0.2 M) at r.t. under N_2. The resulting suspension was stirred for 10 min, then cyclic sulfamidate **1** (1.0 equiv) was added in one portion. The resulting suspension was stirred at r.t. for 16 h. The reaction mixture was acidified with aq 5 M HCl (6 equiv), stirred for 1 h and basified with aq K_2CO_3, then extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product, which was purified by column chromatography.

tert-Butyl *N*-{(2*R*)-2-[*N*-(Prop-2-yn-1-yl)-2-nitrobenzenesulfonamido]propyl}carbamate (3a)

2-Nitro-*N*-(prop-2-yn-1-yl)benzene-1-sulfonamide (2.63 g, 11.0 mmol) and *tert*-butyl (5*R*)-5-methyl-2,2-dioxo-1,2λ⁶,3-oxathiazolidine-3-carboxylate (2.36 g, 9.95 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, CH_2Cl_2) to give sulfonamide **3a** (1.92 g, 49%) as an amorphous yellow solid; R_f = 0.14 (CH_2Cl_2); $[\alpha]_D^{28}$ –39 (*c* = 0.28, MeOH).

IR (ATR): 3428, 3291, 2979, 1706, 1544, 1367, 1159, 584 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 7.4, 1.6 Hz, 1 H, Ns 3-H), 7.73–7.66 (m, 2 H, Ns 4-H and 5-H), 7.64 (dd, *J* = 7.2, 2.0 Hz, 1 H, Ns 6-H), 4.90 (t, *J* = 6.7 Hz, 1 H, NH), 4.19 (dd, *J* = 18.9, 2.4 Hz, 1 H, 1′-H_A), 4.16–4.07 (m, 2 H, 1′-H_B and 2-H), 3.28 (app t, *J* = 6.7 Hz, 2 H, 1-CH_2), 2.21 (t, *J* = 4.2 Hz, 1 H, 3′-H), 1.40 (s, 9 H, *t*-C_4H_9), 1.20 (d, *J* = 6.8 Hz, 3 H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.9, 147.9, 133.7, 133.6, 131.9, 131.7, 124.2, 72.8, 54.3, 43.2, 32.0, 28.4, 16.1, 14.1. Boc quaternary carbons were not observed.

HRMS (ESI): *m*/*z* [M + H]⁺ calcd for $C_{17}H_{23}N_3O_6S$: 398.1386; found: 398.1380, –1.5 ppm error.

tert-Butyl *N*-{2-[*N*-(Prop-2-yn-1-yl)-2-nitrobenzenesulfonamido]ethyl}carbamate (3b)

2-Nitro-*N*-(prop-2-yn-1-yl)benzene-1-sulfonamide (5.98 g, 24.9 mmol) and *tert*-butyl 2,2-dioxo-1,2,3-oxathiazolidine-3-carboxylate (5.05 g, 22.6 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, CH_2Cl_2) to give the sulfonamide **3b**[12] (8.15 g, 94%) as an amorphous yellow solid; R_f = 0.4 (CH_2Cl_2).

IR (ATR): 3289, 2978, 1697, 1591, 1543, 1365, 1163, 589 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 7.4, 1.7 Hz, 1 H, Ns 3-H), 7.76–7.68 (m, 2 H, Ns 4-H and 5-H), 7.66 (dd, *J* = 7.4, 1.7 Hz, 1 H, Ns 6-H), 4.88 (br s, 1 H, NH), 4.27 (d, *J* = 2.2 Hz, 2 H, 1′-CH_2), 3.55 (t, *J* = 5.9 Hz, 2 H, 2-CH_2), 3.38 (br s, 2 H, 1-CH_2), 2.22 (t, *J* = 2.2 Hz, 1 H, 3′-H), 1.44 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.0, 148.3, 133.8, 132.6, 131.7, 131.0, 124.2, 79.6, 77.3, 74.2, 46.7, 38.0, 37.0, 28.3.

tert-Butyl *N*-{1-Phenyl-2-[*N*-(prop-2-yn-1-yl)-4-nitrobenzenesulfonamido]ethyl}carbamate (3c)

4-Nitro-*N*-(prop-2-yn-1-yl)benzene-1-sulfonamide (4.62 g, 19.2 mmol) and *tert*-butyl 4-phenyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (5.23 g, 17.5 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 80:20 to 75:25 hexane–EtOAc) to give the sulfonamide **3c**[12] (6.53 g, 81%) as an amorphous white solid; R_f = 0.3 (80:20 hexane–EtOAc).

^1H NMR (500 MHz, $CDCl_3$): δ = 8.33–8.31 (m, 2 H, Ns 3-H and 5-H), 8.02–7.99 (m, 2 H, Ns 2-H and 4-H), 7.38–7.35 (m, 2 H, C_6H_5), 7.32–7.29 (m, 3 H, C_6H_5), 5.31 (br s, 1 H, NH), 4.94 (br s, 1 H, 1-H), 4.28 (d, *J* = 18.2 Hz, 1 H, 1′-H_A), 4.14–4.11 (m, 1 H, 1′-H_B), 3.56 (dd, *J* = 14.1, 10.0 Hz, 1 H, 2-H_A), 3.34 (dd, *J* = 14.1, 4.4 Hz, 1 H, 2-H_B), 2.06–2.05 (m, 1 H, 3′-H), 1.45 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.5, 150.2, 144.6, 139.2, 129.0, 128.9, 128.1, 126.3, 124.2, 80.1, 75.6, 75.0, 52.0, 51.3, 36.9, 28.3.

HRMS (ESI): *m*/*z* [M + H]⁺ calcd for $C_{22}H_{25}N_3O_6S$: 460.1537; found: 460.1543, 1.3 ppm error.

tert-Butyl *N*-{2-[*N*-(Pent-2-yn-1-yl)-2-nitrobenzenesulfonamido]ethyl}carbamate (3d)

2-Nitro-*N*-(pent-2-yn-1-yl)benzene-1-sulfonamide (4.84 g, 18.0 mmol) and *tert*-butyl 2,2-dioxo-1,2,3-oxathiazolidine-3-carboxylate (3.66 g, 16.4 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 25:25:50 PE–Et_2O–$CHCl_3$) to give the sulfonamide **3d**[12] (3.78 g, 56%) as an amorphous yellow solid; R_f = 0.65 (50:50 PE–EtOAc).

IR (ATR): 3419, 2978, 2937, 1708, 1545, 1366, 1167 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.06 (dd, *J* = 7.4, 1.8 Hz, 1 H, Ns 3-H), 7.72–7.65 (m, 2 H, Ns 4-H and 5-H), 7.63 (dd, *J* = 7.4, 1.8 Hz, 1 H, Ns 6-H), 4.82 (s, 1 H, NH), 4.20 (s, 2 H, 1′-CH_2), 3.51 (t, *J* = 5.8 Hz, 2 H, 2-CH_2), 3.36 (q, *J* = 5.8 Hz, 2 H, 1-CH_2), 2.04 (q, *J* = 7.5 Hz, 2 H, 4′-CH_2), 1.44 (s, 9 H, *t*-C_4H_9), 0.98 (t, *J* = 7.5 Hz, 3 H, 5′-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 148.5, 133.7, 133.0, 131.6, 131.2, 124.2, 88.2, 79.7, 72.3, 46.7, 38.3, 37.6, 28.5, 13.7, 12.3. Boc C=O was not observed.

Gold-Catalysed Hydration of Propargylic Sulfonamides 3; General Procedure

Method A: Au(PPh_3)Cl (5 mol%), $AgSbF_6$ (5 mol%) and cyclisation substrate **3** (1.0 equiv) were combined in 1,4-dioxane (0.2 M) and stirred at 100 °C for 16 h under N_2. The reaction mixture was cooled to r.t. and concentrated in vacuo to give the crude product.

Method B: Au(IPr)Cl (1 mol%), $AgSbF_6$ (1 mol%) and cyclisation substrate **3** (1.0 equiv) were combined in 1,4-dioxane (0.2 M) and stirred at 100 °C under N_2 until completion was observed by TLC. The reaction mixture was cooled to r.t. and concentrated in vacuo to give the crude product.

tert-Butyl (3*R*)-3,6-Dimethyl-4-(2-nitrobenzenesulfonyl)-1,2,3,4-tetrahydropyrazine-1-carboxylate (4a)

By Method A, **3a** (2.42 g, 6.09 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 30:20:50 PE–Et_2O–$CHCl_3$) to give the tetrahydropyrazine **4a** (1.75 g, 72%) as an orange oil; R_f = 0.81 (30:70 PE–EtOAc); $[\alpha]_D^{28}$ +182 (*c* = 0.06, MeOH).

IR (ATR): 3099, 2977, 2933, 1701, 1545, 1366, 1246, 1176 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.07–7.93 (m, 1 H, Ns 3-H), 7.80–7.69 (m, 2 H, Ns 4-H and 5-H), 7.68–7.60 (m, 1 H, Ns 6-H), 5.95 (app t, *J* = 1.1 Hz, 1 H, 5-H), 4.36–4.27 (m, 1 H, 3-H), 4.19 (dd, *J* = 13.1, 1.9 Hz, 1 H, 2-H_A), 2.58 (dd, *J* = 13.1, 2.3 Hz, 1 H, 2-H_B), 2.11 (d, *J* = 1.1 Hz, 3 H, 6-CH_3), 1.50 (s, 9 H, *t*-C_4H_9), 1.17 (d, *J* = 6.6 Hz, 3 H, 3-CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.2, 148.3, 133.9, 131.7, 131.6, 130.8, 124.2, 119.5, 106.5, 81.5, 49.8, 46.1, 28.2, 20.0, 17.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}N_3O_6S$: 398.1386; found: 398.1387, 0.3 ppm error.

tert-Butyl 6-Methyl-4-(2-nitrobenzenesulfonyl)-1,2,3,4-tetrahydropyrazine-1-carboxylate (4b)

By Method A, **3b** (6.22 g, 16.2 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 70:30 PE–EtOAc) to give the tetrahydropyrazine **4b**[12] (4.61 g, 74%) as an amorphous yellow solid; R_f = 0.61 (50:50 PE–EtOAc).

IR (ATR): 2977, 2933, 1702, 1455, 1369, 1171, 776 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.99 (dd, *J* = 7.4, 1.7 Hz, 1 H, Ns 3-H), 7.78–7.70 (m, 2 H, Ns 4-H and 5-H), 7.66 (dd, *J* = 7.4, 1.7 Hz, 1 H, Ns 6-H), 6.01 (s, 1 H, 5-H), 3.68–3.64 (m, 2 H, 3-CH_2), 3.64–3.60 (m, 2 H, 2-CH_2), 2.09 (s, 3 H, CH_3), 1.50 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.5, 148.3, 134.0, 131.7, 131.3, 130.7, 124.2, 120.2, 108.0, 81.7, 44.6, 41.6, 28.3, 20.1.

tert-Butyl 6-Methyl-4-(4-nitrobenzenesulfonyl)-2-phenyl-1,2,3,4-tetrahydropyrazine-1-carboxylate (4c)

By Method B, **3c** (4.59 g, 10.0 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 80:20 PE–EtOAc) to give the tetrahydropyrazine **4c**[12] (4.11 g, 90%) as an amorphous orange solid; R_f = 0.29 (80:20 PE–EtOAc).

^1H NMR (500 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.8 Hz, 2 H, Ns 3-H and 5-H), 7.67 (d, *J* = 8.8 Hz, 2 H, Ns 2-H and 4-H), 7.12–7.08 (m, 3 H, C_6H_5), 7.32–7.29 (d, *J* = 6.9 Hz, 2 H, C_6H_5 2-H and 6-H), 6.00 (s, 1 H, 5-H), 5.59 (br s, 1 H, 2-H), 4.33 (d, *J* = 12.6 Hz, 1 H, 3-H_A), 3.44 (dd, *J* = 12.6, 3.6 Hz, 1 H, 3-H_B), 2.17 (s, 3 H, CH_3), 1.43 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.5, 149.9, 143.7, 137.4, 128.5, 127.7, 127.3, 125.7, 124.2, 118.8, 107.9, 82.2, 53.3, 47.7, 28.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{25}N_3O_6SNa$: 482.1356; found: 482.1356, 0.0 ppm error.

tert-Butyl *N*-{2-[*N*-(3-Oxopentyl)2-nitrobenzenesulfonamido]ethyl}carbamate (5)

By Method B, **3d** (3.78 g, 9.19 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 50:50 PE–EtOAc) to give the ketone **5**[12] (3.39 g, 86%) as an amorphous orange solid; R_f = 0.26 (50:50 PE–EtOAc).

IR (ATR): 3403, 2978, 1709, 1544, 1367, 1164 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 7.3 Hz, 1 H, Ns 3-H), 7.76–7.67 (m, 2 H, Ns 4-H and 5-H), 7.63 (d, *J* = 7.3 Hz, 1 H, Ns 6-H), 4.85 (t, *J* = 6.3 Hz, 1 H, NH), 3.56 (t, *J* = 6.3 Hz, 2 H, 2-CH_2), 3.40 (t, *J* = 6.5 Hz, 2 H, 2′-CH_2), 3.31 (q, *J* = 6.3 Hz, 2 H, 1′-CH_2), 2.81 (t, *J* = 6.5 Hz, 2 H, 1′-CH_2), 2.43 (q, *J* = 7.3 Hz, 2 H, 4′-CH_2), 1.43 (s, 9 H, *t*-C_4H_9), 1.03 (t, *J* = 7.3 Hz, 3 H, 5′-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 209.3, 133.9, 132.7, 131.9, 131.2, 124.4, 48.5, 43.5, 41.7, 39.3, 36.4, 28.5, 7.7, Boc quaternary carbons were not observed.

tert-Butyl *N*-{2-[Benzyl(3-oxobutyl)amino]ethyl}carbamate (8)

Benzaldehyde (2.30 mL, 22.6 mmol) was added dropwise to a stirred suspension of *N*-Boc-ethylenediamine (3.29 g, 20.5 mmol) and 4Å MS (3.0 g) in CH_2Cl_2 (30 mL) at r.t. under N_2. The resulting solution was stirred at r.t. for 16 h, filtered through Celite, washed with CH_2Cl_2 (50 mL), and concentrated under reduced pressure. The residue was taken up in MeOH (30 mL) and cooled to 0 °C. $NaBH_4$ (1.55 g, 41.1 mmol) was added portionwise over 10 min and the resulting solution was allowed to warm to r.t. and stirred at r.t. for 2 h, then concentrated under reduced pressure. H_2O (20 mL), aq 1 M HCl (20 mL) and EtOAc (30 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 20 mL), then basified with aq 2 M NaOH (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude secondary amine **7** (3.91 g, 76%) as a pale yellow oil that was used without further purification.

The crude secondary amine **7** was dissolved in EtOH (30 mL) and methyl vinyl ketone (2.51 mL, 31.0 mmol) was added dropwise under N_2. The resulting solution was stirred at r.t. for 2 h and concentrated under reduced pressure to give the crude product, which was purified by column chromatography (SiO_2, 60:40 to 40:60 hexane–EtOAc) to give the amino ketone **8** (4.33 g, 87%, 66% over 2 steps) as a pale yellow oil; R_f = 0.25 (50:50 PE–EtOAc).

IR (ATR): 3367, 2975, 2931, 2813, 1702, 1495, 1452, 1390, 1363, 1246, 1165, 1049, 964, 734, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.30 (m, 2 H, C_6H_5), 7.30–7.24 (m, 3 H, C_6H_5), 4.95 (br s, 1 H, NH), 3.58 (s, 2 H, CH_2Ph), 3.20 (app d, *J* = 5.5 Hz, 2 H, 1′-CH_2), 2.80 (t, *J* = 6.9 Hz, 2 H, 1-CH_2), 2.60 (t, *J* = 6.9 Hz, 2 H, 2-CH_2), 2.55 (t, *J* = 5.5 Hz, 2 H, 2′-CH_2), 2.10 (s, 3 H, 4-CH_3), 1.46 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 208.1, 156.0, 138.9, 128.8, 128.3, 127.1, 78.9, 58.6, 53.3, 48.5, 41.5, 38.1, 30.0, 28.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{29}N_2O_3$: 321.2178; found: 321.2187, 2.8 ppm error.

3-CR Ugi–Joullié Reaction; General Procedure A

Method A1: TFA (4.0 equiv) was added to a stirred solution of substrate **4** or **5** (1.0 equiv) in CH_2Cl_2 (0.1 M) at r.t. under N_2 and stirred until completion was observed by TLC. Then, the mixture was concentrated under reduced pressure to give a crude product that was dissolved in EtOH (0.05 M) and cooled to 0 °C. Isonitrile (2.0 equiv) was added and the mixture stirred at r.t. until completion was observed by TLC, then concentrated under reduced pressure.

Method A2: TFA (4.0 equiv) was added to a stirred solution of substrate **4c** (1.0 equiv) in CH_2Cl_2 (0.1 M) at r.t. under N_2 and stirred until completion was observed by TLC. Then, the mixture was concentrated under reduced pressure to give a crude product that was dissolved in CH_2Cl_2 (0.05 M) and cooled to 0 °C. Isonitrile (2.0 equiv) was added and the mixture stirred at r.t. until completion was observed by TLC. Then, Et_3N (5.0 equiv) was added and the resulting solution stirred at r.t. for 2 h. H_2O (10–25 mL/mmol) was added, the two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10–25 mL/mmol). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product

N-(2-Methoxyethyl)-5-ethyl-1-(2-nitrobenzenesulfonyl)-4-(trifluoroacetyl)-1,4-diazepane-5-carboxamide (10a)

By Method A1, **5** (450 mg, 1.05 mmol) and 1-isocyano-2-methoxyethane (179 mg, 2.10 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 30:70 PE–EtOAc) to give the trifluoroacetamide **10a** (380 mg, 71%) as a yellow oil; R_f = 0.26 (20:80 PE–EtOAc).

IR (ATR): 3280, 2937, 1742, 1698, 1682, 1545, 1372, 1162 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.01–7.92 (m, 1 H, Ns 3-H), 7.77–7.63 (m, 3 H, Ns 4-H, 5-H and 6-H), 5.99 (t, *J* = 4.7 Hz, 1 H, NH), 4.20 (dd, *J* = 16.5, 5.9 Hz, 1 H, 3-H_A), 4.15–4.03 (m, 1 H, 2-H_A), 3.86 (dd, *J* = 14.1, 6.7 Hz, 1 H, 7-H_A), 3.63–3.54 (m, 1 H, 7-H_B), 3.53–3.43 (m, 4 H, 2-H_B, 3-H_B and 1′-CH_2), 3.42–3.30 (m, 5 H, 2′-CH_2 and 4′-CH_3), 2.72–2.51 (m, 2 H, CH_3CH_2), 1.93 (dd, *J* = 18.7, 6.7 Hz, 1 H, 6-H_A), 1.65 (dt, *J* = 18.7, 7.3 Hz, 1 H, 6-H_B), 0.93 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.9, 148.1, 133.8, 132.6, 131.9, 130.6, 124.4, 70.8, 69.2, 58.8, 49.9, 48.4, 44.0, 39.6, 37.3, 26.9, 7.9, trifluoroacetamide carbons were not observed.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –68.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{25}F_3N_4O_7S$: 511.1474; found: 511.1485, 2.2 ppm error.

N-Benzyl-5-ethyl-1-(2-nitrobenzenesulfonyl)-4-(trifluoroacetyl)-1,4-diazepane-5-carboxamide (10b)

By Method A1, **5** (700 mg, 1.63 mmol) and benzyl isocyanide (400 µL, 3.26 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 40:60 PE–EtOAc) to give the trifluoroacetamide **10b**[12] (710 mg, 80%) as an amorphous white solid; R_f = 0.44 (50:50 PE–EtOAc).

IR (ATR): 3422, 2977, 1695, 1666, 1543, 1371, 1152 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.97 (dd, *J* = 10.1, 4.9 Hz, 1 H, Ns 3-H), 7.78–7.70 (m, 2 H, Ns 4-H and 5-H), 7.68 (dd, *J* = 7.4, 1.6 Hz, 1 H, Ns 6-H), 7.41–7.26 (m, 5 H, C_6H_5), 5.92 (t, *J* = 5.2 Hz, 1 H, NH), 4.54–4.39 (m, 2 H, 1′-CH_2), 4.25 (dd, *J* = 16.8, 5.7 Hz, 1 H, 3-H_A), 4.11 (dd, *J* = 14.4, 5.7 Hz, 1 H, 2-H_A), 3.90 (dd, *J* = 14.8, 7.0 Hz, 1 H, 7-H_A), 3.64 (dd, *J* = 14.8, 10.7 Hz, 1 H, 7-H_B), 3.52 (dd, *J* = 16.8, 9.0 Hz, 1 H, 3-H_B), 3.39 (dd, *J* = 14.4, 9.0 Hz, 1 H, 2-H_B), 2.76–2.56 (m, 2 H, CH_3CH_2), 1.94 (dd, *J* = 16.8, 7.0 Hz, 1 H, 6-H_A), 1.69–1.58 (m, 1 H, 6-H_B), 0.96 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.7, 157.0 (d, *J* = 35.5 Hz), 148.1, 137.8, 133.9, 132.5, 131.9, 130.5, 128.9, 127.7, 124.5, 116.3 (q, *J* = 287.9 Hz), 69.2, 49.8, 48.5, 44.0, 43.9, 37.4, 26.9, 7.9, benzyl C-2 and benzyl C-6 were not observed;

^{19}F NMR (282 MHz, $CDCl_3$): δ = –68.3.

(2*R*,5*R*)-*N*-Benzyl-2,5-dimethyl-4-(2-nitrobenzenesulfonyl)-1-(trifluoroacetyl)piperazine-2-carboxamide (12a)

By Method A1, **4a** (350 mg, 0.880 mmol) and benzyl isocyanide (210 µL, 1.76 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 30:70 PE–EtOAc) to give the trifluoroacetamide **12a** (356 mg, 77%) as an amorphous white solid; R_f = 0.40 (30:70 PE–EtOAc); $[\alpha]_D^{28}$ +49 (*c* = 0.05, MeOH).

IR (ATR): 3367, 2935, 1699, 1543, 1362, 1216, 1154 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.15–8.10 (m, 1 H, Ns 3-H), 7.81–7.73 (m, 2 H, Ns 4-H and 5-H), 7.73–7.68 (m, 1 H, Ns 6-H), 7.39–7.33 (m, 2 H, C_6H_5 3-H and 5-H), 7.32–7.25 (m, 3 H, C_6H_5 2-H, 4-H and 6-H), 6.18 (t, *J* = 5.3 Hz, 1 H, NH), 4.52 (dd, *J* = 14.9, 5.3 Hz, 1 H, 1′-H_A), 4.37–4.31 (m, 1 H, 5-H), 4.28 (dd, *J* = 14.9, 5.3 Hz, 1 H, 1′-H_B), 3.99 (d, *J* = 14.2 Hz, 1 H, 3-H_A), 3.90 (dd, *J* = 14.7, 4.7 Hz, 1 H, 6-H_A), 3.57–3.47 (m, 2 H, 3-H_B and 6-H_B), 1.31–1.27 (m, 6 H, 2-CH_3 and 5-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.2, 157.3 (d, *J* = 36.3 Hz), 137.5, 134.1, 133.3, 132.1, 131.4, 128.7, 127.7, 127.6, 124.6, 115.9 (app d, *J* = 288.5 Hz), 64.9, 51.0, 49.9, 46.8, 44.2, 19.0, 18.0;

^{19}F NMR (282 MHz, $CDCl_3$): δ = –69.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{23}F_3N_4O_6S$: 529.1368; found: 529.1376, 1.5 ppm error.

N-Cyclopropyl-5-ethyl-1-(2-nitrobenzenesulfonyl)-4-(trifluoroacetyl)-1,4-diazepane-5-carboxamide (10f)

By Method A1, **5** (910 mg, 2.12 mmol) and cyclopropyl isocyanide (420 µL, 5.28 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 50:50 PE–EtOAc) to give the trifluoroacetamide **10f** (690 mg, 66%) as an amorphous white solid; R_f = 0.36 (30:70 PE–EtOAc).

IR (ATR): 3401, 2975, 1693, 1664, 1543, 1451, 1370, 1143, 729 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.87 (dd, *J* = 7.3, 1.9 Hz, 1 H, Ns 3-H), 7.68–7.61 (m, 2 H, Ns 4-H and 5-H), 7.59 (dd, *J* = 7.5, 1.7 Hz, 1 H, Ns 6-H), 5.75 (s, 1 H, NH), 4.13 (dd, *J* = 16.7, 5.7 Hz, 1 H, 3-H_A), 4.01 (dd, *J* = 14.3, 5.7 Hz, 1 H, 2-H_A), 3.78 (dd, *J* = 14.7, 6.8 Hz, 1 H, 7-H_A), 3.53 (dd, *J* = 14.7, 10.7 Hz, 1 H, 7-H_B), 3.39 (dd, *J* = 16.7, 8.9 Hz, 1 H, 3-H_B), 3.29

(dd, J = 14.3, 8.9 Hz, 1 H, 2-H_B), 2.61–2.54 (m, 1 H, 1′-H), 2.53–2.44 (m, 2 H, CH_3CH_2), 1.78 (dd, J = 16.4, 6.8 Hz, 1 H, 6-H_A), 1.54–1.42 (m, 1 H, 6-H_B), 0.85 (t, J = 7.4 Hz, 3 H, CH_3CH_2), 0.73–0.63 (m, 2 H, 2′-H_A and 3′-H_A), 0.51–0.44 (m, 1 H, 2′-H_B), 0.40–0.31 (m, 1 H, 3′-H_B).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.3, 157.0 (d, J = 35.6 Hz), 148.1, 133.9, 132.5, 132.0, 130.5, 124.4, 116.3 (q, J = 288.4 Hz), 68.9, 49.8, 48.4, 43.9, 37.1, 26.8, 22.9, 7.8, 6.8, 6.4.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –68.4.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{23}F_3N_4O_6S$: 493.1368; found: 493.1363, –1.0 ppm error.

N-Benzyl-2-methyl-4-(2-nitrobenzenesulfonyl)-1-(trifluoroacetyl)piperazine-2-carboxamide (12e)

By Method A1, **4b** (650 mg, 1.70 mmol) and benzyl isocyanide (410 µL, 3.40 mmol) gave a crude product which was purified by flash column chromatography (SiO_2, 80:20 CH_2Cl_2–Et_2O) to give the trifluoroacetamide **12e**[12] (750 mg, 86%) as an amorphous white solid; R_f = 0.53 (30:70 PE–EtOAc).

IR (ATR): 3368, 2937, 1699, 1673, 1542, 1370, 1216, 1145, 732 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (dd, J = 7.6, 1.2 Hz, 1 H, Ns 3-H), 7.81–7.72 (m, 2 H, Ns 4-H and 5-H), 7.70 (dd, J = 7.6, 1.3 Hz, 1 H, Ns 6-H), 7.43–7.35 (m, 2 H, C_6H_5 2-H and 6-H), 7.34–7.25 (m, 3 H, C_6H_5 3-H, 4-H and 5-H), 6.20 (t, J = 5.0 Hz, 1 H, NH), 4.52–4.36 (m, 2 H, 1′-CH_2), 4.03–3.92 (m, 1 H, 5-H_A), 3.88–3.75 (m, 3 H, 3-H_A, 5-H_B and 6-H_A), 3.70 (d, J = 13.8 Hz, 1 H, 3-HB_b), 3.59–3.46 (m, 1 H, 6-H_B), 1.72 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.2, 156.9 (d, J = 36.6 Hz), 148.1, 137.4, 134.3, 132.0, 131.4, 131.2, 128.8, 127.8, 127.7, 124.5, 115.9 (q, J = 288.5 Hz), 64.3, 51.8, 44.3, 44.2, 41.4, 18.2.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –69.6.

Hydantoin Formation; General Procedure B

Method B1: K_2CO_3 (10 equiv) was added to a stirred solution of substrate **10** or **12** (1.0 equiv) in 2:1 MeOH–H_2O (0.05 M), stirred at r.t. overnight and concentrated under reduced pressure. The residue was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product.

Method B2: The trifluoroacetamide from method A was dissolved in EtOH (0.05 M), K_2CO_3 (5.0 equiv) was added and the resulting mixture stirred at 70 °C for 16 h. The mixture was cooled to r.t. and concentrated under reduced pressure. The residue was partitioned between H_2O (10–25 mL/mmol) and CH_2Cl_2 (10–25 mL/mmol); the two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10–25 mL/mmol). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

Method B3: PhSH (1.2 equiv) was added to a stirred solution of substrate **10** or **12** (1.0 equiv) and K_2CO_3 (3.0 equiv) in DMF or MeCN (0.1 M) and the mixture was stirred at r.t. overnight. The reaction mixture was concentrated under reduced pressure to give the crude product.

9a-Ethyl-2-(2-methoxyethyl)-7-(2-nitrobenzenesulfonyl)octahydro-1*H*-imidazolidino[1,5-*d*][1,4]diazepine-1,3-dione (11a)

By Method B1, **10a** (380 mg, 0.740 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 30:70 PE–EtOAc) to give the hydantoin **11a** (280 mg, 86%) as a yellow oil; R_f = 0.26 (20:80 PE–EtOAc).

IR (ATR): 2936, 1769, 1708, 1544, 1451, 1368, 1165 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (dd, J = 7.6, 1.6 Hz, 1 H, Ns 3-H), 7.77–7.69 (m, 2 H, Ns 4-H and 5-H), 7.67 (dd, J = 7.2, 1.8 Hz, 1 H, Ns 6-H), 4.25–4.16 (m, 1 H, 5-H_A), 3.91–3.82 (m, 2 H, 6-H_A and 8-H_A), 3.81–3.70 (m, 2 H, 1′-CH_2), 3.62–3.55 (m, 2 H, 6-H_B and 8-H_B), 3.32 (s, 3 H, 4′-CH_3), 3.19–3.09 (m, 2 H, 2′-CH_2), 2.69–2.57 (m, 2 H, 5-H_B and 9-H_A), 2.11–2.02 (m, 1 H, 9-H_B), 1.92 (dq, J = 14.6, 7.3 Hz, 1 H, CH_3CH_2 1-H_A), 1.74 (dq, J = 14.6, 7.3 Hz, 1 H, CH_3CH_2 1-H_B), 0.80 (t, J = 7.3 Hz, 3 H, CH_3CH_2).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.3, 156.4, 147.9, 133.9, 132.6, 131.8, 130.9, 124.4, 68.5, 68.1, 58.5, 48.0, 44.8, 41.7, 39.4, 38.3, 29.0, 7.3.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{24}N_4O_7S$: 441.1444; found: 441.1446, –0.5 ppm error.

2-Benzyl-9a-ethyl-7-(2-nitrobenzenesulfonyl)octahydro-1*H*-imidazolidino[1,5-*d*][1,4]diazepine-1,3-dione (11b)

By Method B1, **10b** (630 mg, 0.740 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 40:60 PE–EtOAc) to give the hydantoin **11b** (200 mg, 36%) as an amorphous white solid; R_f = 0.43 (20:80 PE–EtOAc).

IR (ATR): 2927, 1767, 1709, 1544, 1449, 1366, 1165 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (dd, J = 7.6, 1.3 Hz, 1 H, Ns 3-H), 7.86–7.60 (m, 3 H, Ns 4-H, 5-H and 6-H), 7.50–7.18 (m, 5 H, C_6H_5), 4.74–4.63 (m, 2 H, 1′-CH_2), 4.28–4.15 (m, 1 H, 5-H_A), 3.97–3.77 (m, 2 H, 6-H_A and 8-H_A), 3.23–3.04 (m, 2 H, 6-H_B and 5-H_B), 2.68–2.48 (m, 2 H, 8-H_B and 9-H_A), 2.13–2.00 (m, 1 H, 9-H_B), 1.89 (dq, J = 14.7, 7.4 Hz, 1 H, CH_3CH_2 1-H_A), 1.73 (dq, J = 14.7, 7.4 Hz, 1 H, CH_3CH_2 1-H_B), 0.64 (t, J = 7.4 Hz, 3 H, CH_3CH_2).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.0, 156.2, 147.9, 136.0, 133.9, 132.5, 131.8, 130.9, 128.7, 128.5, 128.0, 124.4, 67.9, 48.1, 44.9, 42.7, 41.8, 39.2, 29.1, 7.3.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{22}H_{24}N_4O_6S$: 473.1495; found: 473.1490, –1.1 ppm error.

7-Benzyl-9a-methyl-2-[2-(morpholin-4-yl)ethyl]octahydro-1*H*-imidazolidino[1,5-*d*][1,4]diazepine-1,3-dione (11c)

By Methods A1 and B2, **8** (1.11 g, 3.46 mmol) and 2-morpholinoethyl isocyanide (955 µL, 6.93 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 95:5 CH_2Cl_2–MeOH) to give the hydantoin **11c** (998 mg, 75%) as a pale yellow oil; R_f = 0.21 (95:5 CH_2Cl_2–MeOH).

IR (ATR): 2950, 2853, 2810, 1767, 1704, 1455, 1420, 1354, 1116 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5 H, C_6H_5), 4.01–3.92 (ddd, J = 13.3, 3.0, 2.3 Hz, 1 H, 5-H_A), 3.76–3.60 (m, 7 H, 1′-CH_2, morpholine 2-CH_2 and 6-CH_2 and CH_AH_BPh), 3.57 (d, J = 13.3 Hz, 1 H, CH_AH_BPh), 3.10 (ddd, J = 13.3, 11.2, 1.6 Hz, 1 H, 5-H_B), 2.82 (br d, J = 12.9 Hz, 1 H, 6-H_A), 2.74 (dd, J = 13.3, 7.4 Hz, 1 H, 8-H_A), 2.67–2.45 (m, 7 H, 6-H_B, 2′-CH_2 and morpholine 3-CH_2 and 5-CH_2), 2.42 (dd, J = 15.1, 7.3 Hz, 1 H, 9-H_A), 2.05 (dd, J = 13.3, 10.3 Hz, 1 H, 8-H_B), 1.96 (dd, J = 15.1, 10.2 Hz, 1 H, 9-H_B), 1.40 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.9, 156.2, 138.5, 128.7, 128.3, 127.2, 67.1, 64.4, 63.0, 55.2, 54.9, 53.3, 50.8, 40.8, 38.4, 35.5, 23.6.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{21}H_{31}N_4O_3$: 387.2391; found: 387.2396, 1.3 ppm error.

7-Benzyl-2-butyl-9a-methyloctahydro-1*H*-imidazolidino[1,5-*d*][1,4]diazepine-1,3-dione (11d)

By Methods A1 and B2, **8** (1.00 g, 3.12 mmol) and butyl isocyanide (652 µL, 6.24 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 50:50 hexane–EtOAc) to give the hydantoin **11d** (980 mg, 95%) as a pale yellow oil; R_f = 0.28 (50:50 hexane–EtOAc).

IR (ATR): 2935, 2872, 2813, 1765, 1698, 1450, 1416, 1376, 1352, 1088, 761, 729, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 5 H, C_6H_5), 3.95 (ddd, *J* = 14.9, 3.4, 2.2 Hz, 1 H, 5-H_A), 3.59 (d, *J* = 13.3 Hz, 1 H, C$H_A$$H_B$Ph), 3.54 (d, *J* = 13.3 Hz, 1 H, CH$_A$$H_B$Ph), 3.51 (t, *J* = 7.3 Hz, 2 H, 1′-CH_2), 3.06 (ddd, *J* = 14.9, 11.2, 2.0 Hz, 1 H, 5-H_B), 2.80–2.76 (m, 1 H, 6-H_A), 2.76–2.70 (m, 1 H, 8-H_A), 2.48 (ddd, *J* = 13.1, 11.2, 2.2 Hz, 1 H, 6-H_B), 2.38 (dd, *J* = 14.5, 7.3 Hz, 1 H, 9-H_A), 1.97–1.85 (m, 2 H, 8-H_B and 9-H_B), 1.64–1.57 (m, 2 H, 2′-CH_2), 1.36 (s, 3 H, CH_3), 1.37–1.28 (m, 2 H, 3′-CH_2), 0.93 (t, *J* = 7.4 Hz, 3 H, 4′-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.8, 156.2, 138.5, 128.7, 128.3, 127.2, 64.3, 62.9, 54.7, 51.1, 40.7, 38.6, 38.2, 30.2, 23.6, 19.9, 13.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{27}N_3O_2$: 330.2176; found: 330.2184, 2.4 ppm error.

Ethyl 2-{7-Benzyl-9a-methyl-1,3-dioxooctahydro-1*H*-imidazolidino[1,5-*d*][1,4]diazepin-2-yl}acetate (11e)

By methods A1 and B2, **8** (2.00 g, 6.24 mmol) and ethyl cyanoacetate (1.36 mL, 12.5 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 30:70 hexane–EtOAc) to give the hydantoin **11e** (1.82 g, 81%) as a white solid; mp 72–73 °C; R_f = 0.43 (30:70 hexane–EtOAc).

IR (ATR): 2977, 1767, 1746, 1707, 1449, 1209, 760, 746 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 4 H, C_6H_5), 7.28–7.23 (m, 1 H, C_6H_5), 4.28 (d, *J* 17.4 Hz, 1 H, 3′-H_A), 4.23 (d, *J* = 17.4 Hz, 1 H, 3′-H_B), 4.22 (app dq, *J* = 7.1, 1.6 Hz, 2 H, CH_2Me), 4.01–3.95 (m, 1 H, 5-H_A), 3.61 (d, *J* = 13.3 Hz, 1 H, C$H_A$$H_B$Ph), 3.57 (d, *J* = 13.3 Hz, 1 H, CH$_A$$H_B$Ph), 3.10 (ddd, *J* = 14.7, 11.2, 1.7 Hz, 1 H, 5-H_B), 2.83–2.78 (m, 1 H, 6-H_A), 2.75 (dd, *J* = 13.5, 7.2 Hz, 1 H, 8-H_A), 2.55–2.48 (m, 1 H, 6-H_B), 2.45 (dd, *J* = 15.3, 7.2 Hz, 1 H, 9-H_A), 2.13 (dd, *J* = 13.7, 10.1 Hz, 1 H, 8-H_B), 1.98 (dd, *J* = 14.9, 9.8 Hz, 1 H, 9-H_B), 1.43 (s, 3 H, CH_3), 1.29 (t, *J* = 7.1 Hz, 3 H, 4′-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.4, 167.1, 155.2, 138.7, 128.7, 128.3, 127.2, 65.0, 62.9, 61.8, 54.7, 50.8, 40.9, 39.7, 38.3, 23.6, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{26}N_3O_4$: 360.1918; found: 360.1926, 2.2 ppm error.

(6*R*,8a*R*)-2-Benzyl-6,8a-dimethyl-7-(2-nitrobenzenesulfonyl)octahydroimidazolidino[1,5-*a*]piperazine-1,3-dione (13a)

By method B2, **12a** (93 mg, 0.180 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 30:70 PE–EtOAc) to give the hydantoin **13a** (34 mg, 41%) as a white solid; mp 170–172 °C; R_f = 0.47 (30:70 PE–EtOAc); $[\alpha]_D^{27}$ +41 (*c* = 0.20, MeOH).

IR (ATR): 2934, 1775, 1711, 1542, 1415, 1350, 1157, 734, 583 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.03–7.98 (m, 1 H, Ns 3-H), 7.68–7.61 (m, 2 H, Ns 4-H and 5-H), 7.60–7.56 (m, 1 H, Ns 6-H), 7.29–7.20 (m, 5 H, C_6H_5), 4.50–4.40 (m, 2 H, 1′-CH_2), 4.05 (dd, *J* = 14.3, 6.1 Hz, 1 H, 5-H_A), 3.92–3.82 (m, 1 H, 6-H), 3.61 (d, *J* = 14.7 Hz, 1 H, 8-H_A), 3.49 (d, *J* = 14.7 Hz, 1 H, 8-H_B), 2.68 (dd, *J* = 14.3, 10.2 Hz, 1 H, 5-H_B), 1.36 (s, 3 H, 8a-CH_3), 1.04 (d, *J* = 6.6 Hz, 3 H, 6-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.2, 156.5, 147.6, 135.7, 134.2, 134.0, 132.1, 131.1, 128.7, 128.4, 127.9, 124.4, 61.6, 52.3, 49.0, 42.6, 42.6, 19.3, 16.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}N_4O_6S$: 459.1338; found: 459.1340, 0.4 ppm error.

(5*R,8a*S**)-8a-Methyl-2-[2-(morpholin-4-yl)ethyl]-7-(4-nitrobenzenesulfonyl)-5-phenyloctahydroimidazolidino[1,5-*a*]piperazine-1,3-dione (13b)**

By methods A2 and B2, **4c** (1.00 g, 2.18 mmol) and 2-morpholinoethyl isocyanide (600 µL, 4.35 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 70:30 to 50:50 CH_2Cl_2–EtOAc) to give the hydantoin **13b** (1.09 g, 91%) as a white solid, mp 149–151 °C; R_f = 0.3 (50:50 CH_2Cl_2–EtOAc).

IR (ATR): 2853, 1771, 1702, 1525, 1450, 1420, 1272, 1115, 658 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 8.8 Hz, 2 H, Ns 3-H and 5-H), 8.01 (d, *J* = 8.8 Hz, 2 H, Ns 2-H and 4-H), 7.59 (d, *J* = 7.6 Hz, 2 H, C_6H_5 2-H and 6-H), 7.42 (t, *J* = 7.6 Hz, 2 H, C_6H_5 3-H and 5-H), 7.34 (t, *J* = 7.6 Hz, 1 H, C_6H_5 4-H), 5.49 (d, *J* = 4.4 Hz, 1 H, 5-H), 4.70 (d, *J* = 12.5 Hz, 1 H, 6-H_A), 3.86 (dd, *J* = 11.3, 1.2 Hz, 1 H, 8-H_A), 3.71–3.59 (m, 2 H, 1′-CH_2), 3.49 (br s, 4 H, morpholine 2-CH_2 and 6-CH_2), 2.67–2.52 (m, 3 H, 2′-CH_2 and 6-H_B), 2.50–2.35 (m, 4 H, morpholine 3-CH_2 and 5-CH_2), 2.31 (d, *J* = 11.3 Hz, 1 H, 8-H_B), 1.14 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.8, 155.0, 150.7, 141.0, 137.7, 128.9, 128.8, 128.1, 127.1, 124.7, 67.0, 59.7, 54.7, 51.7, 48.6, 46.7, 35.9, 20.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{30}N_5O_7S$: 544.1860; found: 544.1873, 2.4 ppm error.

(5*R,8a*S**)-2-Benzyl-8a-methyl-7-(4-nitrobenzenesulfonyl)-5-phenyloctahydroimidazolidino[1,5-*a*]piperazine-1,3-dione (13c)**

By methods A2 and B2, **4c** (500 mg, 1.09 mmol) and benzyl isocyanide (265 µL, 2.18 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 70:30 to 50:50 hexane–EtOAc) to give the hydantoin **13c** (412 mg, 72%) as a white solid; mp 180–181 °C; R_f = 0.3 (70:30 hexane–EtOAc).

IR (ATR): 3103, 1771, 1705, 1527, 1461, 1435, 1350, 1200, 696 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 8.9 Hz, 2 H, Ns 3-H and 5-H), 7.99 (d, *J* = 8.9 Hz, 2 H, Ns 2-H and 4-H), 7.59 (d, *J* = 7.6 Hz, 2 H, C_6H_5 2-H and 6-H), 7.42–7.29 (m, 8 H, C_6H_5), 5.49 (d, *J* = 4.5 Hz, 1 H, 5-H), 4.67 (d, *J* = 12.5 Hz, 1 H, 6-H_A), 4.65 (s, 2 H, 1′-CH_2), 3.86 (dd, *J* = 11.3, 1.3 Hz, 1 H, 8-H_A), 2.65 (dd, *J* = 12.5, 4.8 Hz, 1 H, 6-H_B), 2.24 (d, *J* = 11.3 Hz, 1 H, 8-H_B), 1.14 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.3, 154.7, 150.7, 141.1, 137.7, 135.6, 128.9, 128.8, 128.8, 128.7, 128.1, 127.1, 124.7, 59.7, 51.3, 48.7, 46.7, 42.9, 20.8, one C atom of C_6H_5 was not observed.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{25}N_4O_6S$: 521.1489; found: 521.1499, 1.9 ppm error.

(5*R,8a*S**)-2-Butyl-8a-methyl-7-(4-nitrobenzenesulfonyl)-5-phenyloctahydroimidazolidino[1,5-*a*]piperazine-1,3-dione (13d)**

By methods A2 and B2, **4c** (500 mg, 1.09 mmol) and butyl isocyanide (265 µL, 2.18 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 99:1 CH_2Cl_2–Et_2O) to give the hydantoin **13c** (274 mg, 52%) as a white solid, mp 216–217 °C; R_f = 0.3 (99:1 CH_2Cl_2–Et_2O).

IR (ATR): 2958, 2865, 1768, 1702, 1526, 1441, 1418, 1368, 1199, 1115, 659 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 8.9 Hz, 2 H, Ns 3-H and 5-H), 8.01 (d, *J* = 8.9 Hz, 2 H, Ns 2-H and 4-H), 7.60 (d, *J* = 7.6 Hz, 2 H, C_6H_5 2-H and 6-H), 7.41 (t, *J* = 7.6 Hz, 2 H, C_6H_5 3-H and 5-H), 7.34 (t, *J* = 7.6 Hz, 1 H, C_6H_5 4-H), 5.49 (d, *J* = 4.5 Hz, 1 H, 5-H), 4.69 (d, *J* = 12.5 Hz, 1 H, 6-H_A), 3.87 (dd, *J* = 11.3, 1.4 Hz, 1 H, 8-H_A), 3.58–3.43 (m, 2 H, 1′-CH_2), 2.66 (dd, *J* = 12.5, 4.8 Hz, 1 H, 6-H_B), 2.25 (d, *J* = 11.3 Hz, 1 H, 8-H_B), 1.64–1.54 (m, 2 H, 2′-CH_2), 1.32–1.27 (m, 2 H, 3′-CH_2), 1.14 (s, 3 H, CH_3), 0.93 (t, *J* = 7.4 Hz, 3 H, 4′-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.6, 155.0, 150.6, 141.1, 137.8, 128.9, 128.8, 128.1, 127.1, 124.6, 59.7, 51.7, 48.6, 46.7, 39.0, 30.5, 20.7, 19.9, 13.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{27}N_4O_6S$: 487.1651; found: 487.1647, –0.8 ppm error.

2-Cyclopropyl-9a-ethyloctahydro-1*H*-imidazolidino[1,5-*d*][1,4]diazepine-1,3-dione (14)

By method B3, **10f** (370 mg, 0.750 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 90:10 CH_2Cl_2–MeOH) to give the hydantoin **14** (130 mg, 73%) as an amorphous orange solid; R_f = 0.19 (90:10 CH_2Cl_2–MeOH).

IR (ATR): 3461, 2967, 2936, 1766, 1701, 1428, 1352 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.09–3.95 (m, 1 H, 5-H_A), 3.01–2.92 (m, 2 H, 6-H_a and 8-H_A), 2.91–2.81 (m, 2 H, 5-H_B and 6-H_B), 2.67–2.59 (m, 1 H, 8-H_B), 2.50 (dd, *J* = 14.7, 5.9 Hz, 1 H, 9-H_A), 2.22 (dd, *J* = 14.7, 10.8 Hz, 1 H, 9-H_B), 2.09 (br s, 1 H, NH), 1.82 (dq, *J* = 14.2, 7.4 Hz, 1 H, CH_3CH_2 1-H_A), 1.74 (ddd, *J* = 15.3, 10.8, 1.2 Hz, 1 H, 1′-H_A), 1.62 (dq, *J* = 14.2, 7.4 Hz, 1 H, CH_3CH_2 1-H_B), 1.02–0.83 (m, 4 H, 2′-CH_2 and 3′-CH_2), 0.69 (t, *J* = 7.4 Hz, 3 H, CH_3CH_2).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.5, 157.0, 67.6, 48.0, 44.9, 42.8, 41.2, 29.7, 21.8, 7.3, 5.3, 5.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{19}N_3O_2$: 238.1555; found: 238.1555, 0.0 ppm error.

2-Benzyl-8a-methyloctahydroimidazolidino[1,5-*a*]piperazine-1,3-dione (15)

By method B3, **12e** (1.51 g, 2.94 mmol) gave a crude product, which was purified SCX cartridge (eluting with sat. NH_3 in MeOH) to give the hydantoin **15** (665 mg, 87%) as a yellow solid; mp 109–111 °C; R_f = 0.62 (90:10 CH_2Cl_2–MeOH).

IR (ATR): 3337, 2949, 1764, 1702, 1438, 1418, 1141, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.27 (m, 5 H, C_6H_5), 4.78–4.63 (m, 2 H, 1′-CH_2), 4.01 (dd, *J* = 13.2, 3.6 Hz, 1 H, 5-H_A), 3.09 (d, *J* = 12.2 Hz, 1 H, 8-H_A), 3.07–2.95 (m, 2 H, 6-CH_2), 2.68–2.55 (m, 2 H, 5-H_B and 8-H_B), 1.79 (br s, 1 H, NH), 1.55 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.5, 154.4, 136.3, 128.7, 128.3, 127.8, 59.7, 52.1, 45.7, 42.3, 38.2, 17.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}N_3O_2$: 260.1399; found: 260.1401, 0.8 ppm error.

(3*R**,9a*R**)-2-Benzyl-9a-ethyl-1-oxo-3-(trifluoromethyl)octahydro-1*H*-imidazolidino[1,5-*d*][1,4]diazepin-7-ium-3-olate (16)

K_2CO_3 (271 mg, 1.96 mmol) was added to a stirred solution of the sulfonamide **10b** (710 mg, 1.31 mmol) and PhSH (0.20 mL, 1.96 mmol) in MeCN (13 mL), and the mixture was stirred at r.t. overnight. Excess K_2CO_3 was removed by filtration and the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 90:10 CH_2Cl_2–MeOH) to give the zwitterion **16** (330 mg, 70%) as a white solid; mp 140–142 °C; R_f = 0.32 (90:10 CH_2Cl_2–MeOH).

IR (ATR): 3305, 2963, 2936, 2880, 1707, 1453, 1294, 1164 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 7.3 Hz, 2 H, C_6H_5 3-H and 5-H), 7.35–7.30 (m, 2 H, C_6H_5 2-H and 6-H), 7.28–7.22 (m, 1 H, C_6H_5 4-H), 4.67 (q, *J* = 15.3 Hz, 2 H, 1′-CH_2), 3.73–3.62 (m, 1 H, 5-H_A), 3.16 (ddd, *J* = 15.9, 7.3, 3.4 Hz, 1 H, 6-H_A), 2.95–2.85 (m, 3 H, 6-H_B and 8-CH_2), 2.85–2.78 (m, 1 H, 5-H_B), 2.09–1.94 (m, 3 H, 9-CH_2 and NH), 1.78 (dq, *J* = 14.8, 7.4 Hz, 1 H, CH_3CH_2 1-H_A), 1.61 (dq, *J* = 14.8, 7.4 Hz, 1 H, CH_3CH_2 1-H_B), 0.91 (t, *J* = 7.4 Hz, 3 H, CH_3CH_2).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.8, 137.5, 128.5, 128.1, 127.1, 122.6 (app d, *J* = 289.7 Hz), 96.9 (app d, *J* = 33.0 Hz), 67.2, 43.8, 41.9, 40.8, 40.1, 34.5, 30.5, 8.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –79.78.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{22}F_3N_3O_2$: 358.1742; found: 358.1732, –2.8 ppm error.

2-Benzyl-9a-ethyloctahydro-1*H*-imidazolidino[1,5-*d*][1,4]diazepine-1,3-dione (17)

K_2CO_3 (522 mg, 3.78 mmol) was added to a solution of zwitterion **16** (270 mg, 0.760 mmol) in EtOH (4 mL) and stirred at 70 °C for 4 h. The reaction mixture was cooled, concentrated under reduced pressure, diluted with H_2O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a crude product, which was purified by flash chromatography (SiO_2, 90:10 CH_2Cl_2–MeOH) to yield the hydantoin **17** (89 mg, 41%) as a yellow oil; R_f = 0.24 (90:10 CH_2Cl_2–MeOH).

IR (ATR): 3341, 2967, 2937, 1764, 1703, 1448, 1350 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.36 (m, 2 H, C_6H_5 3-H and 5-H), 7.34–7.23 (m, 3 H, C_6H_5 2-H, 4-H and 6-H), 4.71–4.63 (m, 2 H, 1′-CH_2), 4.10–4.00 (m, 1 H, 5-H_A), 3.00–2.83 (m, 4 H, 5-H_B, 6-CH_2 and 8-H_A), 2.51 (dd, *J* = 15.2, 6.4 Hz, 1 H, 8-H_B), 2.18 (dd, *J* = 14.7, 10.7 Hz, 1 H, 9-H_A), 1.84 (dq, *J* = 14.6, 7.4 Hz, 1 H, CH_3CH_2 1-H_A), 1.74 (ddd, *J* = 14.7, 10.8, 1.3 Hz, 1 H, 9-H_B), 1.69–1.58 (m, 2 H, CH_3CH_2 1-H_B and NH), 0.62 (t, *J* = 7.4 Hz, 3 H, CH_3CH_2).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.8, 156.6, 136.4, 128.6, 128.5, 127.8, 68.5, 48.2, 44.9, 43.2, 42.5, 41.5, 29.8, 7.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{21}N_3O_2$: 288.1712; found: 288.1716, 1.4 ppm error.

Debenzylation of Benzylamines 11c–e; General Procedure

Ammonium formate (5.0 equiv) was added to a stirred suspension of diazepine **11** (1.0 equiv) and 20% $Pd(OH)_2$/C (10 wt%) in EtOH (0.1 M). The resulting mixture was heated to 70 °C and stirred at 70 °C for 2 h, cooled to r.t., filtered through Celite, washed with EtOH (100 mL) and concentrated under reduced pressure. The residue was partitioned between sat. aq $NaHCO_3$ (30 mL) and CH_2Cl_2 (30 mL), the two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude secondary amine.

9a-Methyl-2-[2-(morpholin-4-yl)ethyl]octahydro-1*H*-imidazolidino[1,5-*d*][1,4]diazepine-1,3-dione (18)

Diazepine **11c** (990 mg, 2.56 mmol) gave the crude secondary amine **18** (660 mg, 87%) as a pale yellow oil, which was used without further purification.

IR (ATR): 3336, 2938, 2856, 2809, 1759, 1697, 1459, 1421, 1348, 1072, 749 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.03–3.96 (m, 1 H, 5-H_A), 3.72–3.54 (m, 6 H, 1′-CH_2 and morpholine 2-CH_2 and 6-CH_2), 2.98–2.79 (m, 4 H, 5-H_B, 6-CH_2 and 8-H_A), 2.62–2.37 (m, 7 H, 9-H_A, 2′-CH_2 and morpholine 3-CH_2 and 5-CH_2), 2.31 (dd, *J* = 14.1, 10.6 Hz, 1 H, 8-H_B), 1.84–1.68 (m, 2 H, 9-H_B and NH), 1.36 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.1, 157.1, 67.1, 64.3, 55.2, 53.3, 48.2, 44.8, 43.2, 41.9, 35.5, 23.8:

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{24}N_4O_3$: 297.1921; found: 297.1928, 2.4 ppm error.

2-Butyl-9a-methyloctahydro-1*H*-imidazolidino[1,5-*d*][1,4]diazepine-1,3-dione (19)

Diazepine **11d** (906 mg, 2.75 mmol) gave the crude secondary amine **19** (564 mg, 86%) as a pale yellow oil, which was used without further purification.

IR (ATR): 3336, 2934, 2872, 1762, 1693, 1452, 1418, 1378, 1346, 1088, 763 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.07–3.98 (m, 1 H, 5-H_A), 3.51 (t, *J* = 7.3 Hz, 2 H, 1′-CH_2), 2.99–2.82 (m, 4 H, 5-H_B, 6-CH_2 and 8-H_A), 2.52 (dd, *J* = 15.1, 6.5 Hz, 1 H, 9-H_A), 2.20 (dd, *J* = 14.2, 10.5 Hz, 1 H, 8-H_B), 1.77 (ddd, *J* = 15.1, 10.5, 1.4 Hz, 1 H, 9-H_B), 1.69 (br s, 1 H, NH), 1.64–1.55 (m, 2 H, 2′-CH_2), 1.37 (s, 3 H, CH_3), 1.31 (dt, *J* = 14.7, 7.4 Hz, 2 H, 3′-CH_2), 0.92 (t, *J* = 7.4 Hz, 3 H, 4′-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.7, 156.1, 64.2, 48.2, 45.0, 43.1, 41.6, 38.6, 30.2, 23.3, 19.9, 13.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{22}N_3O_2$: 240.1707; found: 240.1713, –2.4 ppm error.

Ethyl 2-[9a-Methyl-1,3-dioxooctahydro-1*H*-imidazolidino[1,5-*d*][1,4]diazepin-2-yl]acetate (20)

Diazepine **11e** (1.0 g, 2.78 mmol) gave the crude secondary amine **20** (726 mg, 97%) as a pale yellow oil, which was used without further purification.

IR (ATR): 2977, 2936, 1771, 1744, 1707, 1452, 1381, 1348, 1208, 1155, 765 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.27 (d, *J* = 17.4 Hz, 1 H, 3′-H_A), 4.22 (d, *J* = 17.4 Hz , 1 H, 3′-H_B), 4.20 (q, *J* = 7.1 Hz, 2 H, 3′-CH_2), 4.04 (br d, *J* = 14.4 Hz, 1 H, 5-H_A), 3.01–2.85 (m, 4 H, 5-H_B, 6-CH_2 and 8-H_A), 2.58 (dd, *J* = 15.2, 6.4 Hz, 1 H, 9-H_A), 2.43 (dd, *J* = 14.1, 10.8 Hz, 1 H, 8-H_B), 1.80 (dd, *J* = 15.2, 10.7 Hz, 1 H, 9-H_B), 1.73 (br s, 1 H, NH), 1.42 (s, 3 H, CH_3), 1.27 (t, *J* = 7.2 Hz, 3 H, 4′-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.4, 167.1, 155.2, 64.9, 61.9, 48.2, 44.8, 43.3, 41.7, 39.7, 23.3, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{20}N_3O_4$: 270.1448; found: 270.1452, 1.5 ppm error.

(5*R**,8a*S**)-8a-Methyl-2-[2-(morpholin-4-yl)ethyl]-5-phenyloctahydroimidazolidino[1,5-*a*]piperazine-1,3-dione (21)

PhSH (410 µL, 4.00 mmol) was added to a stirred solution of 4-nitrosulfonamide **13b** (1.09 g, 2.00 mmol) and K_2CO_3 (829 mg, 6.00 mmol) in MeCN (50 mL) at r.t. The resulting suspension was stirred at r.t. for 16 h and the volatiles removed under reduced pressure. The residue was partitioned between H_2O (50 mL) and CH_2Cl_2 (50 mL), the two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product, which was purified by column chromatography (SiO_2, 98:2 to 95:5 CH_2Cl_2–MeOH) to give the secondary amine **21** (564 mg, 78%) as a white solid; mp 92–93 °C; R_f = 0.3 (95:5 CH_2Cl_2–MeOH).

IR (ATR): 3340, 2806, 1761, 1693, 1452, 1423, 1111, 702 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.30 (d, *J* = 4.7 Hz, 1 H, 5-H), 3.83 (d, *J* = 13.4 Hz, 1 H, 6-H_A), 3.71 (td, *J* = 6.3, 1.6 Hz, 2 H, 1′-CH_2), 3.66 (br t, *J* = 4.6 Hz, 4 H, morpholine 2-CH_2 and 6-CH_2), 3.08 (d, *J* = 12.2 Hz, 1 H, 8-H_A), 3.01 (dd, *J* = 13.4, 4.9 Hz, 1 H, 6-H_B), 2.80 (d, *J* = 12.2 Hz, 1 H, 8-H_B), 2.70–2.59 (m, 2 H, 2′-CH_2), 2.59–2.46 (m, 4 H, morpholine 3-CH_2 and 5-CH_2), 1.75 (br s, 1 H, NH), 1.09 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.9, 155.9, 139.4, 128.5, 127.4, 127.3, 67.2, 59.7, 55.1, 53.4, 52.4, 49.3, 46.5, 35.7, 20.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{27}N_4O_3$: 359.2078; found: 359.2083, 1.4 ppm error.

Denosylation of Nitrosulfonamides 13c,d; General Procedure

PhSH (2.0 equiv) was added to a stirred solution of piperazine **13c**,**d** (1.0 equiv) and K_2CO_3 (3.0 equiv) in DMF (0.1 M) at r.t. The resulting suspension was stirred at r.t. for 1 h, aq 2 M NaOH (20 mL) and EtOAc (20 mL) were added and the layers separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

(5*R**,8a*S**)-2-Benzyl-8a-methyl-5-phenyloctahydroimidazolidino[1,5-*a*]piperazine-1,3-dione (22)

Nitrosulfonamide **13c** (396 mg, 0.76 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 99:1 to 98:2 CH_2Cl_2–MeOH) to give the secondary amine **22** (145 mg, 57%) as a colourless oil; R_f = 0.2 (98:2 CH_2Cl_2–MeOH).

IR (ATR): 3337, 2937, 2865, 2809, 1760, 1697, 1436, 1418, 1348, 1113, 750, 696 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 8.0 Hz, 2 H, C_6H_5), 7.42 (d, *J* = 7.6 Hz, 2 H, C_6H_5) 7.36 (t, *J* = 7.6 Hz, 4 H, C_6H_5), 7.32–7.28 (m, 2 H, C_6H_5), 5.30 (d, *J* = 4.7 Hz, 1 H, 5-H), 4.74 (s, 2 H, 1′-CH_2), 3.80 (d, *J* = 13.4 Hz, 1 H, 6-H_A), 3.08 (d, *J* = 12.2 Hz, 1 H, 8-H_A), 3.00 (dd, *J* = 13.4, 4.9 Hz, 1 H, 6-H_B), 2.73 (d, *J* = 12.2 Hz, 1 H, 8-H_B), 1.73 (br s, 1 H, NH), 1.10 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.4, 155.6, 139.3, 136.2, 128.7, 128.5, 128.3, 127.8, 127.4, 127.4, 59.9, 52.3, 49.4, 46.5, 42.5, 20.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{22}N_3O_2$: 336.1707; found: 336.1708, 0.3 ppm error.

(5*R**,8a*S**)-2-Butyl-8a-methyl-5-phenyloctahydroimidazolidino[1,5-*a*]piperazine-1,3-dione (23)

Nitrosulfonamide **13d** (262 mg, 0.54 mmol) gave a crude product, which was purified by flash column chromatography (SiO_2, 98:2 CH_2Cl_2–MeOH) to give the secondary amine **23** (120 mg, 73%) as a colourless oil; R_f = 0.2 (98:2 CH_2Cl_2–MeOH).

IR (ATR): 3344, 2957, 2932, 1760, 1694, 1443, 1417, 1304, 1071, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 7.6 Hz, 2 H, C_6H_5 2-H and 6-H), 7.36 (t, *J* = 7.6 Hz, 2 H, C_6H_5 3-H and 5-H), 7.29 (t, *J* = 7.6 Hz, 1 H, C_6H_5 4-H), 5.30 (d, *J* = 4.5 Hz, 1 H, 5-H), 3.81 (d, *J* = 13.4 Hz, 1 H, 6-H_A), 3.65–3.51 (m, 2 H, 1′-CH_2), 3.08 (d, *J* = 12.2 Hz, 1 H, 8-H_A), 3.01 (dd, *J* = 13.4, 4.9 Hz, 1 H, 6-H_B), 2.74 (d, *J* = 12.2 Hz, 1 H, 8-H_B), 1.73 (br s, 1 H, NH), 1.71–1.61 (m, 2 H, 2′-CH_2), 1.43–1.32 (m, 2 H, 3′-CH_2), 1.09 (s, 3 H, CH_3), 0.97 (t, *J* = 7.4 Hz, 3 H, 4′-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.6, 155.9, 139.4, 128.5, 127.4, 127.4, 59.7, 52.4, 49.3, 46.5, 38.7, 30.2, 20.7, 20.0, 13.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{24}N_3O_3$: 302.1863; found: 302.1866, 0.9 ppm error.

2-Butyl-9a-methyl-7-(2-methylpropanesulfonyl)octahydro-1*H*-imidazolidino[1,5-*d*][1,4]diazepine-1,3-dione (24)

Isobutanesulfonyl chloride (39 μL, 0.30 mmol) was added to a solution of secondary amine **19** (36 mg, 0.15 mmol) and *i*-Pr_2NEt (65 μL, 0.38 mmol) in DMA (1.2 mL) at r.t. The resulting solution was stirred at r.t. for 16 h. The reaction was quenched with H_2O (0.1 mL) and the product was purified by mass-directed auto-prep (5–95% MeOH–H_2O with 0.1% ammonia buffer) to give the sulfonamide **24** (37 mg, 68%) as a colourless oil.

IR (ATR): 2959, 2933, 1766, 1700, 1450, 1319, 1141, 865, 765 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 4.00 (ddd, *J* = 14.5, 3.4, 2.4 Hz, 1 H, 5-H_A), 3.67–3.59 (m, 2 H, 6-H_A and 8-H_A), 3.41 (t, *J* = 7.1 Hz, 2 H, 1′-CH_2), 3.14 (ddd, *J* = 14.5, 10.6, 2.3 Hz, 1 H, 5-H_B), 3.09–3.01 (m, 1 H, 6-H_B), 2.80 (d, *J* = 6.5 Hz, 2 H, CH_2SO_2), 2.63 (ddd, *J* = 14.7, 9.2, 2.0 Hz, 1 H, 8-H_B), 2.31 (ddd, *J* = 15.5, 7.4, 2.0 Hz, 1 H, 9-H_A), 2.06 (hept, *J* = 6.7 Hz, 1 H, CH), 1.93 (ddd, *J* = 15.5, 9.2, 2.2 Hz, 1 H, 9-H_B), 1.54–1.44 (m, 2 H, 2′-CH_2), 1.32 (s, 3 H, 9a-CH_3), 1.28–1.18 (m, 2 H, 3′-CH_2), 0.98 (d, *J* = 6.7 Hz, 6 H, 2 × CH_3), 0.85 (t, *J* = 7.4 Hz, 3 H, 4′-CH_3).

^{13}C NMR (126 MHz, CD_3OD): δ = 177.9, 157.3, 65.2, 58.8, 48.3, 45.3, 42.7, 41.6, 39.6, 31.3, 25.8, 22.7, 22.5, 20.8, 13.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{30}N_3O_4S$: 360.1952; found: 360.1951, –0.2 ppm error.

2-Butyl-9a-methyl-7-(thiophen-3-ylmethyl)octahydro-1*H*-imidazolidino[1,5-*d*][1,4]diazepine-1,3-dione (25)

3-Thiophenecarboxaldehyde (33 μL, 0.38 mmol) was added to a solution of secondary amine **19** (36 mg, 0.15 mmol) and AcOH (17 μL, 0.30 mmol) in DMA (1.2 mL) and the resulting mixture was stirred at r.t. for 10 min. Sodium triacetoxyborohydride (95 mg, 0.45 mmol) was added and the mixture heated to 60 °C for 16 h. The reaction was quenched with H_2O (0.1 mL) and the product was purified by mass-directed auto-prep (5–95% MeOH–H_2O with 0.1% ammonia buffer) to give the piperidine **25** (37 mg, 74%) as a colourless oil.

IR (ATR): 2935, 2874, 1765, 1700, 1425, 1417, 1378, 1343, 791 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.25 (dd, *J* = 4.9, 3.0 Hz, 1 H, Ar 5-H), 7.13–7.09 (m, 1 H, Ar 2-H), 6.96 (dd, *J* = 4.9, 1.2 Hz, 1 H, Ar 4-H), 3.79 (ddd, *J* = 15.1, 3.5, 2.3 Hz, 1 H, 5-H_A), 3.58 (d, *J* 13.5 Hz, 1 H, C*H*$_A$H$_B$Ar), 3.53 (d, *J* = 13.5 Hz, 1 H, CH$_A$*H*$_B$Ar), 3.39 (t, *J* = 7.1 Hz, 2 H, 1′-CH_2), 3.08 (ddd, *J* = 15.1, 11.1, 2.0 Hz, 1 H, 5-H_B), 2.78–2.66 (m, 2 H, 6-H_A and 8-H_A), 2.35 (ddd, *J* = 13.3, 11.2, 2.3 Hz, 1 H, 6-H_B), 2.29–2.19 (m, 1 H, 9-H_A), 1.89 (ddd, *J* = 15.5, 10.4, 1.4 Hz, 1 H, 9-H_B), 1.79–1.69 (m, 1 H, 8-H_B), 1.50–1.41 (m, 2 H, 2′-CH_2), 1.25 (s, 3 H, CH_3), 1.24–1.14 (m, 2 H, 3′-CH_2), 0.84 (t, *J* = 7.4 Hz, 3 H, 4′-CH_3).

^{13}C NMR (126 MHz, CD_3OD): δ = 178.4, 157.9, 139.9, 139.4, 126.6, 124.3, 65.7, 58.0, 55.3, 51.7, 41.1, 39.4, 38.5, 31.2, 23.6, 20.8, 13.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{26}N_3O_2S$: 336.1740; found: 336.1749, 2.7 ppm error.

***N*-Benzyl-9a-methyl-2-[2-(morpholin-4-yl)ethyl]-1,3-dioxooctahydro-1*H*-imidazolidino[1,5-*d*][1,4]diazepine-7-carboxamide (26)**

Benzyl isocyanate (37 μL, 0.30 mmol) was added to a solution of secondary amine **18** (45 mg, 0.15 mmol) and *i*-Pr_2NEt (65 μL, 0.38 mmol) in DMA (1.2 mL) at r.t. The resulting solution was stirred at r.t. for 16 h. The reaction was quenched with H_2O (0.1 mL) and the product was purified by mass-directed auto-prep (5–95% MeOH–H_2O with 0.1% ammonia buffer) to give the urea **26** (45 mg, 70%) as a white solid; mp 128–130 °C.

IR (ATR): 3369, 1766, 1700, 1585, 1455, 1241, 1056, 933, 755 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.23–7.16 (m, 4 H, C_6H_5), 7.15–7.08 (m, 1 H, C_6H_5), 4.28 (d, *J* = 15.4 Hz, 1 H, C*H*$_A$H$_B$Ph), 4.24 (d, *J* = 15.4 Hz, 1 H, CH$_A$*H*$_B$Ph), 3.99 (ddd, *J* = 14.6, 4.1, 3.2 Hz, 1 H, 5-H_A), 3.81 (dt, *J* = 14.6, 3.4 Hz, 1 H, 6-H_A), 3.63 (ddd, *J* = 15.3, 8.1, 1.6 Hz, 1 H, 8-H_A), 3.55 (t, *J* = 6.2 Hz, 2 H, 1′-CH_2), 3.51–3.48 (m, 4 H, morpholine 2-CH_2 and 6-H), 3.19–3.15 (m, 1 H, 5-H_B), 3.11–3.00 (m, 2 H, 6-H_B and 8-H_B), 2.47 (t, *J* = 6.2 Hz, 2 H, 2′-CH_2), 2.37 (br s, 4 H, morpholine 3-CH_2 and 5-CH_2), 2.16 (ddd, *J* = 15.2, 8.1, 2.5 Hz, 1 H, 9-H_A), 1.86 (ddd, *J* = 15.2, 8.2, 2.3 Hz, 1 H, 9-H_B), 1.31 (s, 3 H, 9a-CH_3).

^{13}C NMR (126 MHz, CD_3OD): δ = 178.2, 159.4, 157.2, 141.5, 129.3, 128.1, 127.8, 68.0, 65.1, 56.2, 54.4, 46.3, 45.3, 43.4, 41.6, 38.6, 36.6, 21.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{31}N_5O_4Na$: 452.2274; found: 452.2260, –3.1 ppm error.

(5*R,8a*S**)-2-Butyl-7-(3-fluorobenzenesulfonyl)-8a-methyl-5-phenyloctahydroimidazolidino[1,5-*a*]piperazine-1,3-dione (27)**

3-Fluorobenzenesulfonyl chloride (40 μL, 0.30 mmol) was added to a solution of secondary amine **23** (45 mg, 0.15 mmol) and *i*-Pr_2NEt (65 μL, 0.38 mmol) in DMA (1.2 mL) at r.t. The resulting solution was stirred at r.t. for 16 h. The reaction was quenched with H_2O (0.1 mL) and the product was purified by mass-directed auto-prep (5–95% MeOH–H_2O with 0.1% ammonia buffer) to give the sulfonamide **27** (24 mg, 35%) as a white solid; mp 132–135 °C.

IR (ATR): 2937, 1766, 1699, 1445, 1419, 1348, 1187, 763, 577 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.72 (dd, *J* = 5.6, 4.0 Hz, 2 H, ArH), 7.69–7.66 (m, 1 H, ArH), 7.66–7.62 (m, 2 H, ArH), 7.55–7.49 (m, 1 H, ArH), 7.43 (t, *J* = 7.6 Hz, 2 H, ArH), 7.36 (t, *J* = 7.2 Hz, 1 H, ArH), 5.47 (d, *J* = 4.7 Hz, 1 H, 5-H), 4.69 (d, *J* = 13.0 Hz, 1 H, 8-H_A), 3.77 (dd, *J* = 11.4, 1.5 Hz, 1 H, 6-H_A), 3.60–3.48 (m, 2 H, 1′-CH_2), 2.78 (dd, *J* = 13.0, 4.7 Hz, 1 H, 8-H_B), 2.51 (d, *J* = 11.4 Hz, 1 H, 6-H_B), 1.69–1.55 (m, 2 H, 2′-CH_2), 1.42–1.29 (m, 2 H, 3′-CH_2), 1.11 (s, 3 H, CH_3), 0.97 (t, *J* = 7.4 Hz, 3 H, 4′-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.9, 162.7 (d, *J* = 253.2 Hz), 155.1, 138.0, 137.3 (d, *J* = 6.6 Hz), 131.4 (d, *J* = 7.8 Hz), 128.8, 128.0, 127.3, 123.4, 120.9 (d, *J* = 21.2 Hz), 115.0 (d, *J* = 24.2 Hz), 59.8, 51.7, 48.6, 46.7, 39.0, 30.1, 20.8, 19.9, 13.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{26}FN_3O_4SNa$: 482.1526; found: 482.1508, 3.7 ppm error.

(5*R,8a*S**)-2-Benzyl-8a-methyl-7-(1-methylpiperidin-4-yl)-5-phenyloctahydroimidazolidino[1,5-a]piperazine-1,3-dione (28)**

N-Methyl-4-piperidone (46 μL, 0.38 mmol) was added to a solution of secondary amine **22** (50 mg, 0.15 mmol) and AcOH (46 μL, 0.30 mmol) in DMA (1.2 mL) and the resulting mixture was stirred at r.t. for 10 min. Sodium triacetoxyborohydride (95 mg, 0.45 mmol) was added and the mixture heated to 60 °C for 16 h. The reaction was quenched with H_2O (0.1 mL) and the product was purified by mass-directed auto-prep (5–95% MeOH–H_2O with 0.1% ammonia buffer) to give the piperidine **28** (48 mg, 74%) as a white solid; mp 72–74 °C.

IR (ATR): 2934, 2779, 1765, 1701, 1496, 1434, 1278, 1073, 696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 8.2 Hz, 2 H, C_6H_5), 7.37–7.22 (m, 8 H, C_6H_5), 5.28 (d, *J* = 4.3 Hz, 1 H, 5-H), 4.71 (d, *J* = 14.9 Hz, 1 H , 1′-H_A), 4.67 (d, *J* = 14.9 Hz, 1 H, 1′-H_B), 3.68 (d, *J* = 12.5 Hz, 1 H, 6-H_A), 2.95–2.93 (m, 3 H, 8-H_A and piperidine 3-CH_2), 2.62 (dd, *J* = 12.5, 4.7

Hz, 1 H, 6-H_B), 2.57 (tt, *J* = 11.5, 3.7 Hz, 1 H, piperidine 4-H), 2.30–2.28 (m, 4 H, 8-H_A and NCH_3), 2.16–2.04 (m, 2 H, piperidine 3-CH_2), 1.92–1.77 (m, 2 H, piperidine 2-CH_2), 1.75–1.57 (m, 2 H, piperidine 2-CH_2), 1.10 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.1, 157.1, 141.6, 137.8, 129.4, 129.2, 128.9, 128.9, 128.6, 128.3, 62.5, 56.2, 56.1, 56.1, 51.7, 51.6, 46.1, 42.5, 28.8, 28.5, 21.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{33}N_4O_2$: 433.2604; found: 433.2602, –0.5 ppm error.

(5*R**,8a*S**)-2-Butyl-*N*-(4-methoxyphenyl)-8a-methyl-1,3-dioxo-5-phenyloctahydroimidazolidino[1,5-*a*]piperazine-7-carboxamide (29)

4-Methoxyphenyl isocyanate (39 μL, 0.30 mmol) was added to a solution of secondary amine **23** (45 mg, 0.15 mmol) and *i*-Pr_2NEt (65 μL, 0.38 mmol) in DMA (1.2 mL) at r.t. The resulting solution was stirred at r.t. for 16 h. The reaction was quenched with H_2O (0.1 mL) and the product was purified by mass-directed auto-prep (5–95% MeOH–H_2O with 0.1% ammonia buffer) to give the urea **29** (36 mg, 53%) as a white solid; mp 89–91 °C.

IR (ATR): 3331, 2955, 2932, 1766, 1697, 1509, 1416, 1230 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.56 (d, *J* = 8.0 Hz, 2 H, ArH), 7.40 (t, *J* = 7.6 Hz, 2 H, ArH), 7.36–7.25 (m, 3 H, ArH), 6.92–6.89 (m, 2 H, ArH), 5.45 (br s, 1 H, 5-H), 4.90 (d, *J* = 14.3 Hz, 1 H, 8-H_A), 4.20 (d, *J* = 13.0 Hz, 1 H, 6-H_A), 3.81 (s, 3 H, OCH_3), 3.66–3.57 (m, 2 H, 1′-CH_2), 3.44 (dd, *J* = 14.3, 5.1 Hz, 1 H, 8-H_B), 3.08 (d, *J* = 13.0 Hz, 1 H, 6-H_B), 1.74–1.63 (m, 2 H, 2′-CH_2), 1.47–1.37 (m, 2 H, 3′-CH_2), 1.16 (s, 3 H, CH_3), 1.01 (t, *J* = 7.4 Hz, 3 H, 4′-CH_3).

^{13}C NMR (126 MHz, CD_3OD): δ = 176.3, 158.2, 158.0, 157.5, 140.3, 133.1, 129.6, 128.1, 125.2, 115.2, 115.0, 61.5, 55.6, 51.9, 50.5, 45.2, 39.8, 30.9, 21.4, 20.7, 13.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{31}N_4O_4$: 451.2340; found: 451.2342, 0.4 ppm error.

(5*R**,8a*S**)-7-Cyclohexanecarbonyl-8a-methyl-2-[2-(morpholin-4-yl)ethyl]-5-phenyloctahydroimidazolidino[1,5-*a*]piperazine-1,3-dione (30)

TBTU (77 mg, 0.24 mmol) was added to a solution of cyclohexane carboxylic acid (29 mg, 0.23 mmol), secondary amine **21** (50 mg, 0.15 mmol) and *i*-Pr_2NEt (65 μL, 0.38 mmol) in DMA (1.2 mL) and the resulting mixture was stirred at r.t. for 16 h. The reaction was quenched with H_2O (0.1 mL) and the product was purified by mass-directed auto-prep (5–95% MeOH–H_2O with 0.1% ammonia buffer) to give the amide **30** (50 mg, 71%) as a white solid; mp 67–69 °C.

IR (ATR): 2928, 2852, 1766, 1701, 1446, 1144, 702 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.4 Hz, 2 H, C_6H_5 2-H and 6-H), 7.35 (t, *J* = 7.4 Hz, 2 H, C_6H_5 3-H and 5-H), 7.32–7.27 (m, 1 H, C_6H_5 4-H), 5.52 (d, *J* = 3.5 Hz, 1 H, 5-H), 5.45 (d, *J* = 14.3 Hz, 1 H, 6-H_A), 4.02 (d, *J* = 13.0 Hz, 1 H, 8-H_A), 3.79–3.73 (m, 2 H, 1′-CH_2), 3.68 (t, *J* = 4.4 Hz, 4 H, morpholine 2-CH_2 and 6-CH_2), 3.16 (d, *J* = 13.0 Hz, 1 H, 8-H_B), 2.96 (dd, *J* = 14.3, 4.0 Hz, 1 H, 6-H_B), 2.74–2.63 (m, 2 H, 2′-CH_2), 2.61–2.41 (m, 5 H, morpholine 3-CH_2 and 5-CH_2 and Cy 1-H), 1.88–1.20 (m, 10 H, Cy), 1.05 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, CD_3OD): δ = 178.0, 176.0, 157.0, 140.0, 129.5, 128.8, 128.0, 68.0, 61.2, 56.2, 54.5, 52.0, 51.6, 43.1, 41.3, 36.8, 30.5, 30.3, 26.8, 26.5, 26.3, 21.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{37}N_4O_4$: 469.2809; found: 469.2806, –0.7 ppm error.

Ethyl 2-[7-(4-Methoxybenzenesulfonyl)-9a-methyl-1,3-dioxooctahydro-1*H*-imidazolidino[1,5-*d*][1,4]diazepin-2-yl]acetate (31)

4-Methoxybenzenesulfonyl chloride (414 mg, 2.01 mmol) was added to a stirred solution of secondary amine **20** (360 mg, 1.34 mmol) and Et_3N (372 μL, 2.67 mmol) in CH_2Cl_2 (5 mL) at 0 °C at r.t. and the resulting solution was warmed to r.t. and stirred for 16 h. H_2O (10 mL) was added, the two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product, which was purified by column chromatography (eluting with 50:50 to 0:100 hexane–EtOAc) to give the sulfonamide **31** (585 mg, 99%) as a white solid; mp 134–136 °C; R_f = 0.16 (50:50 hexane–EtOAc).

IR (ATR): 2980, 2944, 1769, 1739, 1704, 1594, 1576, 1452, 1327, 1259, 1158, 1022, 769 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.9 Hz, 2 H, Ar 2-H and 6-H), 6.96 (d, *J* = 8.9 Hz, 2 H Ar 3-H and 5-H), 4.22 (d, *J* = 17.5 Hz, 1 H, 1′-H_A), 4.18 (d, *J* = 17.5 Hz, 1 H, 1′-H_B), 4.18–4.11 (m, 3 H, 3′-CH_2 and 5-H_A), 3.86 (s, 3 H, OCH_3), 3.85–3.81 (m, 2 H, 6-H_A and 8-H_A), 3.20 (ddd, *J* = 13.6, 11.2, 1.9 Hz, 1 H, 5-H_B), 2.78 (ddd, *J* = 13.1, 11.5, 1.6 Hz, 1 H, 6-H_B), 2.59 (dd, *J* = 15.5, 6.5 Hz, 1 H, 9-H_A), 2.44 (dd, *J* = 14.6, 10.0 Hz, 1 H, 8-H_B), 2.10 (ddd, *J* = 15.5, 10.0, 1.4 Hz, 1 H, 9-H_B), 1.45 (s, 3 H, CH_3), 1.22 (t, *J* = 7.2 Hz, 3 H, 4-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.8, 167.0, 163.1, 154.9, 130.2, 129.1, 114.5, 64.6, 62.0, 55.6, 48.0, 44.7, 41.7, 39.8, 39.4, 23.3, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{26}N_3O_7S$: 440.1486; found: 440.1492, 1.5 ppm error.

N-(Furan-2-ylmethyl)-2-[7-(4-methoxybenzenesulfonyl)-9a-methyl-1,3-dioxooctahydro-1*H*-imidazolidino[1,5-*d*][1,4]diazepin-2-yl]acetamide (32)

LiOH (92 mg, 3.86 mmol) was added to a stirred solution of ester **31** (565 mg, 1.29 mmol) in 4:1:1 THF–MeOH–H_2O (18 mL) at r.t. and the resulting solution was stirred at r.t. for 1 h, then concentrated under reduced pressure. H_2O (10 mL), aq 1 M HCl (10 mL) and EtOAc (20 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude carboxylic acid (530 mg, quant) as a white solid, which was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21 (br s, 1 H, CO_2H), 7.65 (d, *J* = 8.9 Hz, 2 H, Ar 2-H and 6-H), 6.96 (d, *J* = 8.9 Hz, 2 H Ar 3-H and 5-H), 4.26 (d, *J* = 17.9 Hz, 1 H, 1′-H_A), 4.22 (d, *J* = 17.9 Hz, 1 H, 1′-H_B), 4.16–4.10 (m, 1 H, 5-H_A), 3.86 (s, 3 H, OCH_3), 3.85–3.79 (m, 2 H, 6-H_A and 8-H_A), 3.20 (dd, *J* = 13.3, 11.1 Hz, 1 H, 5-H_B), 2.76 (app t, *J* = 11.6 Hz, 1 H, 6-H_B), 2.55 (dd, *J* = 15.5, 6.4 Hz, 1 H, 9-H_A), 2.40 (dd, *J* = 14.2, 9.6 Hz, 1 H, 8-H_B), 2.13–2.05 (m, 1 H, 9-H_B), 1.44 (s, 3 H, CH_3).

TBTU (77 mg, 0.24 mmol) was added to a solution of crude carboxylic acid (66 mg, 0.15 mmol), furfurylamine (20 μL, 0.23 mmol) and *i*-Pr_2NEt (65 μL, 0.38 mmol) in DMA (1.2 mL) and the resulting mixture was stirred at r.t. for 16 h. The reaction was quenched with H_2O (0.1 mL) and the product was purified by mass-directed auto-prep (5–95% MeOH–H_2O with 0.1% ammonia buffer) to give the amide **32** (46 mg, 63%) as a white solid; mp 76–78 °C.

IR (ATR): 3323, 2943, 1770, 1706, 1451, 1256, 1150, 699, 587 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.66–7.59 (m, 2 H, Ar 2-H and 6-H), 7.31 (dd, *J* = 1.9, 0.8 Hz, 1 H, furan 5-H), 7.01–6.94 (m, 2 H, Ar 3-H and 5-H), 6.23 (dd, *J* = 3.2, 1.9 Hz, 1 H, furan 4-H), 6.15–6.11 (m, 1 H, furan 3-H), 4.23 (s, 2 H, 4′-CH_2), 4.05 (d, *J* = 16.5 Hz, 1′-H_A), 4.00 (d, *J* = 16.5 Hz, 1′-H_A), 3.98 (ddd, *J* = 15.0, 3.2, 2.5 Hz, 1 H, 5-H_A), 3.77 (s, 3 H,

OCH_3), 3.73–3.65 (m, 2 H, 6-H_A and 8-H_A), 3.20–3.13 (m, 1 H, 5-H_B) 2.75 (ddd, *J* = 13.4, 11.0, 2.3 Hz, 1 H, 6-H_B), 2.57 (ddd, *J* = 14.6, 9.5, 1.6 Hz, 1 H, 8-H_B), 2.39 (ddd, *J* = 15.6, 7.2, 1.6 Hz, 1 H, 9-H_A), 1.95 (ddd, *J* = 15.6, 9.5, 2.0 Hz, 1 H, 9-H_B), 1.34 (s, 3 H, 9a-CH_3).

^{13}C NMR (126 MHz, CD_3OD): δ = 177.9, 168.1, 164.7, 156.9, 152.5, 143.3, 131.4, 130.3, 115.2, 111.3, 108.2, 65.8, 56.2, 45.6, 45.3, 42.3, 41.6, 39.8, 37.2, 22.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{27}N_4O_7S$: 491.1595; found: 491.1594, –0.1 ppm error.

Acknowledgment

We acknowledge support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no 115489, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in-kind contribution. We also thank EPSRC for a Ph.D. studentship.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378704.

References

(1) (a) Lipinski, C. A. *Drug Discovery Today* **2004**, *1*, 337. (b) Walters, W. P.; Green, J.; Weiss, J. R.; Murcko, M. A. *J. Med. Chem.* **2011**, *54*, 6405. (c) Bickerton, G. R.; Paolini, G. V.; Besnard, J.; Muresan, S.; Hopkins, A. L. *Nat. Chem.* **2012**, *4*, 90. (d) Teague, S. J.; Davis, A. M.; Leeson, P. D.; Oprea, T. *Angew. Chem. Int. Ed.* **1999**, *38*, 3743.

(2) (a) Wenlock, M. C.; Austin, R. P.; Barton, P.; Davis, A. M.; Leeson, P. D. *J. Med. Chem.* **2003**, *46*, 1250. (b) Waring, M. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2844.

(3) (a) Leeson, P. D.; Springthorpe, B. *Nat. Rev. Drug Discovery* **2007**, *6*, 881. (b) Ritchie, T. J.; Macdonald, S. J. F. *Drug Discovery Today* **2009**, *14*, 1011.

(4) (a) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752. (b) Lovering, F. *MedChemComm* **2013**, *4*, 515.

(5) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.

(6) (a) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321. (b) Ugi, I.; Heck, S. *Comb. Chem. High Throughput Screen.* **2001**, *4*, 1. (c) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53.

(7) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* **1997**, *23*, 3.

(8) (a) Nutt, R. F.; Joullie, M. M. *J. Am. Chem. Soc.* **1982**, *104*, 5852. (b) Bowers, M. M.; Carroll, P.; Joullie, M. M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 857.

(9) (a) Koopmanschap, G.; Ruijter, E.; Orru, R. V. A. *Beilstein J. Org. Chem.* **2014**, *10*, 544. (b) Rossen, K.; Sager, J.; DiMichele, L. M. *Tetrahedron Lett.* **1997**, *38*, 3183. (c) Chapman, T. M.; Davies, I. G.; Gu, B.; Block, T. M.; Scopes, D. I. C.; Hay, P. A.; Courtney, S. M.; McNeill, L. A.; Schofield, C. J.; Davis, B. G. *J. Am. Chem. Soc.* **2004**, *127*, 506. (d) Nenajdenko, V. G.; Gulevich, A. V.; Balenkova, E. S. *Tetrahedron* **2006**, *62*, 5922. (e) Banfi, L.; Basso, A.; Cerulli, V.; Rocca, V.; Riva, R. *Beilstein J. Org. Chem.* **2011**, *7*, 976. (f) Xia, L.; Li, S.; Chen, R.; Liu, K.; Chen, X. *J. Org. Chem.* **2013**, *78*, 3120.

(10) (a) Hulme, C.; Ma, L.; Romano, J. J.; Morton, G.; Tang, S.-Y.; Cherrier, M.-P.; Choi, S.; Salvino, J.; Labaudiniere, R. *Tetrahedron Lett.* **2000**, *41*, 1889. (b) Ignacio, J. M.; Macho, S.; Marcaccini, S.; Pepino, R.; Torroba, T. *Synlett* **2005**, 3051. (c) Sañudo, M.; García-Valverde, M.; Marcaccini, S.; Torroba, T. *Tetrahedron* **2012**, *68*, 2621. (d) Brockmeyer, F.; Kröger, D.; Stalling, T.; Ullrich, P.; Martens, J. *Helv. Chim. Acta* **2012**, *95*, 1857.

(11) Compton, R. G.; Bamford, C. H.; Tipper, C. F. H. *Decomposition and Isomerization of Organic Compounds*; Elsevier: Amsterdam, **1971**, 400.

(12) James, T.; Simpson, I.; Grant, J. A.; Sridharan, V.; Nelson, A. *Org. Lett.* **2013**, *15*, 6094.

(13) Bower, J. F.; Rujirawanich, J.; Gallagher, T. *Org. Biomol. Chem.* **2010**, *8*, 1505.

(14) (a) Marion, N.; Ramón, R. S.; Nolan, S. P. *J. Am. Chem. Soc.* **2008**, *131*, 448. (b) Au(IPr)Cl = Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I).

(15) Newman, H. *J. Org. Chem.* **1965**, *30*, 1287.

(16) (a) Varia, S. A.; Schuller, S.; Sloan, K. B.; Stella, V. J. *J. Pharm. Sci.* **1984**, *73*, 1068. (b) Sudo, R. T.; Carmo, P. L. D.; Trachez, M. M.; Zapata-Sudo, G. *Basic Clin. Pharmacol. Toxicol.* **2008**, *102*, 308. (c) Edmunds, J. J.; Klutchko, S.; Hamby, J. M.; Bunker, A. M.; Connolly, C. J. C.; Winters, R. T.; Quin, J.; Sircar, I.; Hodges, J. C. *J. Med. Chem.* **1995**, *38*, 3759.

(17) Use of EtOH as a solvent led to formation of a mixture of the desired trifluoroacetamides and the corresponding secondary amines; the presence of the phenyl substituent presumably slowed the Mumm rearrangement, which led to attack of the intermediate imidate by EtOH.

(18) CCDC-1054376 (zwitterion **16**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; E-mail: deposit@ccdc.cam.ac.uk.

(19) (a) European Lead Factory; https://www.europeanlead-factory.eu/ Accessed 09/02/2015. For our related work on the ELF project, see: (b) Craven, P.; Aimon, A.; Dow, M.; Fleury-Bregeot, N.; Guilleux, R.; Morgentin, R.; Roche, D.; Kalliokoski, T.; Foster, R.; Marsden, S. P.; Nelson, A. *Bioorg. Med. Chem.* **2015**, *23*, 2629.