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# Exploitation of the Ugi–Joullié reaction in the synthesis of libraries of drug-like bicyclic hydantoins

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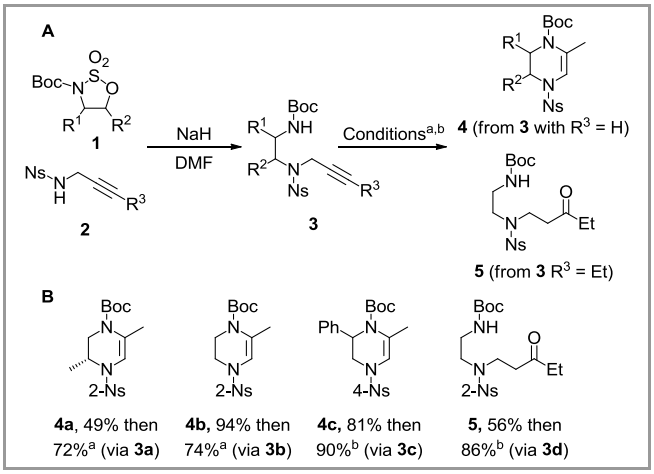
**Abstract:** A general and efficient method for the synthesis of drug-like fused bicyclic hydantoins is reported. An Ugi–Joullié reaction / cyclisation sequence was exploited as the key complexity-generating process in which trifluoroacetic acid was employed as synthetic equivalent for chloroformic 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 >600 compounds for addition to the screening collection of the European Lead Factory.

**Key words:** Multicomponent reactions; Scaffolds; Libraries; Ugi reaction; Hydantoin.

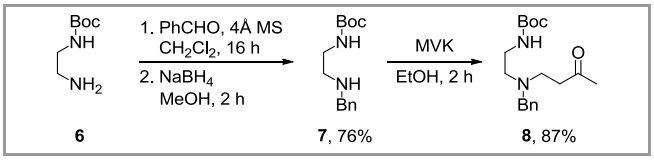
Controlling molecular properties is crucial in drug discovery, and guidelines have been developed to direct medicinal chemists towards drug-like chemical space.[1] Key properties, such as molecular weight,[2] lipophilicity[2,3] and the fraction of $sp^3$-hybridised carbons[4] correlate strongly with 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[13] **1** (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 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]




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

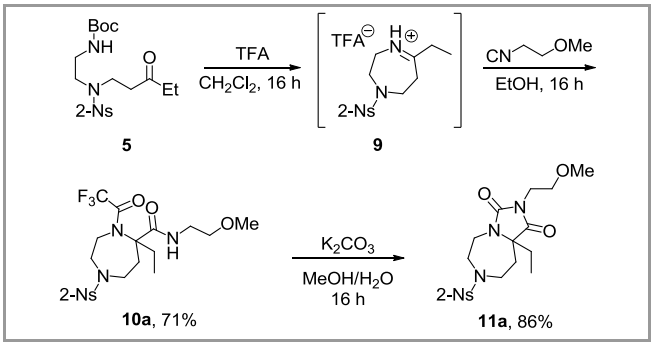
In order to assess the effect of a basic amine on the Ugi-Joullié reaction, we also prepared the benzyl-protected amino ketone **8** (Scheme 2). Reductive amination of benzaldehyde with the amine **6**, to give **7**, was followed by aza-Michael reaction with methyl vinyl ketone to give the *β*-amino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




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

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 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 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 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 (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 (**5**) and benzyl protected (**8**) substrates may thus be exploited in the synthesis of bicyclic hydantoins.

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).

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**-**e** in 52 to 98% 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** 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).

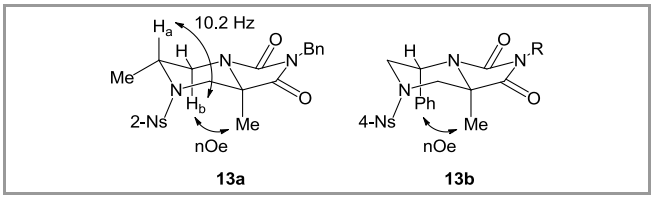
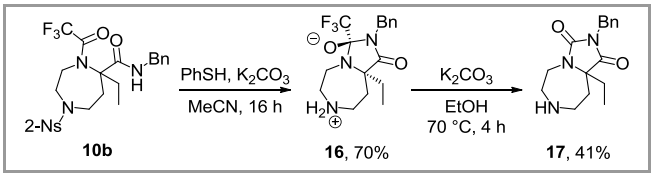



**Figure 1.** Determination of the relative configuration of **13a** and **13b**

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 eq. 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.




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

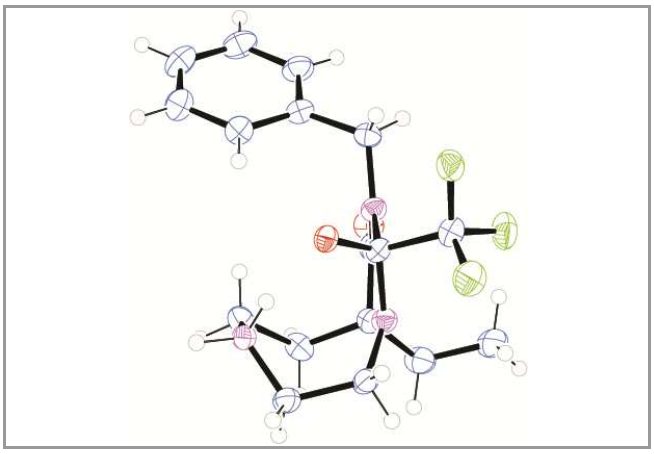
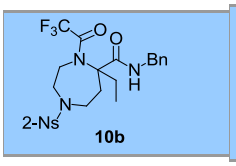
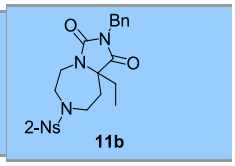
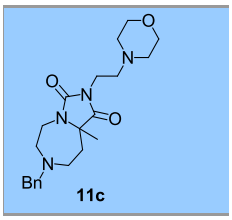
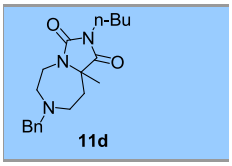
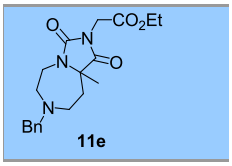
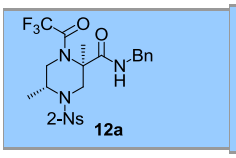
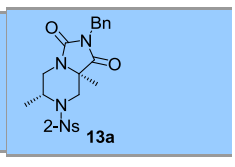
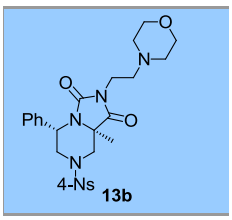
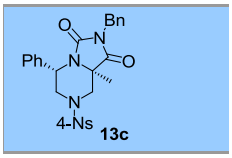
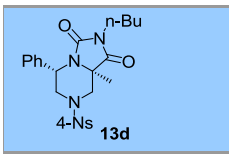
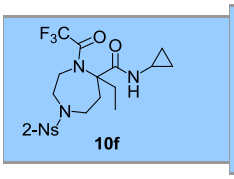
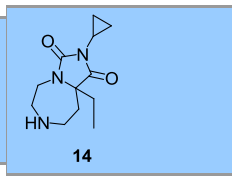
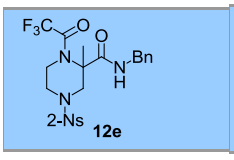
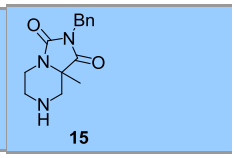


**Figure 2.** X-ray crystal structure of the stable zwitterion **16** (CCDC 1054376).

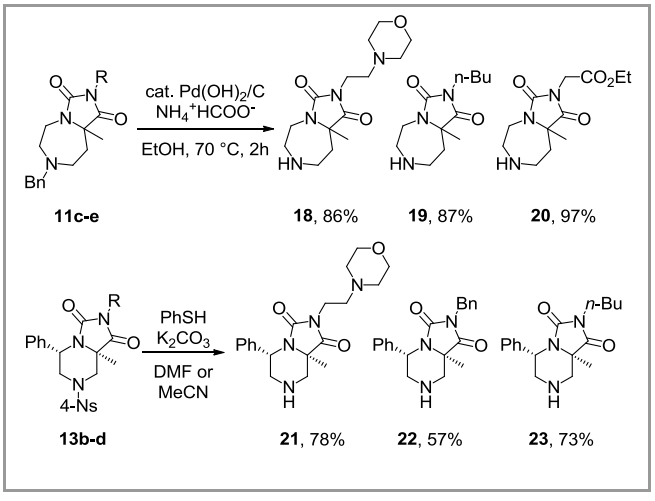
Table 1 Scope of the synthesis of bicyclic hydantoins

| 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] |

| | | | | | |
|---|---|---|---|---|---|
| 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] Reaction conditions: (A1) Isonitrile (2.0 eq.), EtOH, rt; (A2) Isonitrile (2.0 eq.), $CH_2Cl_2$, rt, 1 h, then $Et_3N$ (5.0 eq.), 2 h. [b] Reaction conditions: (B1) $K_2CO_3$ (10 eq.), MeOH/$H_2O$, rt, 16 h; (B2) $K_2CO_3$ (5.0 eq.), EtOH, 70 °C; (B3) PhSH (1.2 eq.) $K_2CO_3$ (3.0 eq.), DMF, rt. [c] Product isolated by flash column chromatography. [d]Yield over 2 steps.

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.




**Scheme 5.** Deprotection of the molecular scaffolds.

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.

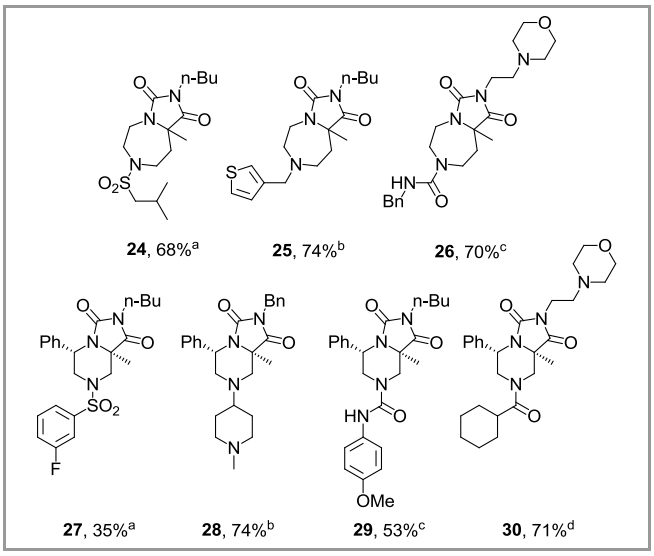
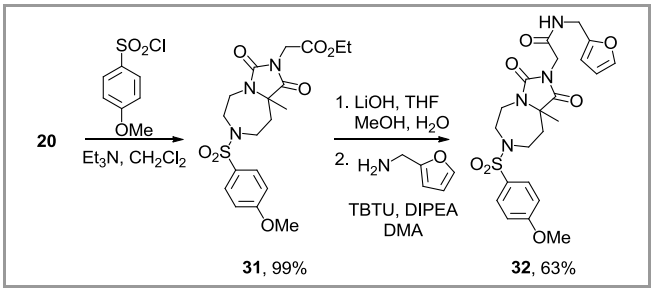



**Figure 3.** Exemplar decorated scaffolds. [a]Method: Sulfonyl chloride, DIPEA, DMA, rt, 16 h. [b]Method: Aldehyde/ketone, $NaBH(OAc)_3$, AcOH, DMA, 60 °C, 16 h. [c]Method: Isocyanate,

DIPEA, DMA, rt, 16 h. [d]Method: Carboxylic acid, TBTU, DIPEA, DMA, rt, 16 h.

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).




**Scheme 6.** Diversification of **20**

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 methodology 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[18]. 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 the case of the library of hydantoins with a fused six-membered heterocyclic ring, a total of 620 screening compounds was subsequently produced, with a success rate of 91% in the final functionalisation step.

In this paper, the development of methodology for the synthesis of bicyclic fused hydantoins via an Ugi–Joullié reaction has been described. This led to the successful synthesis of >600 novel compounds that will be added to the European Lead Factory screening collection (the Joint European Compound Library, JECL).

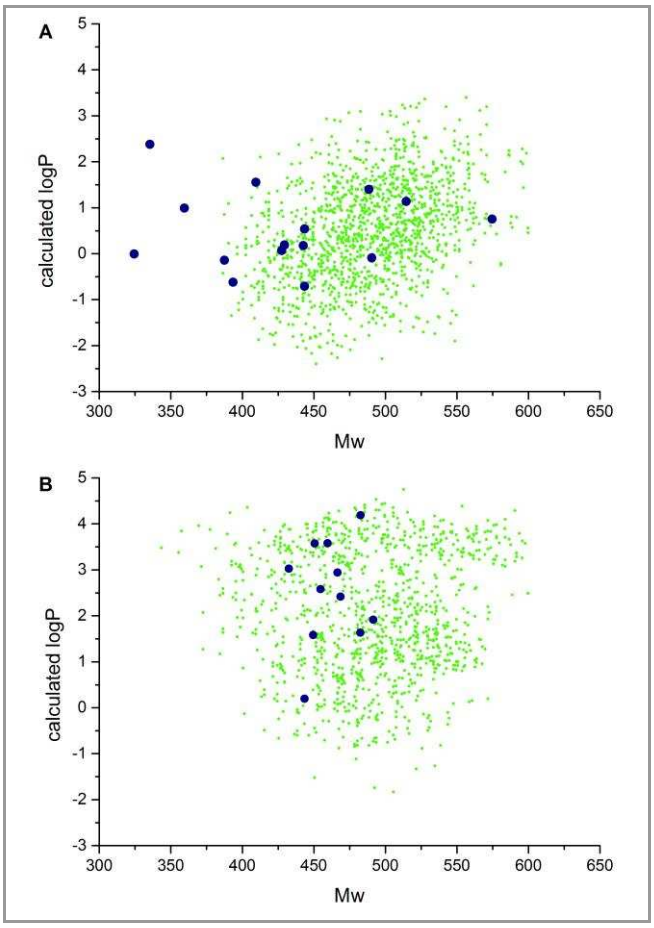



**Figure 4**. Molecular properties of exemplar screening compounds synthesised during validation work (blue, enlarged for clarity) and compounds nominated for library production (green). Panel A: Library based on hydantoins with a fused seven-membered heterocycle. Panel B: Library based on hydantoins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

All non-aqueous reactions were performed under an atmosphere of nitrogen unless otherwise stated. Tetrahydrofuran (THF), $CH_2Cl_2$, toluene and $CH_3CN$ were dried and purified by means of a Pure Solv MD solvent purification system (Innovative Technology Inc.). Anhydrous N,N-dimethylformamide (DMF) and 1,4-dioxane were obtained in SureSeal bottles from Sigma-Aldrich. All other solvents used were of chromatography or analytical grade. Petrol refers to petroleum spirit (b.p. 40-60 °C). Commercially available starting materials were obtained from Sigma-Aldrich, Fluka, Acros or Alfa-Aesar and were used without purification unless stated. Thin layer chromatography (TLC) was carried out on aluminium backed silica (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. Infrared spectra were recorded on a Perkin-Elmer 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 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**

Sodium hydride (60% suspension in mineral oil, 1.1 eq.) was added in one portion to nitrobenzenesulfonamide **2** (1.1 eq.) in DMF (0.2 M) at room temperature under $N_2$. The resulting suspension was stirred for 10 min, then cyclic sulfamidate **1** (1.0 eq.) was added in one portion. The resulting suspension was stirred at room temperature for 16 h. The reaction mixture was acidified with 5M $HCl_{(aq)}$ (6 eq.), stirred for 1 h and basified with $K_2CO_{3(aq)}$, then extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which was purified by column chromatography.

**tert-Butyl N-[(2R)-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 (5R)-5-methyl-2,2-dioxo-1,2λ$^6$,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 a yellow solid. $R_f$ = 0.14 ($CH_2Cl_2$); IR (ATR) 3428, 3291, 2979, 1706, 1544, 1367, 1159, 584 cm$^{-1}$; $[\alpha]_D^{28}$ –39 (c = 0.28, MeOH); $^{1}H$ NMR (500 MHz, $CDCl_3$) δ 8.15 (dd, J 7.4, 1.6, 1H, Ns 3-H), 7.73-7.66 (m, 2H, Ns 4-H and 5-H), 7.64 (dd, J 7.2, 2.0, 1H, Ns 6-H), 4.90 (t, J 6.7, 1H, NH), 4.19 (dd, J 18.9, 2.4, 1H, 1'-$H_A$), 4.16-4.07 (m, 2H, 1'-$H_B$ and 2-H), 3.28 (app t, J 6.7, 2H, 1-$H_2$), 2.21 (t, J 4.2, 1H, 3'-H), 1.40 (s, 9H, $^{t}$Bu), 1.20 (d, J 6.8, 3H, Me); $^{13}C$ NMR (126 MHz, CDCl3) 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 not observed; HRMS (ESI): m/z calcd for $C_{17}H_{23}N_3O_6S$ $[M+H]^+$: 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 a yellow solid. $R_f$ = 0.4 ($CH_2Cl_2$); IR (ATR) 3289, 2978, 1697, 1591, 1543, 1365, 1163, 589 cm$^{-1}$; $^{1}H$ NMR (500 MHz, $CDCl_3$) δ 8.07 (dd, J 7.4, 1.7, 1H, Ns 3-H), 7.76-7.68 (m, 2H, Ns 4-H and 5-H), 7.66 (dd, J 7.4, 1.7, 1H, Ns 6-H), 4.88 (br s, 1H, NH), 4.27 (d, J 2.2, 2H, 1'-$H_2$), 3.55 (t, J 5.9, 2H, 2-$H_2$), 3.38 (br. s, 2H, 1-$H_2$), 2.22 (t, J 2.2, 1H, 3'-H), 1.44 (s, 9H, $^{t}$Bu); $^{13}C$ NMR (126 MHz, CDCl3) 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 a white solid. $R_f$ = 0.3 (80:20 hexane—EtOAc); $^{1}H$ NMR (500 MHz; $CDCl_3$) δ 8.33-8.31 (m, 2H, Ns 3-H and 5-H), 8.02-7.99 (m, 2H, Ns 2-H and 4-H), 7.38-7.35 (m, 2H, Ph), 7.32-7.29 (m, 3H, Ph), 5.31 (br s, 1H, NH), 4.94 (br s, 1H, 1-H), 4.28 (d, J 18.2, 1H, 1'-$H_A$), 4.14-4.11 (m, 1H, 1'-$H_B$), 3.56 (dd, J 14.1, 10.0, 1H, 2-$H_A$), 3.34 (dd, J 14.1, 4.4, 1H, 2-$H_B$), 2.06-2.05 (m, 1H, 3'-H), 1.45 (s, 9H, $^{t}$Bu); $^{13}C$ 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 calcd for $C_{22}H_{25}N_3O_6S$ $[M+H]^+$: 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 Petrol–$Et_2O$–$CHCl_3$) to give the sulfonamide **3d**[12] (3.78 g, 56%) as a yellow solid. $R_f$ = 0.65 (50:50 Petrol–EtOAc); IR (ATR) 3419, 2978, 2937, 1708, 1545, 1366, 1167 cm$^{-1}$; $^{1}H$ NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, J 7.4, 1.8, 1H, Ns 3-H), 7.72-7.65 (m, 2H, Ns 4-H and 5-H), 7.63 (dd, J 7.4, 1.8, 1H, Ns 6-H), 4.82 (s, 1H, NH), 4.20 (s, 2H, 1'-$H_2$), 3.51 (t, J 5.8, 2H, 2-$H_2$), 3.36 (q, J 5.8, 2H, 1-$H_2$), 2.04 (q, J 7.5, 2H, 4'-$H_2$), 1.44 (s, 9H, $^{t}$Bu), 0.98 (t, J 7.5, 3H, 5'-Me); $^{13}C$ NMR (126 MHz, CDCl3) 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 CO 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 eq.) 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 rt 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 eq.) 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 rt and concentrated in vacuo to give the crude product.

**tert-Butyl (3R)-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 petrol–$Et_2O$–$CHCl_3$) to give the tetrahydropyrazine **4a** (1.75 g, 72%) as an orange oil, $R_f$ = 0.81 (30:70 petrol–EtOAc); IR (ATR) 3099, 2977, 2933, 1701, 1545, 1366, 1246, 1176; $[\alpha]_D^{28}$ +182 (c = 0.06, MeOH); $^1$H NMR (500 MHz; $CDCl_3$) δ 8.07-7.93 (m, 1H, Ns 3-H), 7.80-7.69 (m, 2H, Ns 4-H and 5-H), 7.68-7.60 (m, 1H, Ns 6-H), 5.95 (app t, J 1.1, 1H, 5-H), 4.36-4.27 (m, 1H, 3-H), 4.19 (dd, J 13.1, 1.9, 1H, 2-$H_A$), 2.58 (dd, J 13.1, 2.3, 1H, 2-$H_B$), 2.11 (d, J 1.1, 3H, 6-Me), 1.50 (s, 9H, $^t$Bu), 1.17 (d, J 6.6, 3H, 3-Me); $^{13}$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 calcd for $C_{17}H_{23}N_3O_6S$ $[M+H]^+$: 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 petrol—EtOAc) to give the tetrahydropyrazine **4b**[12] (4.61 g, 74%) as a yellow solid. $R_f$ = 0.61 (50:50 Petrol–EtOAc); IR (ATR) 2977, 2933, 1702, 1455, 1369, 1171, 776 cm$^{-1}$; $^1$H NMR (500 MHz; $CDCl_3$) δ 7.99 (dd, J 7.4, 1.7, 1H, Ns 3-H), 7.78-7.70 (m, 2H, Ns 4-H and 5-H), 7.66 (dd, J 7.4, 1.7, 1H, Ns 6-H), 6.01 (s, 1H, 5-H), 3.68-3.64 (m, 2H, 3-$H_2$), 3.64-3.60 (m, 2H, 2-$H_2$), 2.09 (s, 3H, Me), 1.50 (s, 9H, $^t$Bu); $^{13}$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 petrol—EtOAc) to give the tetrahydropyrazine **4c**[12] (4.11 g, 90%) as an orange solid. $R_f$ = 0.29 (80:20 petrol—EtOAc); $^1$H NMR (500 MHz; $CDCl_3$) δ 8.12 (d, J 8.8, 2H, Ns 3-H and 5-H), 7.67 (d, J 8.8, 2H, Ns 2-H and 4-H), 7.12-7.08 (m, 3H, Ph), 7.32-7.29 (d, J 6.9, 2H, Ph 2-H and 6-H), 6.00 (s, 1H, 5-H), 5.59 (br s, 1H, 2-H), 4.33 (d, J 12.6, 1H, 3-$H_A$), 3.44 (dd, J 12.6, 3.6, 1H, 3-$H_B$), 2.17 (s, 3H, Me), 1.43 (s, 9H, $^t$Bu); $^{13}$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 calcd for $C_{22}H_{25}N_3NaO_6S$ $[M+Na]^+$: 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 petrol—EtOAc) to give the ketone **5**[12] (3.39 g, 86%) as an orange solid. $R_f$ = 0.26 (50:50 Petrol–EtOAc); IR (ATR) 3403, 2978, 1709, 1544, 1367, 1164 cm$^{-1}$; $^1$H NMR (500 MHz; $CDCl_3$) δ 8.01 (d, J 7.3, 1H, Ns 3-H), 7.76-7.67 (m, 2H, Ns 4-H and 5-H), 7.63 (d, J 7.3, 1H, Ns 6-H), 4.85 (t, J 6.3, 1H, NH), 3.56 (t, J 6.3, 2H, 2-$H_2$), 3.40 (t, J 6.5, 2H, 2'-$H_2$), 3.31 (q, J 6.3, 2H, 1'-$H_2$), 2.81 (t, J 6.5, 2H, 1'-$H_2$), 2.43 (q, J 7.3, 2H, 4'-$H_2$), 1.43 (s, 9H, $^t$Bu), 1.03 (t, J 7.3, 3H, 5'-$H_3$); $^{13}$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 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 room temperature under $N_2$. The resulting solution was stirred for at room temperature 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 room temperature and stirred for at room temperature for 2 h then concentrated under reduced pressure. Water (20 mL), 1M $HCl_{(aq)}$ (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 2M $NaOH_{(aq)}$ (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give a crude secondary amine **7** (3.91 g, 76%) as a pale yellow oil that was used without further purification. $^1$H NMR (500 MHz; $CDCl_3$) δ 7.38–7.32 (m, 4H, Ph), 7.30–7.26 (m, 1H, Ph), 5.01 (br s, 1H, NH), 3.81 (s, 2H, 1'-$H_2$), 3.26 (app. d, J 5.5, 2H, 1-$H_2$), 2.78 (t, J 5.5, 2H, 2-$H_2$), 1.47 (s, 9H, $^t$Bu), 1.44 (br s, 1H, NH). 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 room temperature 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 petrol—EtOAc); IR (ATR) 3367, 2975, 2931, 2813, 1702, 1495, 1452, 1390, 1363, 1246, 1165, 1049, 964, 734, 698 cm$^{-1}$; $^1$H NMR (500 MHz; $CDCl_3$) δ 7.35–7.30 (m, 2H, Ph), 7.30–7.24 (m, 3H, Ph), 4.95 (br s, 1H, NH), 3.58 (s, 2H, $CH_2$Ph), 3.20 (app. d, J 5.5, 2H,

1'-$H_2$), 2.80 (t, J 6.9, 2H, 1-$H_2$), 2.60 (t, J 6.9, 2H, 2-$H_2$), 2.55 (t, J 5.5, 2H, 2'-$H_2$), 2.10 (s, 3H, 4-Me), 1.46 (s, 9H, $^t$Bu); $^{13}$C NMR (126 MHz, CDCl3) 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 calcd for $C_{18}H_{29}N_2O_3$ $[M+H]^+$: 321.2178; found: 321.2187, 2.8 ppm error.

**3-CR Ugi- Joullié Reaction: General Procedure A**

**Method A1:** TFA was added to a stirred solution of substrate **4** or **5** (1.0 eq.) in $CH_2Cl_2$ (0.1 M) at room temperature 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 eq.) was added and the reaction stirred at room temperature until completion was observed by TLC, then concentrated under reduced pressure.

**Method A2:** TFA was added to a stirred solution of substrate **4c** (1.0 eq.) in $CH_2Cl_2$ (0.1 M) at room temperature 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 eq.) was added and the reaction stirred at room temperature until completion was observed by TLC. Then, $Et_3N$ (5.0 eq.) was added and the resulting solution stirred at room temperature for 2 h. Water was added, the two layers were separated and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product

**N-Benzyl-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 petrol—EtOAc) to give the trifluoroacetamide **10a** (380 mg, 71%) as a yellow oil. $R_f$ = 0.26 (20:80 Petrol–EtOAc); IR (ATR) 3280, 2937, 1742, 1698, 1682, 1545, 1372, 1162 cm$^{-1}$; $^1$H NMR (500 MHz; $CDCl_3$) δ 8.01-7.92 (m, 1H, Ns 3-H), 7.77-7.63 (m, 3H, Ns 4-H, 5-H and 6-H), 5.99 (t, J 4.7, 1H, NH), 4.20 (dd, J 16.5, 5.9, 1H, 3-$H_A$), 4.15-4.03 (m, 1H, 2-$H_A$), 3.86 (dd, J 14.1, 6.7, 1H, 7-$H_A$), 3.63-3.54 (m, 1H, 7-$H_B$), 3.53-3.43 (m, 4H, 2-$H_B$, 3-$H_B$ and 1'-$H_2$), 3.42-3.30 (m, 5H, 2'-$H_2$ and 4'-Me), 2.72-2.51 (m, 2H, ethyl 1-$H_2$), 1.93 (dd, J 18.7, 6.7, 1H, 6-$H_A$), 1.65 (dt, J 18.7, 7.3, 1H, 6-$H_B$), 0.93 (t, J 7.2, 3H, ethyl 2-Me); $^{13}$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 not observed; $^{19}$F NMR (282 MHz, $CDCl_3$) δ -68.4; HRMS (ESI): m/z calcd for $C_{19}H_{25}F_3N_4O_7S$ $[M+H]^+$: 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 petrol—EtOAc) to give the trifluoroacetamide **10b**[12] (710 mg, 80%) as a white solid. $R_f$ = 0.44 (50:50 Petrol–EtOAc); IR (ATR) 3422, 2977, 1695, 1666, 1543, 1371, 1152 cm$^{-1}$; $^1$H NMR (500 MHz; $CDCl_3$) δ 7.97 (dd, J 10.1, 4.9, 1H, Ns 3-H), 7.78-7.70 (m, 2H, Ns 4-H and 5-H), 7.68 (dd, J 7.4, 1.6, 1H, Ns 6-H), 7.41-7.26 (m, 5H, Ph), 5.92 (t, J 5.2, 1H, NH), 4.54-4.39 (m, 2H, 1'-$H_2$), 4.25 (dd, J 16.8, 5.7, 1H, 3-$H_A$), 4.11 (dd, J 14.4, 5.7, 1H, 2-$H_A$), 3.90 (dd, J 14.8, 7.0, 1H, 7-$H_A$), 3.64 (dd, J 14.8, 10.7, 1H, 7-$H_B$), 3.52 (dd, J 16.8, 9.0, 1H, 3-$H_B$), 3.39 (dd, J 14.4, 9.0, 1H, 2-$H_B$), 2.76-2.56 (m, 2H, ethyl 1-$H_2$), 1.94 (dd, J 16.8, 7.0, 1H, 6-$H_A$), 1.69-1.58 (m, 1H, 6-$H_B$), 0.96 (t, J 7.2, 3H, ethyl 2-Me); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 170.7, 157.0 (d, J 35.5), 148.1, 137.8, 133.9, 132.5, 131.9, 130.5, 128.9, 127.7, 124.5, 116.3 (q, J 287.9), 69.2, 49.8, 48.5, 44.0, 43.9, 37.4, 26.9, 7.9, benzyl C-2 and benzyl C-6 not observed; $^{19}$F NMR (282 MHz, $CDCl_3$) δ -68.3.

**(2R,5R)-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 petrol—EtOAc) to give the trifluoroacetamide **12a** (356 mg, 77%) as a white solid. $R_f$ = 0.40 (30:70 Petrol–EtOAc); IR (ATR) 3367, 2935, 1699, 1543, 1362, 1216, 1154 cm$^{-1}$; $[\alpha]_D^{28}$ 49 (c = 0.05, MeOH); $^1$H NMR (500 MHz; $CDCl_3$) δ 8.15-8.10 (m, 1H, Ns 3-H), 7.81-7.73 (m, 2H, Ns 4-H and 5-H), 7.73-7.68 (m, 1H, Ns 6-H), 7.39-7.33 (m, 2H, Ph 3-H and 5-H), 7.32-7.25 (m, 3H, Ph 2-H, 4-H and 6-H), 6.18 (t, J 5.3, 1H, NH), 4.52 (dd, J 14.9, 5.3, 1H, 1'-$H_A$), 4.37-4.31 (m, 1H, 5-H), 4.28 (dd, J 14.9, 5.3, 1H, 1'-$H_B$), 3.99 (d, J 14.2, 1H, 3-$H_A$), 3.90 (dd, J 14.7, 4.7, 1H, 6-$H_A$), 3.57-3.47 (m, 2H, 3-$H_B$ and 6-$H_B$), 1.31-1.27 (m, 6H, 2-Me and 5-Me); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.2, 157.3 (d, J 36.3), 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), 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 calcd for $C_{22}H_{23}F_3N_4O_6S$ $[M+H]^+$: 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 petrol—EtOAc) to give the trifluoroacetamide **10f** (690 mg, 66%) as a white

solid. $R_f$ = 0.36 (30:70 Petrol–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, 1H, Ns 3-H), 7.68-7.61 (m, 2H, Ns 4-H and 5-H), 7.59 (dd, J 7.5, 1.7, 1H, Ns 6-H), 5.75 (s, 1H, NH), 4.13 (dd, J 16.7, 5.7, 1H, 3-$H_A$), 4.01 (dd, J 14.3, 5.7, 1H, 2-$H_A$), 3.78 (dd, J 14.7, 6.8, 1H, 7-$H_A$), 3.53 (dd, J 14.7, 10.7, 1H, 7-$H_B$), 3.39 (dd, J 16.7, 8.9, 1H, 3-$H_B$), 3.29 (dd, J 14.3, 8.9, 1H, 2-$H_B$), 2.61-2.54 (m, 1H, 1'-H), 2.53-2.44 (m, 2H, ethyl 1-$H_2$), 1.78 (dd, J 16.4, 6.8, 1H, 6-$H_A$), 1.54-1.42 (m, 1H, 6-$H_B$), 0.85 (t, J 7.4, 3H, ethyl 2-Me), 0.73-0.63 (m, 2H, 2'-$H_A$ and 3'-$H_A$), 0.51-0.44 (m, 1H, 2'-$H_B$), 0.40-0.31 (m, 1H, 3'-$H_B$); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 172.3, 157.0 (d, J 35.6), 148.1, 133.9, 132.5, 132.0, 130.5, 124.4, 116.3 (q, J 288.4), 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 calcd for $C_{19}H_{23}F_3N_4O_6S$ $[M+H]^+$: 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 a white solid. $R_f$ = 0.53 (30:70 Petrol–EtOAc); IR (ATR) 3368, 2937, 1699, 1673, 1542, 1370, 1216, 1145, 732 $cm^{-1}$; $^1H$ NMR (500 MHz; $CDCl_3$) δ 8.03 (dd, J 7.6, 1.2, 1H, Ns 3-H), 7.81-7.72 (m, 2H, Ns 4-H and 5-H), 7.70 (dd, J 7.6, 1.3, 1H, Ns 6-H), 7.43-7.35 (m, 2H, Ph 2-H and 6-H), 7.34-7.25 (m, 3H, Ph 3-H, 4-H and 5-H), 6.20 (t, J 5.0, 1H, NH), 4.52-4.36 (m, 2H, 1'-$H_2$), 4.03-3.92 (m, 1H, 5-$H_A$), 3.88-3.75 (m, 3H, 3-$H_A$, 5-$H_B$ and 6-$H_A$), 3.70 (d, J 13.8, 1H, 3-$HB_b$), 3.59-3.46 (m, 1H, 6-$H_B$), 1.72 (s, 3H, Me); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 169.2, 156.9 (d, J 36.6), 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), 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 eq.) was added to a stirred solution of substrate **10** or **12** (1.0 eq.) in 2:1 MeOH/$H_2O$ (0.05 M) and stirred at room temperature overnight before being concentrated under reduced pressure, diluted with water and extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product.

**Method B2:** The trifluoroacetamide from method A was dissolved in EtOH (0.05M), $K_2CO_3$ (5.0 eq.) was added and the resulting mixture stirred at 70 °C for 16 h, cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between water and $CH_2Cl_2$, the two layers were separated and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

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

**9a-Ethyl-2-(2-methoxyethyl)-7-(2-nitrobenzenesulfonyl)-octahydro-1H-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 petrol—EtOAc) to give the hydantoin **11a** (280 mg, 86%) as a yellow oil. $R_f$ = 0.26 (20:80 Petrol–EtOAc); IR (ATR) 2936, 1769, 1708, 1544, 1451, 1368, 1165 $cm^{-1}$; $^1H$ NMR (500 MHz; $CDCl_3$) δ 8.01 (dd, J 7.6, 1.6, 1H, Ns 3-H), 7.77-7.69 (m, 2H, Ns 4-H and 5-H), 7.67 (dd, J 7.2, 1.8, 1H, Ns 6-H), 4.25-4.16 (m, 1H, 5-$H_A$), 3.91-3.82 (m, 2H, 6-$H_A$ and 8-$H_A$), 3.81-3.70 (m, 2H, 1'-$H_2$), 3.62-3.55 (m, 2H, 6-$H_B$ and 8-$H_B$), 3.32 (s, 3H, 4'-Me), 3.19-3.09 (m, 2H, 2'-$H_2$), 2.69-2.57 (m, 2H, 5-$H_B$ and 9-$H_A$), 2.11-2.02 (m, 1H, 9-$H_B$), 1.92 (dq, J 14.6, 7.3, 1H, ethyl 1-$H_A$), 1.74 (dq, J 14.6, 7.3, 1H, ethyl 1-$H_B$), 0.80 (t, J 7.3, 3H, ethyl 2-Me); $^{13}C$ 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 calcd for $C_{18}H_{24}N_4O_7S$ $[M+H]^+$: 441.1444; found: 441.1446, –0.5 ppm error.

**2-Benzyl-9a-ethyl-7-(2-nitrobenzenesulfonyl)-octahydro-1H-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 petrol—EtOAc) to give the hydantoin **11b** (200 mg, 36%) as a white solid. $R_f$ = 0.43 (20:80 Petrol–EtOAc); IR (ATR) 2927, 1767, 1709, 1544, 1449, 1366, 1165 $cm^{-1}$; $^1H$ NMR (500 MHz; $CDCl_3$) δ 8.01 (dd, J 7.6, 1.3, 1H, Ns 3-H), 7.86-7.60 (m, 3H, Ns 4-H, 5-H and 6-H), 7.50-7.18 (m, 5H, Ph), 4.74-4.63 (m, 2H, 1'-$H_2$), 4.28-4.15 (m, 1H, 5-$H_A$), 3.97-3.77 (m, 2H, 6-$H_A$ and 8-$H_A$), 3.23-3.04 (m, 2H, 6-$H_B$ and 5-$H_B$), 2.68-2.48 (m, 2H, 8-$H_B$ and 9-$H_A$), 2.13-2.00 (m, 1H, 9-$H_B$), 1.89 (dq, J 14.7, 7.4, 1H, ethyl 1-$H_A$), 1.73 (dq, J 14.7, 7.4, 1H, ethyl 1-$H_B$), 0.64 (t, J 7.4, 3H, ethyl 2-Me); $^{13}C$ 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 calcd for $C_{22}H_{24}N_4O_6S$ $[M+H]^+$: 473.1495; found: 473.1490, –1.1 ppm error.

**7-Benzyl-9a-methyl-2-[2-(morpholin-4-yl)ethyl]-octahydro-1H-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 $cm^{-1}$; $^1H$ NMR (500 MHz; $CDCl_3$) δ 7.36–7.25 (m, 5H, Ph), 4.01–3.92 (ddd, J 13.3, 3.0, 2.3, 1H, 5-$H_A$), 3.76–3.60 (m, 7H, 1'-$H_2$, morpholine 2-$H_2$ and 6-$H_2$ and $CH_AH_BPh$), 3.57 (d, J 13.3, 1H, $CH_AH_BPh$), 3.10 (ddd, J 13.3, 11.2, 1.6, 1H, 5-$H_B$), 2.82 (br d, J 12.9, 1H, 6-$H_A$), 2.74 (dd, J 13.3, 7.4, 1H, 8-$H_A$), 2.67–2.45 (m, 7H, 6-$H_B$, 2'-$H_2$ and morpholine 3-$H_2$ and 5-$H_2$), 2.42 (dd, J 15.1, 7.3, 1H, 9-$H_A$), 2.05 (dd, J 13.3, 10.3, 1H, 8-$H_B$), 1.96 (dd, J 15.1, 10.2, 1H, 9-$H_B$), 1.40 (s, 3H, Me); $^{13}C$ 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 calcd for $C_{21}H_{31}N_4O_3$ $[M+H]^+$: 387.2391; found: 387.2396, 1.3 ppm error.

**7-Benzyl-2-butyl-9a-methyl-octahydro-1H-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, 5H, Ph), 3.95 (ddd, 14.9, 3.4, 2.2, 1H, 5-$H_A$), 3.59 (d, J 13.3, 1H, $CH_AH_BPh$), 3.54 (d, J 13.3, 1H, $CH_AH_BPh$), 3.51 (t, J 7.3, 2H, 1'-$H_2$), 3.06 (ddd, 14.9, 11.2, 2.0, 1H, 5-$H_B$), 2.80–2.76 (m, 1H, 6-$H_A$), 2.76–2.70 (m, 1H, 8-$H_A$), 2.48 (ddd, J 13.1, 11.2, 2.2, 1H, 6-$H_B$), 2.38 (dd, J 14.5, 7.3, 1H, 9-$H_A$), 1.97–1.85 (m, 2H, 8-$H_B$ and 9-$H_B$), 1.64–1.57 (m, 2H, 2'-$H_2$), 1.36 (s, 3H, Me), 1.37–1.28 (m, 2H, 3'-$H_2$), 0.93 (t, J 7.4, 3H, 4'-$H_3$); $^{13}C$ 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 calcd for $C_{19}H_{27}N_3O_2$ $[M+H]^+$: 330.2176; found: 330.2184, 2.4 ppm error.

**Ethyl 2-{7-benzyl-9a-methyl-1,3-dioxo-octahydro-1H-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, 4H, Ph), 7.28–7.23 (m, 1H, Ph), 4.28 (d, J 17.4, 1H, 3'-$H_A$), 4.23 (d, J 17.4, 1H, 3'-$H_B$), 4.22 (app. dq, J 7.1, 1.6, 2H, $CH_2Me$), 4.01–3.95 (m, 1H, 5-$H_A$), 3.61 (d, J 13.3, 1H, $CH_AH_BPh$), 3.57 (d, J 13.3, 1H, $CH_AH_BPh$), 3.10 (ddd, J 14.7, 11.2, 1.7, 1H, 5-$H_B$), 2.83–2.78 (m, 1H, 6-$H_A$), 2.75 (dd, J 13.5, 7.2, 1H, 8-$H_A$), 2.55–2.48 (m, 1H, 6-$H_B$), 2.45 (dd, J 15.3, 7.2, 1H, 9-$H_A$), 2.13 (dd, J 13.7, 10.1, 1H, 8-$H_B$), 1.98 (dd, J 14.9, 9.8, 1H, 9-$H_B$), 1.43 (s, 3H, Me), 1.29 (t, J 7.1, 3H, 4'-Me); $^{13}C$ 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 calcd for $C_{19}H_{26}N_3O_4$ $[M+H]^+$: 360.1918; found: 360.1926, 2.2 ppm error.

**(6R,8aR)-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 petrol—EtOAc) to give the hydantoin **13a** (34 mg, 41%) as a white solid. Mp 170-172 °C; $R_f$ = 0.47 (30:70 Petrol–EtOAc); IR (ATR) 2934, 1775, 1711, 1542, 1415, 1350, 1157, 734, 583 $cm^{-1}$; $[\alpha]_D^{27}$ +41 (c = 0.20, MeOH); $^1H$ NMR (500 MHz; $CDCl_3$) δ 8.03-7.98 (m, 1H, Ns 3-H), 7.68-7.61 (m, 2H, Ns 4-H and 5-H), 7.60-7.56 (m, 1H, Ns 6-H), 7.29-7.20 (m, 5H, Ph), 4.50-4.40 (m, 2H, 1'-$H_2$), 4.05 (dd, J 14.3, 6.1, 1H, 5-$H_A$), 3.92-3.82 (m, 1H, 6-H), 3.61 (d, J 14.7, 1H, 8-$H_A$), 3.49 (d, J 14.7, 1H, 8-$H_B$), 2.68 (dd, J 14.3, 10.2, 1H, 5-$H_B$), 1.36 (s, 3H, 8a-Me), 1.04 (d, J 6.6, 3H, 6-Me); $^{13}C$ 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 calcd for $C_{21}H_{22}N_4O_6S$ $[M+H]^+$: 459.1338; found: 459.1340, 0.4 ppm error.

**(5R*,8aS*)-8a-Methyl-2-[2-(morpholin-4-yl)ethyl]-7-(4-nitrobenzenesulfonyl)-5-phenyl-octahydroimidazolidino[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, 2H, Ns 3-H and 5-H), 8.01 (d, J 8.8, 2H, Ns 2-H and 4-H), 7.59 (d, J 7.6, 2H, Ph 2-H and 6-H), 7.42 (t, J 7.6, 2H, Ph 3-H and 5-H), 7.34 (t, J 7.6, 1H, Ph 4-H), 5.49 (d, J 4.4, 1H, 5-H), 4.70 (d, J 12.5, 1H, 6-$H_A$), 3.86 (dd, J 11.3, 1.2, 1H, 8-$H_A$), 3.71-3.59 (m, 2H, 1'-$H_2$), 3.49 (br s, 4H, morpholine 2-$H_2$ and 6-$H_2$), 2.67-2.52 (m, 3H, 2'-$H_2$ and 6-$H_B$), 2.50-2.35 (m, 4H, morpholine 3-$H_2$ and 5-$H_2$), 2.31 (d, J 11.3, 1H, 8-$H_B$), 1.14 (s, 3H, Me); $^{13}C$ 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 calcd for $C_{25}H_{30}N_5O_7S$ $[M+H]^+$: 544.1860; found: 544.1873, 2.4 ppm error.

**(5R*,8aS*)-2-Benzyl-8a-methyl-7-(4-nitrobenzenesulfonyl)-5-phenyl-octahydroimidazolidino[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, 2H, Ns 3-H and 5-H), 7.99 (d, J 8.9, 2H, Ns 2-H and 4-H), 7.59 (d, 2H, J 7.6, Ph 2-H and 6-H), 7.42-7.29 (m, 8H, Ph), 5.49 (d, J 4.5, 1H, 5-H), 4.67 (d, J 12.5, 1H, 6-$H_A$), 4.65 (s, 2H, 1'-$H_2$), 3.86 (dd, J 11.3, 1.3, 1H, 8-$H_A$), 2.65 (dd, J 12.5, 4.8, 1H, 6-$H_B$), 2.24 (d, J 11.3, 1H, 8-$H_B$), 1.14 (s, 3H, Me); $^{13}C$ 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 Ph was not observed; HRMS (ESI): m/z calcd for $C_{26}H_{25}N_4O_6S$ $[M+H]^+$: 521.1489; found: 521.1499, 1.9 ppm error.

**(5R*,8aS*)-2-Butyl-8a-methyl-7-(4-nitrobenzenesulfonyl)-5-phenyl-octahydroimidazolidino[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 $cm^{-1}$; $^1H$ NMR (500 MHz; $CDCl_3$) δ 8.44 (d, J 8.9, 2H, Ns 3-H and 5-H), 8.01 (d, J 8.9, 2H, Ns 2-H and 4-H), 7.60 (d, J 7.6, 2H, Ph 2-H and 6-H), 7.41 (t, J 7.6, 2H, Ph 3-H and 5-H), 7.34 (t, J 7.6, 1H, Ph 4-H), 5.49 (d, J 4.5, 1H, 5-H), 4.69 (d, J 12.5, 1H, 6-$H_A$), 3.87 (dd, J 11.3, 1.4, 1H, 8-$H_A$), 3.58-3.43 (m, 2H, 1'-$H_2$), 2.66 (dd, J 12.5, 4.8, 1H, 6-$H_B$), 2.25 (d, J 11.3, 1H, 8-$H_B$), 1.64-1.54 (m, 2H, 2'-$H_2$), 1.32-1.27 (m, 2H, 3'-$H_2$), 1.14 (s, 3H, Me), 0.93 (t, 3H, J 7.4, 4'-Me); $^{13}C$ 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 calcd for $C_{23}H_{27}N_4O_6S$ $[M+H]^+$: 487.1651; found: 487.1647, –0.8 ppm error.

**2-Cyclopropyl-9a-ethyl-octahydro-1H-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 orange solid. $R_f$ = 0.19 (90:10 $CH_2Cl_2$—MeOH); IR (ATR) 3461, 2967, 2936, 1766, 1701, 1428, 1352 $cm^{-1}$; $^1H$ NMR (500 MHz; $CDCl_3$) δ 4.09-3.95 (m, 1H, 5-$H_A$), 3.01-2.92 (m, 2H, 6-$H_a$ and 8-$H_A$), 2.91-2.81 (m, 2H, 5-$H_B$ and 6-$H_B$), 2.67-2.59 (m, 1H, 8-$H_B$), 2.50 (dd, J 14.7, 5.9, 1H, 9-$H_A$), 2.22 (dd, J 14.7, 10.8, 1H, 9-$H_B$), 2.09 (br s, 1H, NH), 1.82 (dq, J 14.2, 7.4, 1H, ethyl 1-$H_A$), 1.74 (ddd, J 15.3, 10.8, 1.2, 1H, 1'-$H_A$), 1.62 (dq, J 14.2, 7.4, 1H, ethyl 1-$H_B$), 1.02-0.83 (m, 4H, 2'-$H_2$ and 3'-$H_2$), 0.69 (t, J 7.4, 3H, ethyl 2-Me); $^{13}C$ 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 calcd for $C_{12}H_{19}N_3O_2$ $[M+H]^+$: 238.1555; found: 238.1555, 0.0 ppm error.

**2-Benzyl-8a-methyl-octahydroimidazolidino[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 MeOH—$NH_3$) 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 $cm^{-1}$; $^1H$ NMR (500 MHz; $CDCl_3$) δ 7.42-7.27 (m, 5H, Ph), 4.78-4.63 (m, 2H, 1'-$H_2$), 4.01 (dd, J 13.2, 3.6, 1H, 5-$H_A$), 3.09 (d, J 12.2, 1H, 8-$H_A$), 3.07-2.95 (m, 2H, 6-$H_2$), 2.68-2.55 (m, 2H, 5-$H_B$ and 8-$H_B$), 1.79 (br s, 1H, NH), 1.55 (s, 3H, Me); $^{13}C$ 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 calcd for $C_{14}H_{17}N_3O_2$ $[M+H]^+$: 260.1399; found: 260.1401, 0.8 ppm error.

**(3R*,9aR*)-2-Benzyl-9a-ethyl-1-oxo-3-(trifluoromethyl)-octahydro-1H-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 room temperature overnight. Excess $K_2CO_3$ was removed by filtration and the reaction 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 $cm^{-1}$; $^1H$ NMR (500 MHz; $CDCl_3$) δ 7.44 (d, J 7.3, 2H, Ph 3-H and 5-H), 7.35-7.30 (m, 2H, Ph 2-H and 6-H), 7.28-7.22 (m, 1H, Ph 4-H), 4.67 (q, J 15.3, 2H, 1'-$H_2$), 3.73-3.62 (m, 1H, 5-$H_A$), 3.16 (ddd, J 15.9, 7.3, 3.4, 1H, 6-$H_A$), 2.95-2.85 (m, 3H, 6-$H_B$ and 8-$H_2$), 2.85-2.78 (m, 1H, 5-$H_B$), 2.09-1.94 (m, 3H, 9-$H_2$ and NH), 1.78 (dq, J 14.8, 7.4, 1H, ethyl 1-$H_A$), 1.61 (dq, J 14.8, 7.4, 1H, ethyl 1-$H_B$), 0.91 (t, J 7.4, 3H, ethyl 3-Me); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 174.8, 137.5, 128.5, 128.1, 127.1, 122.6 (app d, J 289.7), 96.9 (app d, J 33.0), 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 calcd for $C_{17}H_{22}F_3N_3O_2$ $[M+H]^+$: 358.1742; found: 358.1732, –2.8 ppm error.

**2-Benzyl-9a-ethyl-octahydro-1H-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 hr. The reaction mixture was cooled, concentrated under reduced pressure, diluted with water (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 $cm^{-1}$; $^1H$ NMR (500 MHz; $CDCl_3$) δ 7.42-7.36 (m, 2H, Ph 3-H and 5-H), 7.34-7.23 (m, 3H, Ph 2-H, 4-H and 6-H), 4.71-4.63 (m, 2H, 1'-$H_2$), 4.10-4.00 (m, 1H, 5-$H_A$), 3.00-2.83 (m, 4H, 5-$H_B$, 6-$H_2$ and 8-$H_A$), 2.51 (dd, J 15.2, 6.4, 1H, 8-$H_B$), 2.18 (dd, J 14.7, 10.7, 1H, 9-$H_A$), 1.84 (dq, J 14.6, 7.4, 1H, ethyl 1-$H_A$), 1.74 (ddd, J 14.7, 10.8, 1.3, 1H, 9-$H_B$), 1.69-1.58 (m, 2H, ethyl 1-$H_B$ and NH), 0.62 (t, J 7.4, 3H, ethyl 2-Me); $^{13}C$ 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 calcd for $C_{16}H_{21}N_3O_2$ $[M+H]^+$: 288.1712; found: 288.1716, 1.4 ppm error.

**Debenzylation of Benzylamines 11c-e: General Procedure**

Ammonium formate (5.0 eq.) was added to a stirred suspension of diazepine **11** (1.0 eq.) 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 room temperature, filtered through Celite®, washed with EtOH and concentrated under reduced pressure. The residue was partitioned between sat. $NaHCO_{3(aq.)}$ and $CH_2Cl_2$, the two layers were separated and the aqueous layer was extracted with $CH_2Cl_2$. 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-1H-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, 1H, 5-$H_A$), 3.72–3.54 (m, 6H, 1'-$H_2$ and morpholine 2-$H_2$ and 6-$H_2$), 2.98–2.79 (m, 4H, 5-$H_B$, 6-$H_2$ and 8-$H_A$), 2.62–2.37 (m, 7H, 9-$H_A$, 2'-$H_2$ and morpholine 3-$H_2$ and 5-$H_2$), 2.31 (dd, J 14.1, 10.6, 1H, 8-$H_B$), 1.84–1.68 (m, 2H, 9-$H_B$ and NH), 1.36 (s, 3H, Me); $^{13}C$ 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 calcd for $C_{14}H_{24}N_4O_3$ $[M+H]^+$: 297.1921; found: 297.1928, 2.4 ppm error.

**2-Butyl-9a-methyl-octahydro-1H-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, 1H, 5-$H_A$), 3.51 (t, J 7.3, 2H, 1'-$H_2$), 2.99–2.82 (m, 4H, 5-$H_B$, 6-$H_2$ and 8-$H_A$), 2.52 (dd, J 15.1, 6.5, 1H, 9-$H_A$), 2.20 (dd, J 14.2, 10.5, 1H, 8-$H_B$), 1.77 (ddd, 15.1, 10.5, 1.4, 1H, 9-$H_B$), 1.69 (br s, 1H, NH), 1.64–1.55 (m, 2H, 2'-$H_2$), 1.37 (s, 3H, Me), 1.31 (dt, J 14.7, 7.4, 2H, 3'-$H_2$), 0.92 (t, J 7.4, 3H, 4'-Me); $^{13}C$ 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 calcd for $C_{12}H_{22}N_3O_2$ $[M+H]^+$: 240.1707; found: 240.1713, –2.4 ppm error.

**Ethyl 2-[9a-methyl-1,3-dioxo-octahydro-1H-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, 1H, 3'-$H_A$), 4.22 (d, J 17.4, 1H, 3'-$H_B$), 4.20 (q, J 7.1, 2H, 3'-$H_2$), 4.04 (br d, J 14.4, 1H, 5-$H_A$), 3.01–2.85 (m, 4H, 5-$H_B$, 6-$H_2$ and 8-$H_A$), 2.58 (dd, J 15.2, 6.4, 1H, 9-$H_A$), 2.43 (dd, J 14.1, 10.8, 1H, 8-$H_B$), 1.80 (dd, J 15.2, 10.7, 1H, 9-$H_B$), 1.73 (br s, 1H, NH), 1.42 (s, 3H, Me), 1.27 (t, J 7.2, 3H, 4'-Me); $^{13}C$ 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 calcd for $C_{12}H_{20}N_3O_4$ $[M+H]^+$: 270.1448; found: 270.1452, 1.5 ppm error.

**(5R*,8aS*)-8a-Methyl-2-[2-(morpholin-4-yl)ethyl]-5-phenyl-octahydroimidazolidino[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 room temperature. The resulting suspension was stirred at room temperature for 16 h and the volatiles removed under reduced pressure. The residue was partitioned between water (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, 1H, 5-H), 3.83 (d, J 13.4, 1H, 6-$H_A$), 3.71 (td, J 6.3, 1.6, 2H, 1'-$H_2$), 3.66 (br t, J 4.6, 4H, morpholine 2-$H_2$ and 6-$H_2$), 3.08 (d, J 12.2, 1H, 8-$H_A$), 3.01 (dd, J 13.4, 4.9, 1H, 6-$H_B$), 2.80 (d, J 12.2, 1H, 8-$H_B$), 2.70-2.59 (m, 2H, 2'-$H_2$), 2.59-2.46 (m, 4H, morpholine 3-$H_2$ and 5-$H_2$), 1.75 (br s, 1H, NH), 1.09 (s, 3H, Me); $^{13}C$ 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 calcd for $C_{19}H_{27}N_4O_3$ $[M+H]^+$: 359.2078; found: 359.2083, 1.4 ppm error.

**Denosylation of Nitrosulfonamides 13c-d: General Procedure**

PhSH (2.0 eq.) was added to a stirred solution of piperazine **13** (1.0 eq.) and $K_2CO_3$ (3.0 eq.) in DMF (0.1 M) at room temperature. The resulting suspension was stirred at room temperature for 1 h, 2M $NaOH_{(aq)}$ and EtOAc were added and the layers separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

**(5R*,8aS*)-2-Benzyl-8a-methyl-5-phenyl-octahydroimidazolidino[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, 2H, Ph), 7.42 (d, J 7.6, 2H, Ph) 7.36 (t, J 7.6, 4H, Ph), 7.32-7.28 (m, 2H, Ph), 5.30 (d, J 4.7, 1H, 5-H), 4.74 (s, 2H, 1'-$H_2$), 3.80 (d, J 13.4, 1H, 6-$H_A$), 3.08 (d, J 12.2, 1H, 8-$H_A$), 3.00 (dd, J 13.4, 4.9, 1H, 6-$H_B$), 2.73 (d, J 12.2, 1H, 8-$H_B$), 1.73 (br s, 1H, NH), 1.10 (s, 3H, Me); $^{13}C$ 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 calcd for $C_{20}H_{22}N_3O_2$ $[M+H]^+$: 336.1707; found: 336.1708, 0.3 ppm error.

**(5R*,8aS*)-2-Butyl-8a-methyl-5-phenyl-octahydroimidazolidino[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, 2H, Ph 2-H and 6-H), 7.36 (t, J 7.6, 2H, Ph 3-H and 5-H), 7.29 (t, J 7.6, 1H, Ph 4-H), 5.30 (d, J 4.5, 1H, 5-H), 3.81 (d, J 13.4, 1H, 6-$H_A$), 3.65-3.51 (m, 2H, 1'-$H_2$), 3.08 (d, J 12.2, 1H, 8-$H_A$), 3.01 (dd, J 13.4, 4.9, 1H, 6-$H_B$), 2.74 (d, J 12.2, 1H, 8-$H_B$), 1.73 (br s, 1H, NH), 1.71-1.61 (m, 2H, 2'-$H_2$), 1.43-1.32 (m, 2H, 3'-$H_2$), 1.09 (s, 3H, Me), 0.97 (t, J 7.4, 3H, 4'-Me); $^{13}C$ 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 calcd for $C_{17}H_{24}N_3O_3$ $[M+H]^+$: 302.1863; found: 302.1866, 0.9 ppm error.

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

Isobutane sulfonyl chloride (39 µL, 0.30 mmol) was added to a solution of secondary amine **19** (36 mg, 0.15 mmol) and DIPEA (65 µL, 0.38 mmol) in DMA (1.2 mL) at room temperature. The resulting solution was stirred at room temperature for 16 h. The reaction was quenched with $H_2O$ (0.1 mL) and product was purified by mass-directed auto-prep (5-95% MeOH–$H_2O$ with 0.1% ammonia buffer) to give sulfonamide **24** (37 mg, 68%) as a colourless oil. IR (ATR) 2959, 2933, 1766, 1700, 1450, 1319, 1141, 865, 765 $cm^{-1}$; $^1H$ NMR (500 MHz; MeOD-d4) δ 4.00 (ddd, J 14.5, 3.4, 2.4, 1H, 5-$H_A$), 3.67–3.59 (m, 2H, 6-$H_A$ and 8-$H_A$), 3.41 (t, J 7.1, 2H, 1'-$H_2$), 3.14 (ddd, J 14.5, 10.6, 2.3, 1H, 5-$H_B$), 3.09–3.01 (m, 1H, 6-$H_B$), 2.80 (d, J 6.5, 2H, $CH_2SO_2$), 2.63 (ddd, J 14.7, 9.2, 2.0, 1H, 8-$H_B$), 2.31 (ddd, J 15.5, 7.4, 2.0, 1H, 9-$H_A$), 2.06 (hept, J 6.7, 1H, CH), 1.93 (ddd, J 15.5, 9.2, 2.2, 1H, 9-$H_B$), 1.54–1.44 (m, 2H, 2'-$H_2$), 1.32 (s, 3H, 9a-Me), 1.28–1.18 (m, 2H, 3'-$H_2$), 0.98 (d, J 6.7, 6H, 2 Me), 0.85 (t, J 7.4, 3H, 4'-$H_3$); $^{13}C$ NMR (126 MHz, MeOD-d4) 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 calcd for $C_{16}H_{30}N_3O_4S$ $[M+H]^+$: 360.1952; found: 360.1951, –0.2 ppm error.

**2-Butyl-9a-methyl-7-(thiophen-3-ylmethyl)-octahydro-1H-imidazolidino[1,5-d][1,4]diazepine-1,3-dion (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 room temperature for 10 min. STAB (95 mg, 0.45 mmol) was added and the reaction heated to 60 °C for 16 h. The reaction was quenched with $H_2O$ (0.1 mL) and product was purified by mass-directed auto-prep (5-95% MeOH–$H_2O$ with 0.1% ammonia buffer) to give piperidine **25** (37 mg, 74%) as a colourless oil. IR (ATR) 2935, 2874, 1765, 1700, 1425, 1417, 1378, 1343, 791 $cm^{-1}$; $^1H$ NMR (500 MHz; MeOD-d4) δ 7.25 (dd, J 4.9, 3.0, 1H, Ar 5-H), 7.13–7.09 (m, 1H, Ar 2-H), 6.96 (dd, J 4.9, 1.2, 1H, Ar 4-H), 3.79 (ddd, J 15.1, 3.5, 2.3, 1H, 5-$H_A$), 3.58 (d, J 13.5, 1H, $CH_AH_BAr$), 3.53 (d, J 13.5, 1H, $CH_AH_BAr$), 3.39 (t, J 7.1, 2H, 1'-$H_2$), 3.08 (ddd, J 15.1, 11.1, 2.0, 1H, 5-$H_B$), 2.78–2.66 (m, 2H, 6-$H_A$ and 8-$H_A$), 2.35 (ddd, J 13.3, 11.2, 2.3, 1H, 6-$H_B$), 2.29–2.19 (m, 1H, 9-$H_A$), 1.89 (ddd, J 15.5, 10.4, 1.4, 1H, 9-$H_B$), 1.79–1.69 (m, 1H, 8-$H_B$), 1.50–1.41 (m, 2H, 2'-$H_2$), 1.25 (s, 3H, Me), 1.24–1.14 (m, 2H, 3'-$H_2$), 0.84 (t, J 7.4, 3H, 4'-Me); $^{13}C$ NMR (126 MHz, MeOD-d4) 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 calcd for $C_{17}H_{26}N_3O_2S$ $[M+H]^+$: 336.1740; found: 336.1749, 2.7 ppm error.

**N-Benzyl-9a-methyl-2-[2-(morpholin-4-yl)ethyl]-1,3-dioxo-octahydro-1H-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 DIPEA (65 µL, 0.38 mmol) in DMA (1.2 mL) at room temperature. The resulting solution was stirred

at room temperature 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 urea **26** (45 mg, 70%) as a white solid. Mp 128-130 °C; IR (ATR) 3369, 1766, 1700, 1585, 1455, 1241, 1056, 933, 755 $cm^{-1}$; $^1H$ NMR (500 MHz; MeOD-d4) δ 7.23-7.16 (m, 4H, Ph), 7.15-7.08 (m, 1H, Ph), 4.28 (d, J 15.4, 1H, $CH_AH_BPh$), 4.24 (d, J 15.4, 1H, $CH_AH_BPh$), 3.99 (ddd, J 14.6, 4.1, 3.2, 1H, 5-$H_A$), 3.81 (dt, J 14.6, 3.4, 1H 6-$H_A$), 3.63 (ddd, J 15.3, 8.1, 1.6, 1H, 8-$H_A$), 3.55 (t, J 6.2, 2H, 1'-$H_2$), 3.51-3.48 (m, 4H, morpholine 2-$H_2$ and 6-H), 3.19-3.15 (m, 1H, 5-$H_B$), 3.11-3.00 (m, 2H, 6-$H_B$ and 8-$H_B$), 2.47 (t, J 6.2, 2H, 2'-$H_2$), 2.37 (br s, 4H, morpholine 3-$H_2$ and 5-$H_2$), 2.16 (ddd, J 15.2, 8.1, 2.5, 1H, 9-$H_A$), 1.86 (ddd, J 15.2, 8.2, 2.3, 1H, 9-$H_B$), 1.31 (s, 3H, 9a-Me); $^{13}C$ NMR (126 MHz, MeOD-d4) 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 calcd for $C_{22}H_{31}N_5NaO_4$ $[M+Na]^+$: 452.2274; found: 452.2260, –3.1 ppm error.

**(5R*,8aS*)-2-Butyl-7-(3-fluorobenzenesulfonyl)-8a-methyl-5-phenyl-octahydroimidazolidino[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 DIPEA (65 µL, 0.38 mmol) in DMA (1.2 mL) at room temperature. The resulting solution was stirred at room temperature 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 sulfonamide **27** (24 mg, 35%) as a white solid. Mp 132-135 °C; IR (ATR) 2937, 1766, 1699, 1445, 1419, 1348, 1187, 763, 577 $cm^{-1}$; $^1H$ NMR (500 MHz; MeOD-d4) δ 7.72 (dd, J 5.6, 4.0, 2H, Ar), 7.69-7.66 (m, 1H, Ar), 7.66-7.62 (m, 2H, Ar), 7.55-7.49 (m, 1H, Ar), 7.43 (t, J 7.6, 2H, Ar), 7.36 (t, J 7.2, 1H, Ar), 5.47 (d, J 4.7, 1H, 5-H), 4.69 (d, J 13.0, 1H, 8-$H_A$), 3.77 (dd, J 11.4, 1.5, 1H, 6-$H_A$), 3.60-3.48 (m, 2H, 1'-$H_2$), 2.78 (dd, J 13.0, 4.7, 1H, 8-$H_B$), 2.51 (d, J 11.4, 1H, 6-$H_B$), 1.69-1.55 (m, 2H, 2'-$H_2$), 1.42-1.29 (m, 2H, 3'-$H_2$), 1.11 (s, 3H, Me), 0.97 (t, J 7.4, 3H, 4'-Me); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 173.9, 162.7 (d, J 253.2), 155.1, 138.0, 137.3 (d, J 6.6), 131.4 (d, J 7.8), 128.8, 128.0, 127.3, 123.4, 120.9 (d, J 21.2), 115.0 (d, J 24.2), 59.8, 51.7, 48.6, 46.7, 39.0, 30.1, 20.8, 19.9, 13.6; HRMS (ESI): m/z calcd for $C_{23}H_{26}FN_3NaO_4S$ $[M+Na]^+$: 482.1526; found: 482.1508, 3.7 ppm error.

**(5R*,8aS*)-2-Benzyl-8a-methyl-7-(1-methylpiperidin-4-yl)-5-phenyl-octahydroimidazolidino[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 room temperature for 10 min. STAB (95 mg, 0.45 mmol) was added and the reaction 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 piperidine **28** (48 mg, 74%) as a white solid. Mp 72-74 °C; IR (ATR) 2934, 2779, 1765, 1701, 1496, 1434, 1278,1073, 696 $cm^{-1}$; $^1H$ NMR (500 MHz; $CDCl_3$) δ 7.49 (d, J 8.2, 2H, Ph), 7.37-7.22 (m, 8H, Ph), 5.28 (d, J 4.3, 1H, 5-H), 4.71 (d, J 14.9, 1H, 1'-$H_A$), 4.67 (d, J 14.9, 1H, 1'-$H_B$), 3.68 (d, J 12.5, 1H, 6-$H_A$), 2.95-2.93 (m, 3H, 8-$H_A$ and piperidine 3-$H_2$), 2.62 (dd, J 12.5, 4.7, 1H, 6-$H_B$), 2.57 (tt, J 11.5, 3.7, 1H, piperidine 4-H), 2.30-2.28 (m, 4H, 8-$H_A$ and NMe), 2.16-2.04 (m, 2H, piperidine 3-$H_2$), 1.92-1.77 (m, 2H, piperidine 2-$H_2$), 1.75-1.57 (m, 2H, piperidine 2-$H_2$), 1.10 (s, 3H, Me); $^{13}C$ 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 calcd for $C_{26}H_{33}N_4O_2$ $[M+H]^+$: 433.2604; found: 433.2602, –0.5 ppm error.

**(5R*,8aS*)-2-Butyl-N-(4-methoxyphenyl)-8a-methyl-1,3-dioxo-5-phenyl-octahydroimidazolidino[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 DIPEA (65 µL, 0.38 mmol) in DMA (1.2 mL) at room temperature. The resulting solution was stirred at room temperature 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 urea **29** (36 mg, 53%) as a white solid. Mp 89-91 °C; IR (ATR) 3331, 2955, 2932, 1766, 1697, 1509, 1416, 1230 $cm^{-1}$; $^1H$ NMR (500 MHz; MeOD-d4) δ 7.56 (d, J 8.0, 2H, Ar), 7.40 (t, J 7.6, 2H, Ar), 7.36-7.25 (m, 3H, Ar), 6.92-6.89 (m, 2H, Ar), 5.45 (br s, 1H, 5-H), 4.90 (d, J 14.3, 1H, 8-$H_A$), 4.20 (d, J 13.0, 1H, 6-$H_A$), 3.81 (s, 3H, OMe), 3.66-3.57 (m, 2H, 1'-$H_2$), 3.44 (dd, J 14.3, 5.1, 1H, 8-$H_B$), 3.08 (d, J 13.0, 1H, 6-$H_B$), 1.74-1.63 (m, 2H, 2'-$H_2$), 1.47-1.37 (m, 2H, 3'-$H_2$), 1.16 (s, 3H, Me), 1.01 (t, J 7.4, 3H, 4'-Me); $^{13}C$ NMR (126 MHz, MeOD-d4) 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 calcd for $C_{25}H_{31}N_4O_4$ $[M+H]^+$: 451.2340; found: 451.2342, 0.4 ppm error.

**(5R*,8aS*)-7-Cyclohexanecarbonyl-8a-methyl-2-[2-(morpholin-4-yl)ethyl]-5-phenyl-octahydroimidazolidino[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 DIPEA (65 µL, 0.38 mmol) in DMA (1.2 mL) and the resulting mixture was stirred at room temperature 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 amide **30** (50 mg, 71%) as a white solid. Mp

67-69 °C; IR (ATR) 2928, 2852, 1766, 1701, 1446, 1144, 702 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J 7.4, 2H, Ph 2-H and 6-H), 7.35 (t, J 7.4, 2H, Ph 3-H and 5-H), 7.32-7.27 (m, 1H, Ph 4-H), 5.52 (d, J 3.5, 1H, 5-H), 5.45 (d, J 14.3, 1H, 6-$H_A$), 4.02 (d, J 13.0, 1H, 8-$H_A$), 3.79-3.73 (m, 2H, 1'-$H_2$), 3.68 (t, J 4.4, 4H, morpholine 2-$H_2$ and 6-$H_2$), 3.16 (d, J 13.0, 1H, 8-$H_B$), 2.96 (dd, J 14.3, 4.0, 1H, 6-$H_B$), 2.74-2.63 (m, 2H, 2'-$H_2$), 2.61-2.41 (m, 5H, morpholine 3-$H_2$ and 5-$H_2$ and Cy 1-H), 1.88-1.20 (m, 10H, Cy), 1.05 (s, 3H, Me); $^{13}C$ NMR (126 MHz, MeOD-d4) 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 calcd for $C_{26}H_{37}N_4O_4$ $[M+H]^+$: 469.2809; found: 469.2806, –0.7 ppm error.

**Ethyl 2-[7-(4-methoxybenzenesulfonyl)-9a-methyl-1,3-dioxo-octahydro-1H-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 rt and the resulting solution was warmed to room temperature and stirred for 16 h. Water (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 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 $cm^{-1}$; $^1H$ NMR (500 MHz; $CDCl_3$) δ 7.66 (d, J 8.9, 2H, Ar 2-H and 6-H), 6.96 (d, J 8.9, 2H Ar 3-H and 5-H), 4.22 (d, J 17.5, 1H, 1'-$H_A$), 4.18 (d, J 17.5, 1H, 1'-$H_B$), 4.18–4.11 (m, 3H, 3'-$H_2$ and 5-$H_A$), 3.86 (s, 3H, OMe), 3.85–3.81 (m, 2H, 6-$H_A$ and 8-$H_A$), 3.20 (ddd, J 13.6, 11.2, 1.9, 1H, 5-$H_B$), 2.78 (ddd, J 13.1, 11.5, 1.6, 1H, 6-$H_B$), 2.59 (dd, J 15.5, 6.5, 1H, 9-$H_A$), 2.44 (dd, J 14.6, 10.0, 1H, 8-$H_B$), 2.10 (ddd, J 15.5, 10.0, 1.4, 1H, 9-$H_B$), 1.45 (s, 3H, Me), 1.22 (t, J 7.2, 3H, 4-Me); $^{13}C$ 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 calcd for $C_{19}H_{26}N_3O_7S$ $[M+H]^+$: 440.1486; found: 440.1492, 1.5 ppm error.

**N-(Furan-2-ylmethyl)-2-[7-(4-methoxybenzenesulfonyl)-9a-methyl-1,3-dioxo-octahydro-1H-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 **30** (565 mg, 1.29 mmol) in 4:1:1 THF/MeOH/$H_2O$ (18 mL) at room temperature and the resulting solution was stirred for at room temperature for 1 h then concentrated under reduced pressure. Water (10 mL), 1M $HCl_{(aq)}$ (10 mL) and EtOAc (20 mL) were added 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 a crude carboxylic acid (530 mg, quant.) as a white solid which was used without further purification. $^1H$ NMR (500 MHz; $CDCl_3$) δ 7.21 (br s, 1H, $CO_2H$), 7.65 (d, J 8.9, 2H, Ar 2-H and 6-H), 6.96 (d, J 8.9, 2H Ar 3-H and 5-H), 4.26 (d, J 17.9, 1H, 1'-$H_A$), 4.22 (d, J 17.9, 1H, 1'-$H_B$), 4.16–4.10 (m, 1H, 5-$H_A$), 3.86 (s, 3H, OMe), 3.85–3.79 (m, 2H, 6-$H_A$ and 8-$H_A$), 3.20 (dd, J 13.3, 11.1, 1H, 5-$H_B$), 2.76 (app. t, J 11.6, 1H, 6-$H_B$), 2.55 (dd, J 15.5, 6.4, 1H, 9-$H_A$), 2.40 (dd, J 14.2, 9.6, 1H, 8-$H_B$), 2.13–2.05 (m, 1H, 9-$H_B$), 1.44 (s, 3H, Me). 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 DIPEA (65 µL, 0.38 mmol) in DMA (1.2 mL) and the resulting mixture was stirred at room temperature 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 amide **32** (46 mg, 63%) as a white solid. Mp 76-78 °C; IR (ATR) 3323, 2943, 1770, 1706, 1451, 1256, 1150, 699, 587 $cm^{-1}$; $^1H$ NMR (500 MHz; MeOD-d4) δ 7.66-7.59 (m, 2H, Ar 2-H and 6-H), 7.31 (dd, J 1.9, 0.8, 1H, furan 5-H), 7.01–6.94 (m, 2H, Ar 3-H and 5-H), 6.23 (dd, J 3.2, 1.9, 1H, furan 4-H), 6.15–6.11 (m, 1H, furan 3-H), 4.23 (s, 2H, 4'-$H_2$), 4.05 (d, J 16.5, 1'-$H_A$), 4.00 (d, J 16.5, 1'-$H_A$), 3.98 (ddd, J 15.0, 3.2, 2.5, 1H, 5-$H_A$), 3.77 (s, 3H, OMe), 3.73-3.65 (m, 2H, 6-$H_A$ and 8-$H_A$), 3.20-3.13 (m, 1H, 5-$H_B$) 2.75 (ddd, J 13.4, 11.0, 2.3, 1H, 6-$H_B$), 2.57 (ddd, J 14.6, 9.5, 1.6, 1H, 8-$H_B$), 2.39 (ddd, J 15.6, 7.2, 1.6, 1H, 9-$H_A$), 1.95 (ddd, J 15.6, 9.5, 2.0, 1H, 9-$H_B$), 1.34 (s, 3H, 9a-Me); $^{13}C$ NMR (126 MHz, MeOD-d4) 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 calcd for $C_{22}H_{27}N_4O_7S$ $[M+H]^+$: 491.1595; found: 491.1594, –0.1 ppm error.

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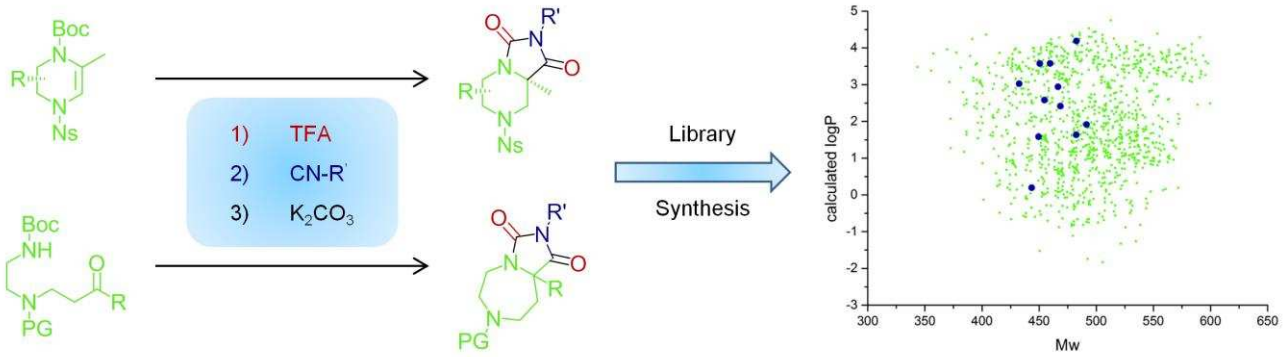


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