Bioorganic & Medicinal Chemistry 20 (2012) 6019–6033

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Identification and development of the 1,4-benzodiazepin-2-one and quinazoline-2,4-dione scaffolds as submicromolar inhibitors of HAT

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ARTICLE INFO

Article history:
Received 8 June 2012
Revised 15 August 2012
Accepted 24 August 2012
Available online 31 August 2012

Keywords:
Trypanosomiasis
Benzodiazepines

ABSTRACT

A library of 1,4-benzodiazepines has been synthesised and evaluated for activity against *Trypanosoma brucei*, a causative parasite of Human African Trypanosomiasis (HAT). The most potent of these derivatives has an MIC value of 0.97 μM. Herein we report the design, synthesis and biological evaluation of the abovementioned compounds.

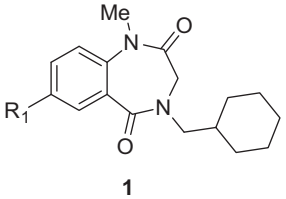
1. Introduction

Trypanosoma brucei, the causative agent of Human African Trypanosomiasis (HAT or sleeping sickness) threatens approximately 60 million people in 36 countries in sub-Saharan Africa. Recent decline in incidence following concerted international action led by the World Health Organisation (WHO) has precipitated hopes that the disease might be eliminated within this century. However, the unsatisfactory nature of current drugs means that a pipeline of compounds is required. Without treatment, the disease has the propensity to develop into an epidemic, making it a major public health problem.[1] Currently only four drugs are licenced for the treatment of HAT, two for the early stage and two for the late stage when the parasites have crossed the blood–brain barrier.[2] Recently nifurtimox, a drug not registered for HAT but shown to be efficacious when used in combination with eflornithine, has also been introduced and the nifurtimox–eflornithine combination therapy (NECT) is currently first line treatment. The toxicity of the existing agents and continual increase in drug resistance means that new drugs need to be identified and approved.[2b]

Economic considerations in the developing world dictate the need for broad-spectrum antiparasitic agents whenever possible. We recently reported the synthesis and activity of a benzodiazepine series against *Leishmania donovani*, a causative agent of visceral leishmaniasis,[3] and a related series against HAT.[3,4] Here we report on compounds arising from the modification of the benzodiazepine scaffold used in the leishmania screen (exemplified by compound **1b**, Fig. 1), that showed activity against *T.b. brucei* as depicted in Figure 2. Furthermore, in response to the limited water solubility of our first library, we describe the effect of introducing water-solubilising moieties to meet the needs of oral administration, another primary economic requirement for treating neglected diseases.[3]

2. Results and discussion

The antitrypanosomal activity of compound **1** previously reported by us,[3] highlighted the necessity for the methylcyclohexyl group at position N_4 to achieve antitrypanosomal activity. Both the bulky cyclohexylmethyl N_4 substituent and a halogen substituent in the aromatic ring at position 7, typically a chloro substituent,



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	R_1	MIC (μM)
1a	H	125
1b	Cl	62.5

Figure 1. The lead compounds with antitrypanosomal activity.

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http://dx.doi.org/10.1016/j.bmc.2012.08.049

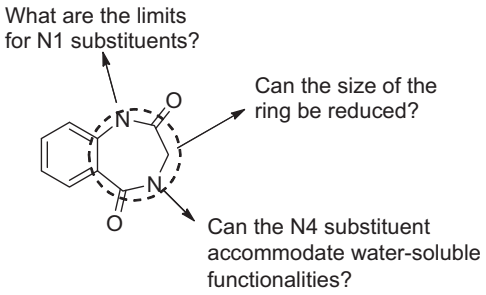
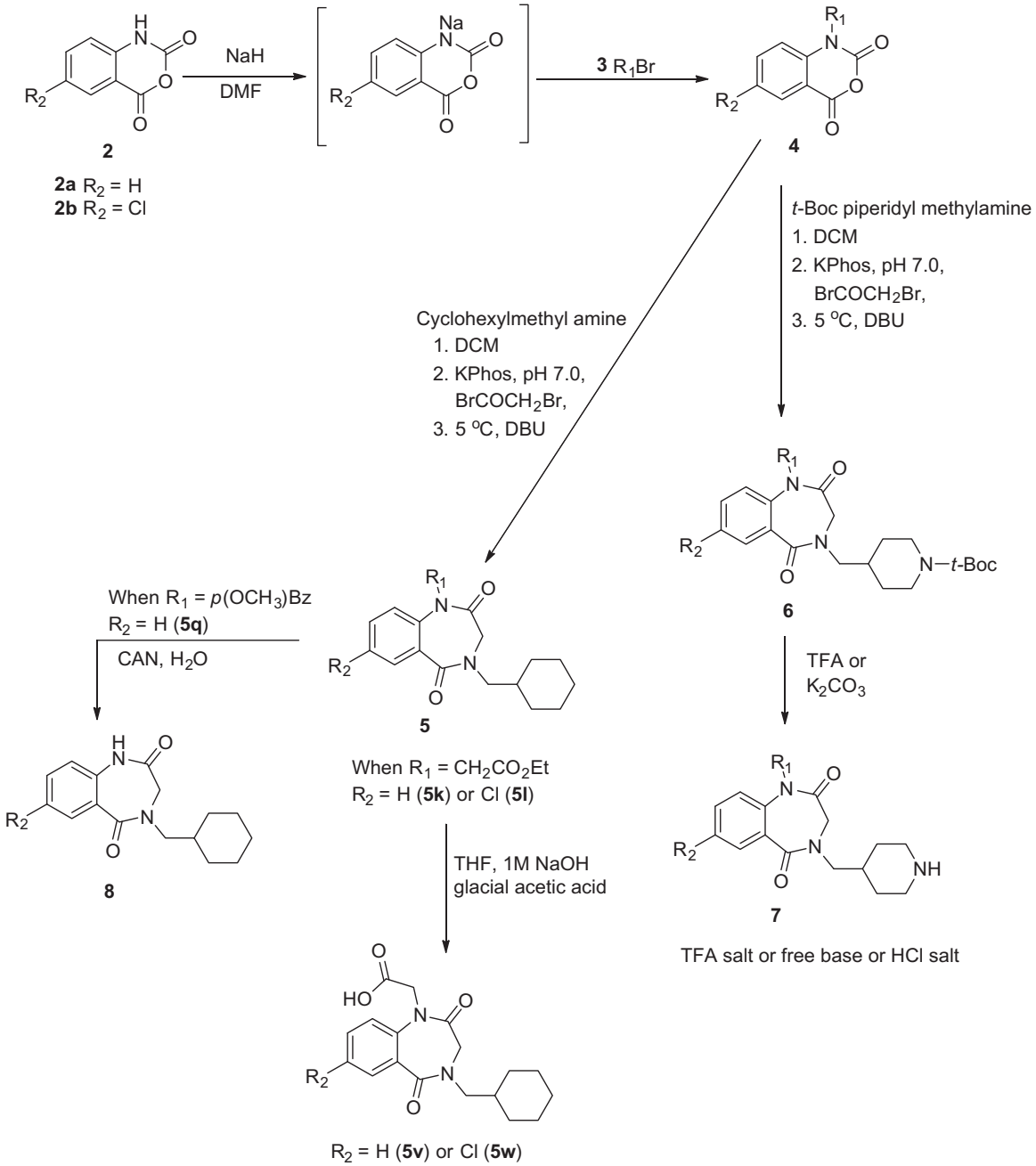


Figure 2. Probing antitrypanosomal SAR around the benzodiazepine scaffold.

appeared to be important for activity. Taking **1b** as a lead from our first library, we set about probing the chemical space around the N_1 substituent by including a variety of flexible alkyl and aromatic groups of varying size at this position, whilst retaining the methylcyclohexyl substituent at N_4 and varying the substituent, between H and Cl, at position 7 of the aromatic ring.

The general procedure used to synthesise compounds **1**, **5**, **6** and **7** was to react the appropriate isatoic anyhydrides and primary amines in a 'one-pot' protocol described by Robarge et al.[5] From the commercially available isatoic anhydrides **2**, a variety of N_1 substituted derivatives could be made in variable yields (8–97%) using sodium hydride in DMF to deprotonate the isatoic anhydride, followed by the alkylation with the required alkyl bromide (Scheme 1).[6] The 'one-pot' synthetic procedure adopted involved treatment of the isatoic anhydride **4** with the primary amine, cyclohexylmethylamine or *t*-Boc protected piperidyl methylamine, followed by bromoacetyl bromide and then DBU in DCM at room temperature. Compounds **5** were prepared in order to determine



Scheme 1. Synthetic route to the 1,4-benzodiazepine library.

the effect of varying substituents at R_1 on biological activity. Based on this activity a selection of amines **7** were synthesised to explore the effect of the free amine on the cyclohexyl ring and to counteract the increasing lipophilicty of the larger, more potent R_1 substituents. Therefore a selection of isatoic anhydrides **4** (Table 1) were used to synthesise the corresponding amines **7** from their protected derivatives **6**. Compounds **5** and **7** were formed in yields of 14–98% (Scheme 1).[5] Deprotection of the *t*-Boc amines **6** took place at room temperature with trifluoroacetic acid (TFA) by standard methods to give compounds **7** (Scheme 1).[7] TFA salts may not be ideal for use in biological systems due to their effect on proliferating cells, cell membranes and proteins.[8] Therefore, compounds **7a** and **7b** underwent counterion replacement to the HCl salt via the free amine by reaction with potassium carbonate followed by saturated ethereal HCl.[7] In order to determine whether the ester derivatives (**5k**, **5l**) were necessary for activity, the corresponding carboxylic acid derivatives (**5v**, **5w**) were synthesised. To determine whether a substituent at N_1 was required at all, a substituted benzyl derivative **5q** was subjected to deprotection using cerium ammonium nitrate (CAN) yielding **8** in 40% yield, according to the method of Aquino and co-workers, (Scheme 1).[9] The activities for these derivatives are shown in Table 1.[10]

Table 1
Activity of 1,4-benzodiazepine library versus *T. brucei* (N.T. = not tested; N.A. = not applicable)

	R_1	R_2	*T.b. brucei* MIC (μM) ($N = 2$)	Yield (%)
4a	Methyl	H	N.T.	N.A.
4b	Methyl	Cl	N.T.	72
4c	Ethyl	H	N.T.	72
4d	Ethyl	Cl	N.T.	60
4e	*n*-Propyl	H	N.T.	59
4f	*n*-Propyl	Cl	N.T.	39
4g	Allyl	H	N.T.	82
4h	Allyl	Cl	N.T.	60
4i	*n*-Butyl	H	N.T.	31
4j	*n*-Butyl	Cl	N.T.	39
4k	Ethyl acetyl	H	N.T.	97
4l	Ethyl acetyl	Cl	N.T.	71
4m	Methyl cyclopropyl	H	N.T.	41
4n	Methyl cyclopropyl	Cl	N.T.	32
4o	Benzyl	H	N.T.	50
4p	Benzyl	Cl	N.T.	47
4q	*p*-(OCH_3)benzyl	H	N.T.	74
4r	2-Biphenyl methyl	H	N.T.	78
4s	2-Bipehnyl methyl	Cl	N.T.	54
4t	4-Biphenyl methyl	H	N.T.	31
4u	4-Biphenyl methyl	Cl	N.T.	50
5a	Methyl	H	125	43
5b	Methyl	Cl	62.5	49
5c	Ethyl	H	62.5	38
5d	Ethyl	Cl	62.5	58
5e	*n*-Propyl	H	62.5	45
5f	*n*-Propyl	Cl	31.2	45
5g	Allyl	H	125	49
5h	Allyl	Cl	62.5	64
5i	*n*-Butyl	H	31.25	31
5j	*n*-Butyl	Cl	15.6	52
5k	Ethyl acetyl	H	125	32
5l	Ethyl acetyl	Cl	62.5	69
5m	Methyl cyclopropyl	H	62.5	17
5n	Methyl cyclopropyl	Cl	31.25	71
5o	Benzyl	H	31.25	44
5p	Benzyl	Cl	15.6	32
5q	*p*-(OCH_3)benzyl	H	N.T.	61
5r	2-Biphenyl methyl	H	125*	15
5s	2-Biphenyl methyl	Cl	7.8	59
5t	4-Biphenyl methyl	H	7.8	60
5u	4-Biphenyl methyl	Cl	3.9	40
5v	2-Acetyl	H	Inactive	58
5w	2-Acetyl	Cl	Inactive	33
7a	Methyl	H	Inactive	60
7b	Methyl	Cl	Inactive Inactive 250	98
7c	Allyl	H	62.5	63
7d	Allyl	Cl	250	89
7e	*n*-butyl	H	250	88
7f	*n*-butyl	Cl	125	73
7g	Benzyl	H	31.25	83
7h	Benzyl	Cl	7.8	83
7i	2-Biphenyl methyl	H	N.T.	81
7j	2-Biphenyl methyl	Cl		66
8	H	H		40

The MIC values obtained for these derivatives indicated that a variety of lipophilic substituents are tolerated at N_1 with the large, bulky groups 4-biphenyl methyl, **5u**, being the most active at 3.9 μM) in the methyl cyclohexyl series. Exchanging a lipophilic ester at N_1 (**5l**) with the hydrophilic carboxylic acid through hydrolysis (**5w**) completely abolishes activity, which reinforces the need for lipophilicity in this region. In general, a chloro substituent at position 7 tends to improve activity, which is fortuitous as its introduction can block aromatic oxidation in this series, as we have previously shown. Introducing water solubility by replacing the cyclohexyl group with a piperidine in N_4-space has a profound effect. All the N_1-analogues of these N_4-congeners that were prepared displayed reduced activity, with the exception of **7j**, which had comparable activity. These data imply that lipophilicity is also a primary requirement where the N_4-substituent binds, although likely repositioning enforced through the accommodation of the bulky N_1-(2-biphenylmethyl) group suggests room for manoeuvre is possible.

In order to examine whether the seven-membered diazepine ring was essential for antityrypanosomal activity, a 'one-pot' approach was developed using the method of Lee[11] to produce the related series of N_3 substituted quinazoline-2,4-diones (Scheme 2). The N_3 substituent (equivalent to N_4 in the benzodiazepines) was retained as the optimised methylcyclohexyl group[3,12] to allow a direct comparison between the two heterocyclic scaffolds from an SAR perspective (e.g., **5a** cf. **9a**; Table 2). The piperydyl analogues of the most potent quinazoline-2,4-diones were also prepared as the piperidyl derivatives (**11**) via the *t*-Boc protected intermediates (**10**).

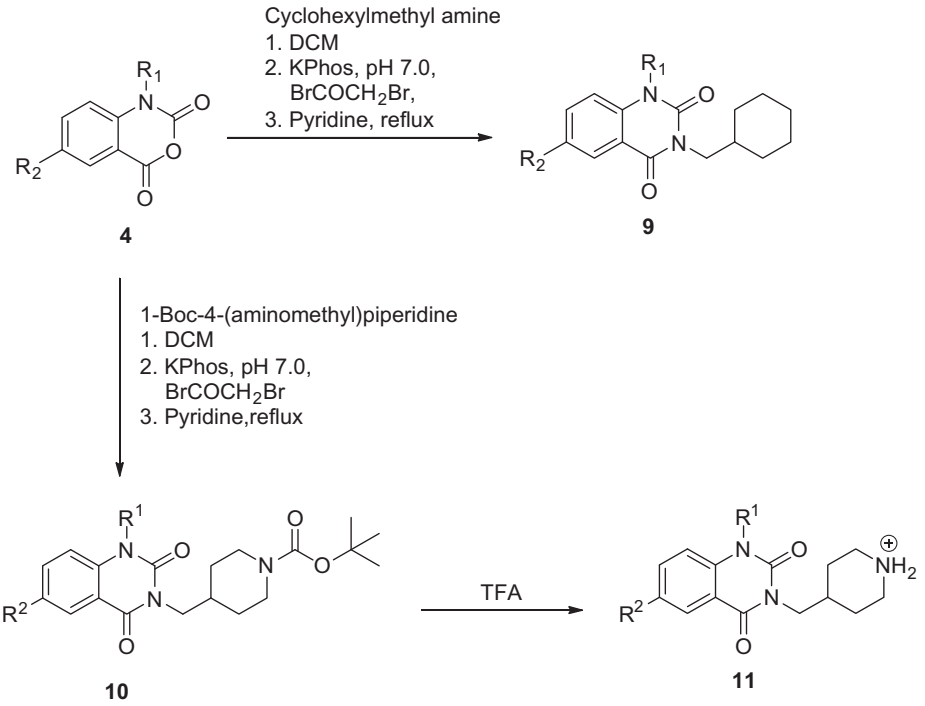
Reducing the ring size from a seven-membered diazepine to a six-membered quinazoline does not produce the same SAR-profile between the two series. For example, an ester in the N_1 position of the quinazolines (**9k**) has comparable activity with N_1-alkyl groups (e.g., **9c**), whereas it was less active in the diazepine series. Furthermore, a consistent improvement in activity through the introduction of a chloro substituent is not reproduced (cf. **9k** & **9l**; **9o** & **9p**; **9r** & **9s**). The two heterocyclic scaffolds are quite different from a conformational perspective; the quinazoline is planar whereas the diazepine is not, and the consequent orientation of the N-substituents will be quite different. The change in the SAR profiles could imply that the two series are acting against distinct targets.

Translating the most active N_1-biphenyl substituents into the quinazolines with an N_3-methylpiperidyl group has a more dramatic effect. **11c** and **11d** are the first submicromolar antritrypanosomal compounds from the quinazoline libraries to date. These compounds have predicted physicochemical properties (Table 3) more in line with drug-like compounds that would still be able to cross the blood–brain-barrier to treat stage 2 HAT.[12b] Future work will involve the development of compounds bearing recognisable P2 transporter motifs such as the addition of a guanidine moiety and shall be reported in due course.[12c]

3. Experimental

3.1. Strains and reagents

Unless otherwise stated, chemicals and solvents were of reagent or anhydrous grade and used as obtained from commercial sources



Scheme 2. Synthetic route to the quinazoline-2,4-diones and their activity against *T. brucei* following the method by Räz et al.[10]

Table 2
Activity data for the *N*-3 substituted quinazoline-2,4-diones

	R_1	R_2	*T.b. brucei* MIC (μM) (*N* = 2)	Yield (%)
9a	Methyl	H	62.5	65
9b	Methyl	Cl	31.2	58
9c	Ethyl	H	31.2	30
9d	Ethyl	Cl	15.6	59
9e	*n*-Butyl	Cl	62.5	59
9f	Ethoxycarbonyl methyl	H	31.25	50
9g	Ethoxycarbonyl methyl	Cl	250	50
9h	Benzyl	H	15.6	38
9i	Benzyl	Cl	62.5	40
9j	2-Biphenyl methyl	H	7.8	54
9k	2-Biphenyl methyl	Cl	62.5	53
9l	4-Biphenyl methyl	Cl	125	53
10a	Benzyl	Cl	62.5	56
10b	2-Biphenyl methyl	H	125	18
10c	2-Biphenyl methyl	Cl	7.8	33
10d	4-Biphenyl methyl	Cl	125	33
11a	Benzyl	Cl	15.6	52
11b	2-Biphenyl methyl	H	3.9	96
11c	2-Biphenyl methyl	Cl	0.97	90
11d	4-Biphenyl methyl	Cl	0.97	90

Table 3
Predicted physiochemical properties of selected derivatives

Sample	Total polar surface area	Log *P*	Log *D*
5a	40.620	3.1090	3.1090
5s	40.620	6.2110	6.2110
7j	52.650	4.1750	2.9440
9k	52.650	6.9310	6.9310
11c	40.620	4.8950	3.6650

without further purification. *T.b. brucei* bloodstream form strain 427 isolated from sheep in Uganda[13] was used for the in vitro screening. The cells were provided by Professor M.P. Barrett, IBLS, University of Glasgow, UK. The cells were cultured in HMI-9 medium[14] containing 20% heat activated (Foetal Calf Serum) FCS, in a 5% CO_2 atmosphere at 37 °C. Alamar Blue solution was prepared by dissolving resazurin (12.5 mg; Trek Diagnostics) in phosphate buffered saline (PBS; 100 mL) and filter/sterilized.

3.2. Antityrpanosomal activity

Minimum inhibitory concentrations (MIC's) were determined using an in vitro Alamar Blue assay on the *T.b. brucei* S427 strain according to Räz et al.[10] in sterile conditions. MIC determinations were carried out in duplicate. The assay was conducted on 96-well plates, from a 0.1 M DMSO solution of each compound, were prepared 50 μM, 200 μM and 400 μM solutions in HMI-9 medium into each well. Serial dilution of the top concentration resulted in a 100 μL compound solution in each well, to which a 100 μL suspension of trypanosome cells (2×10^4 cells/mL) were added and the plates incubated at 37 °C in a 5% CO_2 atmosphere for 48 h. Alamar Blue solution (20 μL) was added to each well and incubated for a further 24 h. Plates were read for Alamar Blue fluorescence intensity using a Perkin Elmer LS Luminescence spectrometer at 530 nm excitation and 590 nm emission.

3.3. Analytical techniques

Melting points (mp) were determined on a Stuart Scientific Melting Point Apparatus SMP1 and are in °C. IR spectra were recorded with a Mattson Genesis Series FTIR spectrometer or Jasco FT/IR-4200, solid samples were pressed potassium bromide (KBr) discs and liquid samples were films in sodium chloride (NaCl) discs. ^1H and ^{13}C NMR spectra were recorded on JEOL EX-270 (270 MHz), Bruker DPX-400 (400 MHz) and JEOL Lamda-delta 400 (400 MHz) spectrometers. The deuterated solvent used is specified for each compound, chemical shifts are expressed in parts per million. When NMR has been used as the basis of structural identification, the peaks have been assigned, due to the number of related compound, one example has been assigned fully and the remaining compounds have very similar spectral features. Reactions and column chromatographic separations were followed by

thin-layer chromatography using silica gel (with 254 nm fluorescent indicator) on alumina plates. Compounds were visualized using both short- and long-wavelength UV light. Silica gel flash chromatography was achieved using 230–400 mesh silica gel. All yields reported refer to yields of isolated compounds. Samples were submitted for elemental analysis on a Perkin Elmer 2400 Analyser. C, H and N determined simultaneously, halogens and sulfur separately, by standard methods. Samples for assay had a purity of greater than 95% by elemental analysis. Physiochemical properties were calculated using Pipeline Pilot 8.5 (Accelrys®) using standard protocols to calculate total polar surface area, Log *D* and Log *P*.

3.4. The general method for the synthesis of N1-derivatives of 1*H*-benzo[*d*][1,3]oxazine-2,4-diones (4)

Sodium hydride (0.011 mol) was added to a solution of isatoic anhydride **2** (0.01 mol) in anhydrous DMF (30 mL) and stirred for 1 h at room temperature. The required haloalkane **3** (0.011 mol) was added and the reaction mixture stirred for a further 18 h. The reaction mixture was poured onto ice and water (200 mL) to precipitate the product which was filtered, washed with water and dried then recrystallised from a suitable solvent.

3.4.1. 1-Methyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (4a)

This compounds was bought directly from Sigma Aldrich and used without further purification.

3.4.2. 6-Chloro-1-methyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (4b)

Reagents **2b** (1.98 g), sodium hydride (0.26 g) and **3a** (1.04 g) gave **4b** (1.52 g, 72%) as a white solid when recrystallised from ethylacetate: mp 202–204 °C (lit. 192–195 °C[6]); ^{1}H NMR (400 MHz; DMSO-d_6): δ 3.46 (3H, s), 7.47 (1H, d, J = 9.2 Hz), 7.89 (1H, dd, J = 2.6 Hz, J = 8.8 Hz), 7.94 (1H, d, J = 2.6 Hz), ^{13}C NMR (400 MHz; DMSO-d_6): δ 32.50, 113.86, 117.72, 128.16, 128.52, 137.20, 141.71, 148.00, 158.60; Anal. Calcd for $C_9H_6NO_3Cl$: C, 51.08; H, 2.86; N, 6.62; Cl, 16.75. Found: C 51.42; H, 2.84; N, 6.59; Cl, 16.21.

3.4.3. 1-Ethyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (4c)

Reagents **2a** (1.63 g), sodium hydride (0.26 g) and **3b** (1.20 g) gave **4c** (1.38 g, 72%) as off white crystals when recrystallised from ether/hexane: mp 113–115 °C (lit. 121–123 °C[6]); ^{1}H NMR (270 MHz; DMSO-d_6): δ 1.23 (3H, t, J = 7.1 Hz), 4.60 (2H, q, J = 7.1 Hz), 7.33 (1H, dt, J = 8.0, 0.8 Hz), 7.50 (1H, d, J = 8.5 Hz), 7.85 (1H, dt, J = 8.8, 1.6 Hz), 8.01 (1H, dd, J = 7.8, 1.6 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 12.21, 40.19, 111.84, 113.93, 124.00, 131.01, 137.51, 141.20, 147.62, 158.72; Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 63.09; H, 4.52; N, 7.51.

3.4.4. 6-Chloro-1-ethyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (4d)

Reagents **2b** (1.98 g), sodium hydride (0.26 g) and **3b** (1.20 g) gave **4d** (1.35 g, 60%) as a pale yellow solid when recrystallised from dichloromethane: mp 142–146 °C (143–145 °C[6]); ^{1}H NMR (270 MHz; $CDCl_3$): δ 1.38 (3H, t, J = 7.1 Hz), 4.14 (2H, q, J = 7.1 Hz); 7.17 (1H, d, J = 8.9 Hz), 7.20 (1H, dd, J = 8.9, 2.5 Hz), 8.12 (1H, d, J = 2.5 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 12.02, 40.32, 113.12, 115.26, 129.59, 130.20, 130.82, 137.17, 146.92, 157.46; Anal. Calcd for $C_{10}H_8NO_3Cl$: C, 53.22; H, 3.57; N, 6.20; Cl, 15.71. Found: C, 53.15; H, 3.73; N, 6.25; Cl, 15.54.

3.4.5. 1-Propyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (4e)

Reagents **2a** (1.63 g), sodium hydride (0.26 g) and **3c** (1.35 g) gave **4e** (1.21 g, 59%) as a white solid when recrystallised from methanol: mp 93–95 °C (lit. 79–81 °C[6]); ^{1}H NMR (270 MHz; $CDCl_3$): δ 1.06 (3H, t, J = 7.0 Hz), 1.74–1.88 (2H, sextet, J = 7.6 Hz), 4.35 (2H, t, J = 7.6 Hz), 7.16 (1H, d, J = 7.9 Hz), 7.32 (1H, t, J = 7.4 Hz), 7.77 (1H, td, J = 7.4 Hz), 8.18 (1H, d, J = 1.6 Hz); ^{13}C NMR (270 MHz; DMSO-d_6): δ 11.20, 20.42, 46.61, 112.00, 114.09, 124.06, 131.61, 137.41, 141.57, 147.97, 158.75; Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.34; H, 5.40; N, 6.83. Found: C, 64.61; H, 4.80; N, 6.93.

3.4.6. 6-Chloro-1-propyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (4f)

Reagents **2b** (1.98 g), sodium hydride (0.26 g) and **3c** (1.35 g) gave **4f** (0.93 g, 39%) when recrystallised from dichloromethane: mp 108–110 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.96 (3H, t, J = 7.6 Hz), 1.67–1.77 (2H, sextet, J = 7.6 Hz), 3.93 (2H, t, J = 7.6 Hz), 7.05 (1H, d, J = 8.8 Hz), 7.62 (1H, dd, J = 8.8, 2.4 Hz), 8.04 (1H, d, J = 2.4 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 11.00, 20.22, 46.71, 113.09, 115.60, 129.63, 130.17, 137.21, 139.94, 147.29, 157.48; Anal. Calcd for $C_{11}H_{10}NO_3Cl$: C, 55.13; H, 4.21; N, 5.84; Cl, 14.79. Found: C, 56.50; H, 4.89; N, 5.50; Cl, 13.63.

3.4.7. 1-Allyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (4g)

Reagents **2a** (1.63 g), sodium hydride (0.26 g) and **3d** (1.33 g) gave **4g** (1.67 g, 82%) when recrystallised methanol: mp 108–110 °C (lit. 102–104 °C[6]); ^{1}H NMR (270 MHz; DMSO-d_6): δ 4.66 (2H, dt, J = 4.3 Hz), 5.17–5.35 (2H, dd, J = 17.3, 10.5 Hz), 5.85–5.99 (1H, qd, J = 10.8, 4.6 Hz), 7.23–7.36 (2H, t, J = 7.8 Hz), 7.73 (1H, t, J = 7.3 Hz), 8.05 (1H, d, J = 7.8 Hz); ^{13}C NMR (270 MHz; DMSO-d_6): δ 46.42, 111.80, 115.16, 117.15, 123.59, 129.42, 131.17, 136.95, 141.29, 147.57, 158.91; Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.05; H, 4.13; N, 6.89.

3.4.8. 1-Allyl-6-chloro-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (4h)

Reagents **2b** (1.98 g), sodium hydride (0.26 g) and **3d** (1.33 g) gave **4h** (1.43 g, 60%) when recrystallised from methanol: mp 97–98 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 4.69 (2H, d, J = 5.1 Hz), 5.25–5.38 (2H, dd, J = 10.5 Hz), 5.84–5.98 (1H, dq, J = 10.3, 5.1 Hz), 7.11 (1H, d, J = 9.2 Hz), 7.64 (1H, dd, J = 8.9, 2.7 Hz), 8.11 (1H, d, J = 2.4 Hz); ^{13}C NMR (270 MHz; DMSO-d_6): δ 47.55, 113.19, 116.39, 119.11, 129.91, 129.97, 130.06, 137.34, 140.05, 147.42, 157.48; Anal. Calcd for $C_{11}H_8NO_3Cl$: C, 55.59; H, 3.39; N, 5.89; Cl, 14.91. Found: C, 55.61; H, 3.27; N, 5.94; Cl, 14.24.

3.4.9. 1-Butyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (4i)

Reagents **2a** (1.63 g), sodium hydride (0.26 g) and **3e** (1.51 g) gave **4i** (0.68 g, 31%) when recrystallised from methanol: mp 57–59 °C (lit. 59–61 °C[6]); ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.01 (3H, t, J = 7.6 Hz), 1.45–1.50 (2H, sextet, J = 7.6 Hz), 1.73–1.81 (2H, quintet, J = 7.6 Hz) 4.07 (2H, t, J = 7.6 Hz), 7.19 (1H, d, J = 8.4 Hz), 7.30 (1H, dt, J = 8.0, 0.8 Hz), 7.77 (1H, dt, J = 7.2, 1.2 Hz), 8.17 (1H, dd, J = 8.0, 1.2 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 13.74, 19.94, 28.91, 44.79, 111.82, 113.92, 123.88, 130.97, 137.26, 141.38, 147.75, 158.60; Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.78; H, 6.23; N, 6.26.

3.4.10. 1-Butyl-6-chloro-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (4j)

Reagents **2b** (1.98 g), sodium hydride (0.26 g) and **3e** (1.51 g) gave **4j** (0.99 g, 39%) when recrystallised from dichloromethane: mp 103–105 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.91 (3H, t, J = 7.6 Hz), 1.35–1.42 (2H, sextet, J = 7.6 Hz), 1.60–1.69 (2H, quintet, J = 8.0 Hz), 3.90–3.99 (2H, t, J = 8.0 Hz), 7.06 (1H, d, J = 9.2 Hz), 7.62 (1H, dd, J = 8.8, 2.4 Hz), 8.02 (1H, d, J = 2.4 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 13.87, 19.90, 28.86, 45.07, 113.09, 115.63, 129.60, 130.12, 137.22, 139.93, 147.24, 157.50; Anal. Calcd for $C_{12}H_{12}NO_3Cl$: C, 56.81; H, 4.77; N, 5.52; Cl, 13.98. Found C, 57.00; H, 4.49; N, 5.52; Cl, 14.15.

3.4.11. Ethyl-2-(2,4-dioxo-2*H*-benzo[*d*][1,3]oxazin-1(4*H*)-yl)acetate (4k)

Reagents **2a** (1.63 g), sodium hydride (0.26 g) and **3f** (1.84 g) gave **4k** (2.42 g, 97%) when recrystallised from ethylacetate: mp 149–151 °C (lit. 150–152 °C[6]); ^{1}H NMR (270 MHz; DMSO-d_6): δ 1.21 (3H, t, J = 7.2 Hz), 4.17 (2H, q, J = 7.2 Hz) 4.92 (2H, s), 7.36 (1H, dt, J = 7.6 Hz), 7.43 (1H, d, J = 8.8 Hz), 7.84 (1H, t, J = 8.8, 1.6 Hz), 8.05 (1H, dd, J = 7.6, 1.6 Hz); ^{13}C NMR (270 MHz; DMSO-d_6): δ 13.95, 45.69, 61.47, 111.13, 114.72, 124.13, 129.7, 137.42, 141.23, 147.73, 158.33, 167.52; Anal. Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.44; N, 5.62. Found: C, 57.79; H, 4.42; N, 5.57.

3.4.12. Ethyl 2-(6-chloro-2,4-dioxo-2*H*-benzo[*d*][1,3]oxazin-1(4*H*)-yl)acetate (4l)

Reagents **2b** (1.98 g), sodium hydride (0.26 g) and **3f** (1.84 g) gave **4l** (2.01 g, 71%) when recrystallised from ethylacetate: mp 187–189 °C (lit. 183–185 °C[6]); ^{1}H NMR (270 MHz; DMSO-d_6): δ 1.19 (3H, t, J = 7.2 Hz), 4.22 (2H, q, J = 7.2 Hz), 4.49 (2H, s), 7.54 (1H, d, J = 9.2 Hz), 7.89 (1H, dd, J = 9.2, 2.4 Hz), 8.05 (1H, d, J = 2.4 Hz); ^{13}C NMR (270 MHz; DMSO-d_6): δ 13.94, 45.95, 61.52, 112.98, 117.10, 128.16, 128.36, 136.84, 140.15, 147.40,157.33, 167.35; Anal. Calcd for $C_{12}H_{10}NO_5Cl$: C, 50.80; H, 3.55; N, 4.94; Cl, 12.49. Found: C, 51.12; H, 3.32; N, 4.76; Cl, 12.02.

3.4.13. 1-(Cyclopropylmethyl)-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (4m)

Reagents **2a** (1.63 g), sodium hydride (0.26 g) and **3g** (1.49 g) gave **4m** (0.89 g, 41%) as colourless crystals when recrystallised from DCM: mp 114–115 °C (lit. 118–121 °C[6]); ^{1}H NMR (270 MHz; DMSO-d_6): δ 0.50 (4H, m), 1.22 (1H, m), 3.97 (2H, d, J = 6.9 Hz), 7.34 (1H, dt, J = 7.9, 0.8 Hz), 7.58 (1H, d, J = 8.5 Hz), 7.85 (1H, dt, J = 8.7, 1.7 Hz), 8.02 (1H, dd, J = 7.8, 1.6 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 4.17, 9.36, 49.28, 112.06, 114.35, 124.08, 131.16, 137.36, 141.83, 148.44, 158.80; Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.36; H, 5.10; N, 6.45. Found: C, 66.49; H, 5.03; N, 6.56.

3.4.14. 1-(Cyclopropylmethyl)-6-chloro-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (4n)

Reagents **2b** (1.98 g), sodium hydride (0.26 g) and **3g** (1.49 g) gave **4n** (0.81 g, 32%) when recrystallised from ethylacetate: mp 187–189 °C (lit. 183–185 °C[6]); ^{1}H NMR (270 MHz; DMSO-d_6): δ 1.19 (3H, t, J = 7.2 Hz), 4.22 (2H, q, J = 7.2 Hz), 4.49 (2H, s), 7.54 (1H, d, J = 9.2 Hz), 7.89 (1H, dd, J = 9.2, 2.4 Hz), 8.05 (1H, d, J = 2.4 Hz); ^{13}C NMR (270 MHz; DMSO-d_6): δ 13.94, 45.95, 61.52, 112.98, 117.10, 128.16, 128.36, 136.84, 140.15, 147.40,157.33, 167.35; Anal. Calcd for $C_{12}H_{10}NO_3Cl$: C, 57.27; H, 4.01; N, 5.57; Cl, 14.09. Found: C, 57.66; H, 3.92; N, 5.56; Cl, 13.64.

3.4.15. 1-Benzyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (4o)

Reagents **2a** (1.63 g), sodium hydride (0.26 g) and **3h** (1.88 g) gave **4o** (1.27 g, 50%) when recrystallised from methanol: mp 142–144 °C (lit. 140–142 °C[6]); ^{1}H NMR (270 MHz; $CDCl_3$): δ 5.26 (2H, s), 7.06 (1H, d, J = 8.4 Hz), 7.19–7.35 (6H, m), 7.59 (1H, dt, J = 8.5, 1.6 Hz), 8.09 (1H, dd, J = 9.5, 1.6 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 48.86, 112.35, 115.09, 124.52, 126.94, 128.47, 129.49, 131.18, 134.73, 137.57, 141.50, 150.50, 158.50; Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 70.91; H, 3.89; N, 5.50.

3.4.16. 1-Benzyl-6-chloro-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (4p)

Reagents **2b** (1.98 g), sodium hydride (0.26 g) and **3h** (1.88 g) gave **4p** (1.35 g, 47%) when recrystallised from methanol: mp 146–148 °C (lit. 147–149 °C[6]); ^{1}H NMR (270 MHz; $CDCl_3$): δ 4.45 (2H, s), 6.66 (1H, d, J = 9.2 Hz), 7.22 (1H, dd, J = 9.2, 2.4 Hz), 7.29 (5H, m), 7.81 (1H, d, J = 2.4 Hz); ^{13}C NMR (270 MHz; DMSO-d_6): δ 47.86, 104.00, 117.49, 126.64, 127.55, 127.84, 128.27, 128.74, 135.10, 136.53, 140.20, 148.00, 158.00; Anal. Calcd for $C_{15}H_{10}NO_3Cl$: C, 62.61; H, 3.50; N, 4.86; Cl, 12.32. Found: C, 62.42; H, 3.37; N, 4.48; Cl, 12.27.

3.4.17. 1-(4-Methoxybenzyl)-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (4q)

Reagents **2a** (1.63 g), sodium hydride (0.26 g) and **3i** (2.20 g) gave **4q** (2.01 g, 74%) when recrystallised from methanol: mp 142–144 °C (lit. 140–142 °C[6]); ^{1}H NMR (270 MHz; $CDCl_3$): δ 3.78 (3H, s), 5.27 (2H, s), 6.85 (2H,d, J = 8.2 Hz), 7.16–7.25 (4H, m), 7.60 (1H, m), 8.12 (1H, dd, J = 8.2 Hz); Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 70.91; H, 3.89; N, 5.50.

3.4.18. 1-(2-phenyl)benzyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (4r)

Reagents **2a** (1.63 g), sodium hydride (0.26 g) and **3j** (2.72 g) gave **4r** (2.57 g, 78%) when recrystallised from dichloromethane: mp 159–161 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 5.28 (2H, s), 6.61 (1H, d, J = 8.4 Hz), 7.03–7.59 (11H, m), 8.10 (1H, dd, J = 7.8, 1.5 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): 46.97, 112.10, 114.97, 124.24, 126.01, 128.08, 128.11, 128.45, 128.92, 129.21, 130.73, 130.84, 131.65, 136.50, 137.22, 140.20, 141.25, 149.20, 158.70; Anal. Calcd for $C_{21}H_{15}NO_3$: C, 76.58; H, 4.60; N, 4.25. Found: C, 76.50; H, 4.29; N, 4.26.

3.4.19. 6-Chloro-1-(2-phenyl)benzyl-1*H*-benzo[*d*][1.3]oxazine-2,4-dione (4s)

Reagents **2b** (1.98 g), sodium hydride (0.26 g) and **3j** (2.72 g) gave **4s** (1.96 g, 54%) when recrystallised from dichloromethane: mp 171–173 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 5.10 (2H, s), 6.94 (1H, d, J = 9.0 Hz), 7.28–7.55 (9H, m), 7.72–7.76 (1H, dd, J = 8.9, 2.5 Hz), 7.96 (1H, d, J = 2.5 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 46.95, 113.06, 116.48, 126.03, 128.06, 128.15, 128.41, 128.83, 129.01, 129.84, 130.66, 131.12, 136.99, 139.58, 139.73, 141.13, 148.09, 157.24; Anal. Calcd for $C_{21}H_{14}NO_3Cl$: C, 73.63; H, 6.18; N, 5.92; Cl, 7.49. Found: C, 73.72; H, 5.81; N, 6.13; Cl, 8.09.

3.4.20. 1-(4-Phenyl)benzyl-1*H*-benzo[*d*][1.3]oxazine-2,4-dione (4t)

Reagents **2a** (1.63 g), sodium hydride (0.26 g) and **3k** (2.72 g) gave **4t** (1.02 g, 31%) when purified by column chromatography, mobile phase: dichloromethane, R_f = 0.59: mp 153–154 °C; ^{1}H NMR (270 MHz $CDCl_3$): δ 5.27 (2H, s), 6.62 (1H, d, J = 8.4 Hz), 7.18–7.55 (11H, m), 8.12 (1H, dd, J = 7.8, 1.6 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 47.01, 112.06, 114.99, 124.24, 126.77, 128.45, 128.49, 128.85, 129.23, 130.76, 130.89, 131.69, 137.19, 141.31, 148.65, 158.52; Anal. Calcd for $C_{21}H_{15}NO_3$: C, 76.58; H, 4.59; N, 4.25. Found: C, 76.47; H, 4.40; N, 4.27.

3.4.21. 1-(4-Phenyl)benzyl-6-chloro-1*H*-benzo[*d*][1.3]oxazine-2,4-dione (4u)

Reagents **2b** (1.98 g), sodium hydride (0.26 g) and **3k** (2.72 g) gave **4u** (1.82 g, 50%) when recrystallised from dichloromethane: mp 172–174 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 4.45 (2H, d, J = 3.7 Hz), 6.62 (1H, d, J = 9.1 Hz), 7.26–7.66 (10H, m), 7.99 (1H, d, J = 1.7 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 46.53, 110.72, 112.95, 119.25, 126.82, 127.13, 128.30, 128.45, 130,60, 134.34, 134.60, 137.06, 139.60, 140.05, 148.85, 167.05. Anal. Calcd for $C_{21}H_{14}NO_3Cl$: C, 69.33; H, 3.88; N, 3.85; Cl, 9.75. Found: C, 69.29; H, 3.88; N, 3.88; Cl, 9.44.

3.5. The general method for the synthesis of 4-cyclohexylmethyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,4-diones and 4-(1-Boc-piperidin-4-yl)methyl analogues 5, 6 and 7

To cyclohexane methylamine or 1-Boc-4(aminomethyl)piperidine (6.5 mmol, 1.15 equiv) in dry DCM (50 mL) (if amine hydrochloride salt is used then stir with 1.15 equiv triethylamine to give free base) was added finely powdered N-substituted isatoic anhydride **4** (5.65 mmol, 1 equiv) at a rate to keep the DCM below reflux temperature. The reaction was stirred until TLC (EtOAc:hexane, 50:50) showed that the reaction was complete (1–16 h). The DCM washed with water (2 × 25 mL), separated and returned to the flask was stirred vigorously with 1 M phosphate buffer (see below) (50 mL) at 5 °C. Bromoacetyl bromide (7.5 mmol, 1.33 equiv) was added dropwise and the reaction monitored by TLC (EtOAc:hexane, 50:50, 30 min to 4 h). The DCM was separated, dried and returned to the flask then DBU (6.4 mmol, 1.13 equiv) was added dropwise to ensure minimal rise in temperature, and the reaction stirred until TLC showed complete conversion (DCM:acetone, 90:10) 1–16 h. The DCM was washed with water (2 × 25 mL), 1 N citric acid (25 mL) and 1 N HCl (2 × 25 mL), then the combined aqueous extracts were back-extracted with DCM (2 × 50 mL). The combined organic layers were dried with magnesium sulfate then evaporated. The crude mixture was recrystallised from a suitable solvent or if necessary applied to a silica gel column.

3.6. Preparation of 1 M phosphate buffer

A 1 M phosphate buffer was prepared from a mixture of 1 M potassium phosphate monobasic and 1 M potassium phosphate dibasic buffers made separately then mixed together until pH 7 is obtained (approximately 1:1.2 ratio).

3.6.1. 4-(Cyclohexylmethyl)-1-methyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,4-dione (5a)

Reagents *N*-methyl isatoic anhydride (1.00 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5a** (0.70 g, 43%) when recrystallised from dichloromethane/hexane: mp 89–91 °C (lit. 89–91 °C[3]); ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.97–1.06 (2H, d, J = 3.6, 11.4 Hz), 1.11–1.28 (3H, m), 1.59–1.81 (6H, m), 3.37 (3H, s), 3.50 (2H, sext, J = 8.0 Hz), 3.68 (1H, d, J = 14.7 Hz), 4.00 (1H, d, J = 14.7 Hz), 7.60 (1H, dd, J = 8.2, 1.0 Hz), 7.27 (1H, dt, J = 7.8, 1.1 Hz), 7.49 (1H, dt, J = 8.2, 1.7 Hz), 7.85 (1H, dd, J = 7.8, 1.7 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 25.85, 25.90, 26.54, 30.79, 35.01, 36.50, 52.12, 54.91, 120.94, 125.79, 129.36, 131.08, 132.07, 141.09, 167.22, 169.11; Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.31; H, 7.74; N, 9.78. Found: C, 71.95; H, 7.40; N, 9.65.

3.6.2. 7-Chloro-4-(cyclohexylmethyl)-1-methyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,4-dione (5b)

Reagents **4b** (1.31 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g), DBU (0.90 g) gave **5b** (0.89 g, 49%) when purified by column chromatography, mobile phase: dichloromethane, R_f = 0.73: mp 123–125 °C (lit. 123–125 °C[3]); ^{1}H NMR (270 MHz; $CDCl_3$): δ 0.98–1.09 (2H, m), 1.15–1.29 (3H, m), 1.63–1.81 (6H, m), 3.37 (3H, s), 3.44 (1H, dd, J = 13.5, 8.0 Hz), 3.56 (1H, dd, J = 13.4, 6.9 Hz), 3.73 (1H, d, J = 14.7 Hz), 4.00 (1H, d, J = 14.6 Hz), 7.12 (1H, d, J = 8.7 Hz), 7.46 (1H, dd, J = 8.7, 2.6 Hz), 7.86 (1H, d, J = 2.5 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 25.84, 25.88, 26.51, 30.77, 35.01, 36.48, 51.98, 55.02, 122.43, 129.92, 130.87, 131.47, 132.11, 139.57, 166.19, 168.91; Anal. Calcd for $C_{17}H_{21}N_2O_2Cl$: C, 63.65; H, 6.60; N, 8.73; Cl, 11.05. Found: C, 63.54; H, 6.54; N, 8.60; Cl, 11.16.

3.6.3. 4-(Cyclohexylmethyl)-1-ethyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,4-dione (5c)

Reagents **4c** (1.08 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5c** (0.64 g, 38%) when purified by column chromatography (mobile phase dichloromethane): mp 99–98 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 1.01–1.10 (2H, m), 1.15–1.29 (3H, m), 1.19 (3H, t, J = 7.1 Hz), 1.61–1.83 (6H, m), 3.45 (1H, dd, J = 13.4, 6.5 Hz), 3.58 (1H, dd, J = 13.5, 8.5 Hz), 3.67 (1H, d, J = 14.5 Hz), 3.73 (1H, sextet, J = 7.0 Hz), 3.97 (1H, d, J = 14.5 Hz), 4.19 (1H, sextet, J = 7.1 Hz), 7.25–7.33 (2H, m), 7.51 (1H, dt, J = 7.4, 1.7 Hz), 7.88 (1H, dd, J = 7.7, 1.6 Hz); Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 72.15; H, 8.12; N, 9.29.

3.6.4. 7-Chloro-4-(cyclohexylmethyl)-1-ethyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,4-dione (5d)

Reagents **4d** (1.27 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g), DBU (0.90 g) gave **5d** (1.10 g, 58%) when purified by column chromatography, mobile phase: DCM: mp 140–141 °C); ^{1}H NMR (270 MHz; $CDCl_3$): δ 1.25–1.95 (2H, m), 1.30–1.40 (3H, m), 1.76–1.89 (6H, m), 3.49 (3H, s), 3.58 (1H, d, J = 8.0 Hz), 3.64 (1H, d, J = 7.0 Hz), 3.82 (1H, d, J = 14.8 Hz), 4.09 (1H, d, J = 14.8 Hz), 7.24 (1H, d, J = 8.7 Hz), 7.58 (1H, dd, J = 8.7, 2.6 Hz), 7.97 (1H, d, J = 2.6 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 25.72, 26.38, 30.63, 34.94, 36.33, 51.83, 54.00, 122.32, 130.54, 130.71, 131.31, 131.98, 139.44, 166.05, 168.77; Anal. Calcd for $C_{18}H_{23}N_2O_2Cl$: C, 63.64; H, 6.60; N, 8.73; Cl, 11.05. Found: C, 63.74; H, 6.41; N, 8.80; Cl, 11.22.

3.6.5. 4-(Cyclohexylmethyl)-1-propyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (5e)

Reagents **4e** (1.16 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5e** (0.80 g, 45%) when recrystallised from ethylacetate: mp 95–96 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 0.81 (3H, t, J = 7.3 Hz), 0.99 (2H, m), 1.14–1.25 (5H, m), 1.45–1.81 (6H, m), 3.42–3.62 (3H, m), 3.63 (1H, d, J = 14.6 Hz), 3.95 (1H, d, J = 14.6 Hz), 4.16–4.27 (1H, q, J = 7.0 Hz), 7.22–7.32 (2H, m), 7.46–7.52 (1H, t, J = 7.3 Hz), 7.84 (1H, d, J = 7.8 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 11.31, 21.20, 25.91, 26.51, 30.83, 36.54, 48.71, 52.43, 54.86, 121.76, 126.01, 130.49, 131.49, 131.93, 139.80, 167.43, 168.74; Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 73.56; H, 8.34; N, 8.90. Found: C, 73.54; H, 8.63; N, 8.27.

3.6.6. 7-Chloro-4-(cyclohexylmethyl)-1-propyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (5f)

Reagents **4f** (1.35 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5f** (0.89 g, 45%) when recrystallised from ethylacetate/hexane: mp 82–84 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 0.89 (3H, t, J = 7.4 Hz), 1.06–1.15 (2H, m), 1.21–1.35 (3H, m), 1.48–1.87 (8H, m), 3.55–3.64 (3H, m), 3.72 (1H, d, J = 14.5 Hz), 4.01 (1H, d, J = 14.6 Hz), 4,22–4.33 (1H, quintet, J = 8.7 Hz), 7.24 (1H, d, J = 8.8 Hz), 7.50 (1H, dd, J = 8.8, 2.6 Hz), 7.91 (1H, d, J = 2.6 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 11.30, 21.17, 25.79, 25.91, 26.50, 30.82, 36.53, 48.77, 52.30, 54.98, 123.29, 130.89, 131.70, 131.80, 132.01, 138.50, 166.70, 168.80; Anal. Calcd for $C_{19}H_{25}N_2O_2Cl$: C, 65.41; H, 7.22; N, 8.03; Cl, 10.16. Found: C, 65.47; H, 7.30; N, 7.94; Cl, 10.22.

3.6.7. 1-Allyl-4-(cyclohexylmethyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (5g)

Reagents **4g** (1.15 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5g** (0.86 g, 49%) when recrystallised from ethylacetate/hexane: mp 90–92 °C; ^{1}H NMR (270 MHz $CDCl_3$): δ 0.94–1.06 (2H, m), 1.09–1.27 (3H, m), 1.65–1.84 (6H, m), 3.50 (2H, d, J = 7.7 Hz), 3.68 (1H, d,

J = 14.6 Hz), 4.02 (1H, d, J = 14.3 Hz), 4.36–4.48 (2H, qd, J = 7.0, 3.0 Hz), 5.17–5.23 (2H, d, J = 10.0 Hz), 5.81–5.96 (1H, m), 7.26–7.32 (2H, m), 7.44 (1H, td, J = 7.6, 1.9 Hz), 7.85 (1H, d, J = 1.9 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 25.82, 25.91, 26.53, 30.78, 36.43, 50.64, 52.22, 54.91, 117.80, 121.41, 126.05, 129.86, 131.10, 132.02, 133.03, 140.31, 167.45, 168.38; Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.03; H, 7.75; N, 8.96. Found: C, 73.03; H, 7.59; N, 9.02.

3.6.8. 1-Allyl-7-chloro-4-(cyclohexylmethyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (5h)

Reagents **4h** (1.34 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5h** (1.25 g, 64%) when recrystallised from methanol: mp 101–102 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 0.88–1.08 (2H, m), 1.30–1.24 (3H, m), 1.59–1.80 (6H, m), 3.42–3.57 (2H, m), 3.69 (1H, d, J = 14.6 Hz), 3.99 (1H, d, J = 14.6 Hz), 4.34 (2H, qd, J = 14.3, 7.0 Hz), 5.14–5.19 (1H, d, J = 12.2 Hz), 5.21–5.23 (1H, d, J = 5.7 Hz), 5.78–5.93 (1H, m), 7.23 (1H, d, J = 8.6 Hz), 7.39 (1H, dd, J = 8.7, 2.4 Hz), 7.83 (1H, d, J = 2.4 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 25.78, 25.87, 26.47, 30.74, 36.43, 50.60, 52.05, 54.99, 118.10, 122.90, 130.84, 131.19, 131.66, 132.02, 132.73, 138.74, 166.34, 167.94; Anal. Calcd for $C_{19}H_{23}N_2O_2Cl$: C, 65.78; H, 6.69; N, 8.07; Cl, 10.22. Found: C, 66.07; H, 6.64; N, 7.98; Cl, 9.96.

3.6.9. 1-Butyl-4-(cyclohexylmethyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (5i)

Reagents **4i** (1.24 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5i** (0.58 g, 31%) when recrystallised from ethylacetate: mp 87–88 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.82 (3H, t, J = 7.0 Hz), 0.93–1.09 (2H, m), 1.14–1.29 (5H, m), 1.41–1.59 (2H, sextet, J = 8.1 Hz), 1.63–1.85 (6H, m), 3.43 (1H, q, J = 6.7 Hz), 3.53–3.61 (2H, m), 3.64 (1H, d, J = 14.5 Hz), 3.95 (1H, d, J = 14.5 Hz), 4.24 (1H, quintet, J = 7.0 Hz), 7.22 (1H, d, J = 7.8 Hz), 7.27 (1H, t, J = 7.7 Hz), 7.49 (1H, td, J = 7.9, 1.6 Hz), 7.84 (1H, dd, J = 7.8, 1.6 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 13.74, 19.93, 25.82, 26.42, 29.89, 30.70, 36.43, 46.77, 52.35, 54.82, 121.68, 125.92, 130.36, 130.98, 131.86, 139.72, 167.33, 168.59; Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.12; H, 8.60; N, 8.52. Found: C, 73.08; H, 8.34; N, 8.57.

3.6.10. 1-Butyl-7-chloro-4-(cyclohexylmethyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (5j)

Reagents **4j** (1.43 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5j** (1.07 g, 52%) when recrystallised from ethylacetate/hexane: mp 80–82 °C; ^{1}H NMR (270 MHz $CDCl_3$): δ 0.81–0.86 (3H, t, J = 7.3 Hz), 0.97–1.08 (2H, quintet, J = 6.0 Hz), 1.13–1.29 (4H, sextet, J = 7.4 Hz), 1.39–1.56 (2H, m), 1.68–1.79 (7H, m), 3.40–3.58 (3H, m), 3.65 (1H, d, J = 14.5 Hz), 3.93 (1H, d, J = 14.5 Hz), 4.21–4.32 (1H, quintet, J = 7.0 Hz), 7.17 (1H, d, J = 8.8 Hz), 7.42 (1H, dd, J = 8.8, 2.6 Hz), 7.83 (1H, d, J = 2.6 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 14.26, 20.50, 26.25, 26.36, 26.94, 30.39, 31.24, 36.97, 47.35, 52.77, 55.47, 123.73, 131.33, 131.60, 131.70, 132.45, 138.80, 165.80, 168.72; Anal. Calcd for $C_{20}H_{27}N_2O_2$ Cl: C, 66.19; H, 7.51; N, 7.72; Cl, 9.77. Found: C, 65.88; H, 7.48; N, 7.61; Cl, 10.06.

3.6.11. Ethyl-2-(4-(cyclohexylmethyl)-2,5-dioxo-2,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-1-yl)acetate (5k)

Reagents **4k** (1.33 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5k** (0.65 g, 32%) when recrystallised from ethylacetate/hexane: mp 96–98 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 1.12–1.15 (2H, m), 1.28–1.41 (6H, m), 1.77 (6H, m), 3.51–3.71 (1H, dd, J = 13.4, 8.1 Hz), 3.64–3.72 (1H, dd, J = 13.4, 6.9 Hz), 3.80 (1H, dd, J = 14.6 Hz), 4.18 (1H, dd, J = 14.6 Hz), 4.31–4.40 (3H, m), 4.69 (1H, d, J = 13.6 Hz), 7.24 (1H, d, J = 8.0 Hz), 7.37 (1H, t, J = 7.6 Hz), 7.56 (1H, t, J = 7.7 Hz), 7.97 (1H, d, J = 7.7 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 14.10, 25.68, 26.35, 30.61, 36.32, 50.12, 51.53, 54.71, 61.82, 120.98, 126.23, 129.55, 130.96, 132.12, 139.85, 167.21, 168.57, 168.63; Anal. Calcd for $C_{20}H_{26}N_2O_4$: C, 67.01; H, 7.32; N, 7.81. Found: C, 67.04; H, 7.43; N, 7.79.

3.6.12. Ethyl-2-(7-chloro-4-(cyclohexylmethyl)-2,5-dioxo-2,3,4,5-tetrahydro benzo[*e*][1,4]diazepin-1-yl)acetate (5l)

Reagents **4l** (1.52 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5l** (1.53 g, 69%) when recrystallised from ethylacetate/hexane: mp 120–122 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 1.02–1.08 (2H, m), 1.18–1.32 (6H, m), 1.64–1.78 (6H, m), 3.37–3.45 (1H, dd, J = 13.5, 7.9 Hz), 3.55–3.63 (1H, dd, J = 13.4, 6.9 Hz), 3.71 (1H, d, J = 14.7 Hz), 4.06 (1H, d, J = 14.7 Hz), 4.21–4.29 (3H, m), 4.57 (1H, d, J = 17.4 Hz), 7.10 (1H, d, J = 8.8 Hz), 7.42 (1H, dd, J = 8.7, 2.6 Hz), 7.86 (1H, d, J = 2.5 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 14.10, 25.65, 25.70, 26.31, 30.58, 36.29, 50.07, 51.39, 54.82, 61.96, 122.56, 130.72, 130.93, 131.98, 132.09, 138.34, 165.92, 168.23, 168.40; Anal. Calcd for $C_{20}H_{25}N_2O_4Cl$: C, 61.13; H, 6.42; N, 7.13; Cl, 9.02. Found: C 61.21; H, 6.60; N, 7.02; Cl, 8.86.

3.6.13. 1-Cyclopropylmethyl-4-(cyclohexylmethyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (5m)

Reagents **4m** (1.23 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5m** (0.31 g, 17%) when purified by column chromatography, mobile phase DCM: mp 123–125 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.15–0.23 (2H, m), 0.39–0.47 (2H, m), 0.91–0.99 (1H, m), 0.99–1.10 (2H, m), 1.14–1.33 (3H, m), 1.66–1.79 (5H,m), 1.79–1.86 (1H, m), 3.37 (1H, dd, J = 13.4, 6.1 Hz), 3.61 (1H, dd, J = 14.3, 6.1 Hz), 3.67 (1H, dd, J = 13.4, 8.9 Hz), 3.68 (1H, d, J = 14.5 Hz), 4.01 (1H, d, J = 14.5 Hz), 4.06 (1H, dd, J = 14.3, 8.0 Hz), 7.31 (1H, m), 7.32 (1H, m), 7.50 (1H, dt, J = 8.2, 1.7 Hz), 7.89 (1H, dd, J = 8.1, 1.8 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 4.12, 4.20, 10.09, 25.85, 25.94, 26.55, 30.72, 30.88, 36.53, 51.59, 52.44, 54.99, 122.18, 126.05, 130.66, 131.08, 131.86, 140.01, 167.43, 168.75, 168.40; Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C 73.62; H, 8.25; N, 8.50.

3.6.14. 1-Cyclopropylmethyl-7-chloro-4-(cyclohexylmethyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (5n)

Reagents **4n** (1.42 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5n** (71%) when purified by column chromatography, mobile phase DCM: mp 123–125 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.15–0.23 (2H, m), 0.39–0.47 (2H, m), 0.91–0.99 (1H, m), 0.99–1.10 (2H, m), 1.14–1.33 (3H, m), 1.66–1.79 (5H,m), 1.79–1.86 (1H, m), 3.37 (1H, dd, J = 13.4, 6.1 Hz), 3.61 (1H, dd, J = 14.3, 6.1 Hz), 3.67 (1H, dd, J = 13.4, 8.9 Hz), 3.68 (1H, d, J = 14.5 Hz), 4.01 (1H, d, J = 14.5 Hz), 4.06 (1H, dd, J = 14.3, 8.0 Hz), 7.31 (1H, m), 7.32 (1H, m), 7.50 (1H, dt, J = 8.2, 1.7 Hz), 7.89 (1H, dd, J = 8.1, 1.8 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 4.12, 4.20, 10.09, 25.85, 25.94, 26.55, 30.72, 30.88, 36.53, 51.59, 52.44, 54.99, 122.18, 126.05, 130.66, 131.08, 131.86, 140.01, 167.43, 168.75, 168.40; Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 66.56; H, 6.98; N, 7.76; Cl, 9.82; Found: C 66.10; H, 6.84; N, 7.82, Cl, 10.35.

3.6.15. 1-Benzyl-4-(cyclohexylmethyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (5o)

Reagents **4o** (1.43 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5o** (0.90 g, 44%) when recrystallised from ethylacetate/hexane: mp 132–133 °C (lit. 117–120 °C[14]); ^{1}H NMR (270 MHz; $CDCl_3$): δ 0.91–1.08 (2H, quintet, J = 11.8 Hz), 1.13–1.21 (3H, m), 1.54–1.82 (6H, m),

3.44–3.61 (2H, dq, J = 7.0 Hz), 3.74 (1H, d, J = 14.4 Hz), 4.10 (1H, d, J = 14.5 Hz), 5.09 (2H, s), 7.15–7.32 (7H, m), 7.41 (1H, dt, J = 7.5, 1.7 Hz), 7.85 (1H, dd, J = 7.8, 1.7 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 26.33, 26.98, 31.21, 31.32, 36.95, 51.77, 52.68, 55.47, 122.06, 126.62, 127.75, 128.12, 129.39, 130.40, 131.65, 132.60, 137.30, 140.50, 168.30, 169.20; Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 75.98; H, 7.50; N, 7.55.

3.6.16. 1-Benzyl-7-chloro-4-(cyclohexylmethyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (5p)

Reagents **4p** (1.63 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5p** (0.72 g, 32%) when recrystallised from ethylacetate: mp 138–140 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 0.95–1.04 (2H, m), 1.13–1.26 (3H, m), 1.54–1.79 (6H, m), 3.49–3.53 (2H, d, J = 8.4 Hz), 3.76 (1H, d, J = 14.6 Hz), 4.07 (1H, d, J = 14.6 Hz), 4.99–5.14 (2H, dd, J = 14.7, 10.3 Hz), 7.13–7.16 (3H, d, J = 8.6 Hz), 7.23–7.32 (3H, m), 7.33 (1H, dd, J = 8.9, 1.4 Hz), 7.83 (1H, d, J = 1.4 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 25.84, 26.47, 30.72, 36.46, 51.19, 52.08, 55.09, 123.10, 127.29, 127.85, 128.84, 130.39, 131.42, 131.79, 132.01, 136.38, 138.57, 166.07, 168.31; Anal. Calcd for $C_{23}H_{25}N_2O_2Cl$: C, 69.59; H, 6.36; N, 7.05; Cl, 8.93. Found: C, 69.64; H, 6.19; N, 7.02; Cl, 8.75.

3.6.17. 1-(4-Methoxybenzyl)-4-(cyclohexylmethyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (5q)

Reagents **4q** (1.60 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5q** (1.35 g, 61%) when recrystallised from ethylacetate/hexane: mp 132–133 °C (lit. 117–120 °C[14]); ^{1}H NMR (270 MHz; $CDCl_3$): δ 0.97–1.74 (11H, m), 3.69 (2H, m), 3.75 (4H, m), 4.04 (1H, d, J = 14.5 Hz), 4.93 (1H, d, J = 15.1 Hz), 5.08 (1H, d, J = 15.1 Hz), 6.75 (2H, m), 7.05 (2H, m), 7.08–7.24 (3H, m), 7.84 (1H, dd, J = 7.5 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 25.7, 26.4, 30.7, 36.4, 50.5, 52.2, 54.9, 55.3, 114.2, 121.7, 126.0, 128.7, 130.1, 130.2, 131.0, 131.8, 140.0, 159.0, 167.2, 168.6; Anal. Calcd for $C_{24}H_{28}N_2O_3$: C, 76.21; H, 7.23; N, 7.73. Found: C, 75.98; H, 7.50; N, 7.55.

3.6.18. 4-Cyclohexylmethy-1-(2-phenyl)benzyl-3,4-dihydro-1*H*-1,4-benzo[*e*][1,4] diazepine-2,5-dione (5r)

Reagents **4r** (1.86 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5r** (0.37 g, 15%) when recrystallised from ethylacetate: mp 164–165 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 1.02–1.27 (5H, m), 1.66–1.81 (6H, m), 3.41–3.48 (1H, dd, J = 12.4, 8.0 Hz), 3.54–3.61 (1H, dd, J = 12.4, 6.8 Hz), 3.71 (1H, d, J = 14.5 Hz), 4.03 (1H, d, J = 14.5 Hz), 4.94 (1H, d, J = 16.9 Hz), 5.15 (1H, d, J = 16.9 Hz), 6.82 (1H, dd, J = 8.4, 1.2 Hz), 7.16–7.44 (11H, m), 7.78 (1H, dd, J = 7.6, 1.8 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 25.92, 26.52, 30.85, 36.58, 48.34, 52.13, 54.92, 121.31, 125.92, 127.17, 127.38, 127.47, 128.05, 128.51, 129.34, 130.05, 130.30, 131.03, 131.79, 133.84, 139.80, 140.65, 141.45, 167.30, 168.80; Anal. Calcd for $C_{29}H_{30}N_2O_2$: C, 79.41; H, 6.91; N, 6.39. Found: C, 78.98; H, 6.95; N, 6.30.

3.6.19. 7-Chloro-4-cyclohexylmethy-1-(2-phenyl)benzyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (5s)

Reagents **4s** (2.06 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5s** (1.57 g, 59%) when recrystallised from ethylacetate/hexane: mp 132–134 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 1.03–1.14 (2H, m), 1.24–1.26 (3H, m), 1.64–1.81 (6H, m), 3.43–3.66 (2H, m), 3.77 (1H, d, J = 14.5 Hz), 4.04 (1H, d, J = 14.5 Hz), 4.95 (1H, d, J = 15.8 Hz), 5.27 (1H, d, J = 15.8 Hz), 6.77 (1H, d, J = 8.9 Hz), 7.22–7.50 (10H, m), 7.81 (1H, d, J = 2.6 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 25.89, 26.49, 30.82, 36.54, 48.10, 52.00, 55.03, 122.86, 127.50, 127.65, 128.12, 128.59, 129.31, 130.43, 130.74, 131.32, 131.52, 131.71, 133.42, 138.06, 140.53, 141.63, 166.02, 168.47; Anal. Calcd for $C_{29}H_{29}N_2O_2Cl$: C, 73.63; H, 6.18; N, 5.92; Cl, 7.49. Found: C, 73.72; H, 5.81; N, 6.13; Cl, 8.09.

3.6.20. 4-Cyclohexylmethy-1-(4-phenyl)benzyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (5t)

Reagents **4t** (1.86 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5t** (1.48 g, 60%) when purified by column chromatography, mobile phase: DCM, R_f = 0.3: mp 157–160 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 0.98–1.28 (5H, m), 1.61–1.81 (6H, m), 3.44 (1H, dd, J = 13.5, 8.0 Hz), 3.58 (1H, dd, J = 13.4, 6.7 Hz), 3.73 (1H, d, J = 14.4 Hz), 4.06 (1H, d, J = 14.5 Hz), 4.95 (1H, d, J = 15.9 Hz), 5.18 (1H, d, J = 15.9 Hz), 6.84 (1H, dd, J = 8.3, 1.3 Hz), 7.16–7.44 (11H, m), 7.80 (1H, dd, J = 7.6, 1.8 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 25.89, 25.96, 26.56, 30.91, 36.64, 48.38, 52.20, 54.98, 121.36, 125.95, 127.23, 127.42, 127.51, 128.09, 128.28, 128.55, 129.34, 130.34, 131.08, 131.81, 133.91, 139.78, 140.70, 141.59, 167.39, 168.90; Anal. Calcd for $C_{29}H_{30}N_2O_2$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.74; H, 6.79; N, 6.48.

3.6.21. 7-Chloro-4-cyclohexylmethy-1-(4-phenyl)benzyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (5u)

Reagents **4u** (2.06 g), cyclohexanemethylamine (0.74 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **5u** (1.07 g, 40%) when recrystallised from ethylacetate/hexane: mp 160–162 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.98–1.01 (2H, m), 1.03–1.18 (3H, m), 1.54–1.75 (6H, m), 3.43–3.66 (2H, m), 3.77 (1H, d, J = 14.5 Hz), 4.09 (1H, d, J = 14.5 Hz), 5.04–5.15 (2H, dd, J = 15.8, 26.8 Hz), 7.22 (3H, m), 7.32–7.41 (4H, m), 7.51 (4H, m), 7.84 (1H, d, J = 2.6 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 25.89, 26.49, 30.82, 36.54, 48.10, 52.00, 55.03, 122.86, 127.50, 127.65, 128.12, 128.59, 129.31, 130.43, 130.74, 131.32, 131.52, 131.71, 133.42, 138.06, 140.53, 141.63, 166.02, 168.47; Anal. Calcd for $C_{29}H_{29}N_2O_2Cl$: C, 73.64; H, 6.18; N, 5.95; Cl, 7.49. Found: C, 73.83; H, 6.13; N, 5.87; Cl, 8.09.

3.6.22. Hydrolysis of *N*1-ethoxycarbonylmethyl derivatives 5v and 5w

To a suspension of *N*1-ethoxycarbonylmethyl derivative (ester) (0.456 mmol) in THF (20 mL) was added 1 N aqueous NaOH (3.0 mL). The reaction mixture was stirred at room temperature for 24 h, quenched with glacial acetic acid and the solvent removed under reduced pressure. The residue was recrystallised from diethylether.

3.6.23. 2-(4-(Cyclohexylmethyl)-2,5-dioxo-2,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-1-yl)acetic acid (5x)

Compound **5x** achieved in 58% yield (87 mg): mp 198–200 °C; ^{1}H NMR (400 MHz; DMSO-d_6): δ 0.91 (2H, m), 1.08–1.18 (3H, m), 1.60–1.69 (6H, m), 3.31 (1H, quintet, J = 6.2 Hz), 3.49 (1H, quintet, J = 6.2 Hz), 3.76 (1H, d, J = 14.9 Hz), 4.07 (1H, d, J = 14.9 Hz), 4.47 (2H, dd, J = 20.2, 17.6 Hz), 7.33 (2H, m), 7.55 (1H, dt, J = 8.3, 1.3 Hz), 7.72 (1H, dd, J = 8.3, 1.3 Hz), 12.90 (1H, s); ^{13}C NMR (400 MHz; DMSO-d_6): δ 25.81, 26.58, 30.48, 36.14, 49.77, 51.38, 54.21, 122.04, 126.02, 129.59, 130.79, 132.49, 140.27, 166.96, 169.16, 170.50; Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.09; H, 7.27; N, 8.13.

3.6.24. 2-(7-Chloro-4-(cyclohexylmethyl)-2,5-dioxo-2,3,4,5-tetrahydrobenzo [*e*][1,4]diazepin-1-yl)acetic acid (5y)

Compound **5y** achieved in 33% yield (55 mg): mp 172–174 °C; ^{1}H NMR (400 MHz; DMSO-d_6): δ 0.91 (2H, m), 1.08–1.17 (3H, m), 1.56–1.76 (6H, m), 3.30 (1H, quintet, J = 7.0 Hz), 3.46 (1H, quintet, J = 8.8 Hz), 3.76 (1H, d, J = 14.9 Hz); 4.15 (1H, d, J = 14.9 Hz); 4.46 (2H, dd, J = 28.6, 17.6 Hz), 7.37 (1H, d, J = 8.4 Hz), 7.66 (2H, m),

13.10 (1H, s); ^{13}C NMR (400 MHz; DMSO-d_6): δ 25.93, 26.55, 30.64, 36.07, 49.67, 51.22, 54.34, 124.38, 130.03, 130.10, 131.27, 132.22, 139.18, 165.73, 168.94, 170.41; Anal. Calcd for $C_{18}H_{21}ClN_2O_4$: C, 59.26; H, 5.80; N, 7.68; Cl, 9.72. Found: C, 59.01; H, 5.73; N, 7.58; Cl, 9.52.

3.6.25. *tert*-Butyl-4-(1-methyl-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)methyl)piperidine-1-carboxylate (6a)

N-Methyl isatoic anhydride **4a** (1.00 g), 1-Boc-4-(aminomethyl)piperidine (1.39 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **6a** (0.90 g, 41%) when recrystallised from ethylacetate/hexane: mp 137–139 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.23–1.31 (2H, dd, J = 12.0, 7.6 Hz), 1.47 (9H, s), 1.58–1.66 (2H, dd, J = 13.2, 9.2 Hz), 1.97–2.05 (1H, m), 2.74 (2H, q, J = 7.2 Hz), 3.40 (3H, s), 3.54 (2H, t, J = 5.6 Hz), 3.70 (1H, d, J = 14.4 Hz), 4.05 (1H, d, J = 14.8 Hz), 4.13 (2H, t, J = 8.0 Hz), 7.21 (1H, d, J = 8.4 Hz), 7.29 (1H, t, J = 7.6 Hz), 7.52 (1H, t, J = 7.6 Hz), 7.88 (1H, d, J = 7.6 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 28.4, 29.65, 30.80, 34.89, 43.50, 52.17, 54.06, 79.38, 120.87, 125.75, 128.89, 130.90, 132.12, 140.90, 154.74, 167.39, 169.01; Anal. Calcd for $C_{21}H_{30}N_3O_4$: C, 65.08; H, 7.55; N, 10.84. Found: C, 65.26; H, 7.29; N, 10.62.

3.6.26. *tert*-Butyl-4-(7-chloro-1-methyl-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)methyl)piperidine-1-carboxylate (6b)

Reagents **4b** (1.31 g), 1-Boc-4-(aminomethyl)piperidine (1.39 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **6b** (1.05 g, 44%) when recrystallised from ethylacetate: mp 109–111 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 1.16–1.28 (2H, d quintet, J = 12.3, 4.0 Hz), 1.41 (9H, m), 1.42–1.63 (2H, m), 1.92 (1H, m), 2.65 (2H, d, J = 9.2 Hz), 3.33 (3H, s), 3.51 (2H, m), 3.67 (1H, d, J = 15.0 Hz), 3.99 (1H, d, J = 15.0 Hz), 4.07 (2H, m), 7.11 (1H, d, J = 8.8 Hz), 7.44 (1H, dd, J = 8.8, 2.6 Hz), 7.80 (1H, d, J = 2.6 Hz); ^{13}C NMR (400 MHz $CDCl_3$): δ 28.51, 29.67, 34.95, 35.01, 43.50, 52.06, 54.21, 79.49, 122.44, 130.24, 130.70, 131.44, 132.20, 139.42, 154.77, 166.16, 168.62; Anal. Calcd for $C_{21}H_{29}N_3O_4Cl$: C, 59.77; H, 6.70; N, 9.96; Cl, 8.40. Found: C, 59.83; H, 6.77; N, 9.68; Cl, 8.27.

3.6.27. *tert*-Butyl-4-((1-allyl-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)methyl)piperidine-1-carboxylate (6c)

Reagents **4g** (1.15 g), 1-Boc-4-(aminomethyl)piperidine (1.39 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **6c** (1.15 g, 49%) when recrystallised from ethylacetate: mp 131–132 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.20 (2H, d quintet, J = 12.3, 4.0 Hz), 1.42 (9H, s), 1.59 (2H, q, J = 13.6 Hz), 1.96 (1H, m), 2.66 (2H, q, J = 11.4 Hz), 3.38–3.66 (2H, m), 3.66 (1H, d, J = 14.5 Hz), 4.08 (3H, m, J = 14.7 Hz), 4.42 (2H, dq, J = 21.1, 5.7 Hz), 5.17 (2H, t, J = 8.8 Hz), 5.85 (1H, m), 7.29 (2H, m), 7.45 (1H, td, J = 7.5, 1.8 Hz), 7.84 (1H, dd, J = 7.9, 1.8 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 28.53, 29.71, 34.97, 50.57, 52.33, 54.11, 79.45, 117.84, 121.40, 126.08, 129.48, 130.98, 132.14, 132.77, 140.19, 154.81, 167.45, 168.12; Anal. Calcd for $C_{24}H_{32}N_3O_4$: C, 66.81; H, 7.56; N, 10.16. Found: C 66.47; H, 7.77; N, 10.03.

3.6.28. *tert*-Butyl-4-((1-allyl-7-chloro-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)piperidine-1-carboxylate (6d)

Reagents **4h** (1.34 g), 1-Boc-4-(aminomethyl)piperidine (1.39 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **6d** (0.66 g, 26%) when recrystallised from ethylacetate: mp 97–99 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 1.21 (2H, d quintet, J = 11.9, 4.0 Hz), 1.42 (9H, s), 1.46 (2H, dd, J = 21.3, 6.4 Hz), 1.94 (1H, m), 2.65 (2H, q, J = 11.4 Hz), 3.51 (2H, m), 3.68 (1H, d, J = 14.5 Hz), 4.03–4.10 (3H, m), 4.39 (2H, dq, J = 20.7, 6.2 Hz), 5.18 (2H, t, J = 9.7 Hz), 5.83 (1H, dq, J = 10.6, 6.6 Hz), 7.23 (1H, d, J = 8.8 Hz), 7.40 (1H, dd, J = 8.8, 2.6 Hz), 7.81 (1H, J = 2.6 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 28.52, 29.67, 34.94, 50.55, 52.18, 54.21, 79.48, 118.14, 122.89, 130.73, 130.82, 131.71, 132.13, 132.48, 138.63, 154.78, 166.14, 167.69; Anal. Calcd for $C_{24}H_{31}N_3O_4Cl$: C, 61.67; H 6.75; N, 9.38; Cl, 7.91. Found: C, 61.89; H, 6.76; N, 9.44; Cl, 7.59.

3.6.29. *tert*-butyl-4-((1-butyl-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)methyl)piperidine-1-carboxylate (6e)

Reagents **4i** (1.23 g), 1-Boc-4-(aminomethyl)piperidine (1.39 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **6e** (0.34 g, 14%) when recrystallised from ethylacetate/hexane: mp: 111–113 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.82 (3H, t, J = 7.5 Hz), 1.17–1.23 (4H, m), 1.42 (9H, s), 1.45–1.62 (4H, m), 1.94 (1H, m), 2.67 (2H, d, J = 11.4 Hz), 3.45–3.60 (3H, m), 3.62 (1H, d, J = 14.5 Hz), 3.98 (1H, d, J = 14.5 Hz), 4.08 (2H, m), 4.25 (1H, quintet, J = 7.0 Hz), 7.22–7.30 (2H, m), 7.49 (1H, dt, J = 7.9, 0.6 Hz), 7.82 (1H, dd, J = 7.9, 1.3 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 13.70, 19.95, 28.51, 29.76, 29.89, 35.06, 43.45, 46.77, 52.56, 54.10, 79.43, 121.74, 126.03, 130.11, 130.97, 132.04, 139.70, 154.82, 167.41, 168.39; Anal. Calcd for $C_{24}H_{36}N_3O_4$: C, 67.11; H, 8.21; N, 9.78. Found: C, 67.06; H, 8.72; N, 9.76.

3.6.30. *tert*-Butyl-4-((1-butyl-7-chloro-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)methyl)piperidine-1-carboxylate (6f)

Reagents **4j** (1.43 g), 1-Boc-4-(aminomethyl)piperidine (1.39 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **6f** (1.46 g, 56%) when recrystallised from ethylacetate/hexane: mp 137–138 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.82 (3H, t, J = 7.5 Hz), 1.17–1.23 (4H, m), 1.40 (9H, s), 1.42–1.58 (4H, m), 1.93 (1H, m), 2.69 (2H, d, J = 11.9 Hz), 3.45 (2H, m), 3.53 (1H, quintet, J = 8.4 Hz), 3.64 (1H, d, J = 14.5 Hz), 3.97 (1H, d, J = 14.5 Hz), 4.08 (2H, m), 4.24 (1H, quintet, J = 8.8 Hz), 7.17 (1H, d, J = 8.8 Hz), 7.44 (1H, dd, J = 8.8, 2.6 Hz), 7.81 (1H, d, J = 2.6 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 13.67, 19.91, 28.51, 29.82, 35.03, 43.45, 46.79, 52.41, 54.20, 79.49, 123.24, 130.76, 131.44, 131.65, 132.09, 138.16, 154.80, 166.11, 167.97; Anal. Calcd for $C_{24}H_{35}N_3O_4Cl$: C, 62.12; H, 7.39; N, 9.06; Cl, 7.64. Found: C, 62.16; H, 7.32; N, 9.07; Cl, 7.70.

3.6.31. *tert*-Butyl-4-((1-benzyl-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)methyl)piperidine-1-carboxylate (6g)

Reagents **4o** (1.43 g), 1-Boc-4-(aminomethyl)piperidine (1.39 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **6g** (0.94 g, 36%) when recrystallised from ethylacetate/hexane: mp 152–154 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.08–1.28 (2H, dq, J = 12.3, 3.9 Hz), 1.43 (9H, s), 1.54 (2H, d, J = 12.7 Hz), 1.90 (1H, m), 2.51–2.66 (2H, m), 3.36 (1H, m), 3.73 (2H, m), 4.11 (3H, m, J = 14.5 Hz), 4.99 (1H, d, J = 15.4 Hz), 5.08 (1H, d, J = 15.4 Hz), 7.14 (2H, d, J = 7.5 Hz), 7.21–7.27 (5H, m), 7.44 (1H, dt, J = 7.9, 1.3 Hz), 7.83 (1H, d, J = 1.3 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 28.53, 29.52, 34.90, 43.50, 51.45, 52.32, 54.20, 79.39, 121.75, 126.21, 127.37, 127.71, 128.83, 129.78, 131.05, 132.18, 136.54, 140.17, 154.81, 167.32, 168.38; Anal. Calcd for $C_{27}H_{32}N_3O_4$: C, 69.95; H, 7.18; N, 9.06. Found: C, 69.86; H, 7.57; N, 9.07.

3.6.32. *Tert*-butyl-4-((1-benzyl-7-chloro-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)methyl)piperidine-1-carboxylate (6h)

Reagents **4p** (1.63 g), 1-Boc-4-(aminomethyl)piperidine (1.39 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **6h**

(0.93 g, 33%) when recrystallised from ethylacetate/hexane: mp 155–157 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 1.08–1.28 (2H, d quintet, J = 12.6, 3.6 Hz), 1.33–1.59 (11H, m), 1.90 (1H, m), 2.61 (2H, quintet, J,=,11.0,Hz), 3.41 (1H, m), 3.66–3.77 (2H, m), 4.09–4.17 (3H, m), 4.95–5.15 (2H, d, J = 15.3 Hz), 7.11–7.30 (6H, m), 7.37 (1H, dd, J = 7.1, 2.6 Hz), 7.82 (1H, d, J = 2.6 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 28.53, 29.50, 34.89, 43.50, 51.37, 52.18, 54.30, 79.45, 123.45, 127.35, 127.90, 128.94, 130.81, 131.14, 131.87, 132.18, 136.15, 138.56, 154.79, 166.03, 167.99; Anal. Calcd for $C_{27}H_{31}N_3O_4Cl$: C, 65.11; H, 6.49; N, 8.44; Cl, 7.12. Found: C, 64.94; H, 6.54; N, 8.41; Cl, 7.09.

3.6.33. *tert*-Butyl-4-((1-(2-benzyl)phenyl-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)methyl)piperidine-1-carboxylate (6i)

Reagents **4q** (1.86 g), 1-Boc-4-(aminomethyl)piperidine (1.39 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **6i** (1.04 g, 34%) when recrystallised from ethylacetate/hexane: mp 152–154 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 1.15–1.29 (2H, q, J = 7.2 Hz), 1.46–1.58 (11H, m), 1.75 (1H, m), 2.65 (2H, m), 3.54 (2H, m), 3.67 (1H, d, J = 14.5 Hz), 4.05 (3H, d, J = 14.5 Hz), 4.93 (1H, d, J = 15.7 Hz), 5.14 (1H, d, J = 15.7 Hz), 6.85 (1H, d, J = 7.7 Hz), 7.17–7.42 (11H, m), 7.77 (1H, dd, J = 7.6, 1.8 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 29.10, 29.90, 35.59, 43.45, 48.07, 52.83, 55.50, 79.99, 121.90, 126.49, 127.82, 127.88, 127.97, 128.45, 128.98, 129.76, 130.30, 130.84, 131.45, 132.48, 134.20, 140.30, 141.10, 142.20, 155.40, 168.00, 169.16; Anal. Calcd for $C_{33}H_{38}N_3O_4$: C, 73.44; H, 6.91; N, 7.79. Found: C, 73.19; H, 6.74; N, 7.88.

3.6.34. *tert*-Butyl-4-(7-chloro-1-(2-phenyl)benzyl-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)methyl) piperidine-1-carboxylate (6j)

Reagents **4r** (2.06 g), 1-Boc-4-(aminomethyl)piperidine (1.39 g), bromoacetyl bromide (1.51 g) and DBU (0.90 g) gave **6i** (2.17 g, 67%) when recrystallised from ethylacetate/hexane: mp 154–156 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 0.83–0.98 (2H, q, J = 7.4 Hz), 1.13–1.68 (11H, m), 1.90 (1H, m), 2.65 (2H, quintet, J = 10.2 Hz), 3.50 (2H, m), 3.67 (1H, d, J = 14.6 Hz), 4.01 (3H, m), 4.89 (1H, d, J = 15.6 Hz), 5.19 (1H, d, J = 15.6 Hz), 6.73 (1H, d, J = 8.8 Hz), 7.16–7.40 (10H, m), 7.74 (1H, d, J = 2.5 Hz); ^{13}C NMR13C NMR (270 MHz; $CDCl_3$): δ 28.64, 29.65, 35.07, 43.45, 48.70, 52.30, 54.50, 79.85, 122.97, 127.49, 127.78, 128.04, 128.61, 129.25, 130.51, 130.67, 130.80, 131.50, 131.92, 133.40, 138.20, 140.50, 141.60, 154.80, 166.20, 168.30; Anal. Calcd for $C_{33}H_{37}N_3O_4Cl$: C, 69.04; H, 6.32; N, 7.32; Cl, 6.18. Found: C, 69.24; H, 6.43; N, 7.07; Cl, 6.09.

3.7. The general method for the *t*-Boc deprotection with TFA to the trifluoroacetate salt or to the free base and hydrochloride salt (7 and 11)[7]

To 5 mL of TFA was added 1.0 g of the *t*-Boc protected compound **6** or **10** and the mixture left to stand for 1 h. The TFA was removed under reduced pressure and the residue triturated with 30 mL of ether, filtered under suction and washed several times with fresh ether. The crude product was recrystallised from a suitable solvent.

To generate the free base, the crude product was dissolved in 2 M K_2CO_3 (30 mL) and extracted with ethylacetate (4 × 30 mL). The organic extract was dried over $MgSO_4$ and evaporated to dryness.

The formation of the HCl salt was achieved by adding a saturated ethereal HCl solution (25 mL) to a DCM solution of the compound (approx. 10 mL) and the amine salt was collected by filtration.

3.7.1. 1-Methyl-4-(piperidin-4-ylmethyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione hydrochloride (7a)

Reagents **6a** (1.0 g) and 2 M K_2CO_3 (30 mL) gave **7a** (HCl salt; 0.50 g, 60%) when filtered: mp 245–247 °C; ^{1}H NMR (270 MHz; D_2O): δ 1.24–1.43 (2H, dquintet, J = 11.5 Hz), 1.61–1.82 (2H, dd, J = 29.3, 14.1 Hz), 1.99 (1H, m), 2.49–2.91 (2H, q, J = 13.1 Hz), 3.21 (3H, s), 3.28–3.35 (2H, q, J = 13.7 Hz), 3.52–3.58 (2H, q, J = 13.7 Hz), 3.62–3.67 (1H, d, J = 15.1 Hz), 4.01–4.07 (1H, d, J = 15.1 Hz), 4.71 (2H, s), 7.22–7.28 (2H, m), 7.47–7.60 (2H, m); ^{13}C NMR (270 MHz; D_2O): δ 26.33, 32.41, 35.50, 44.05, 52.12, 53.52, 122.54, 126.88, 128.20, 130.21, 133.59, 140.15, 170.30, 171.90; Anal. Calcd for $C_{16}H_{22}N_3O_2Cl.H_2O$: C, 56.21; H, 7.09; N, 12.29; Cl, 10.37. Found: C, 56.60; H, 7.33; N, 12.11; Cl, 10.20.

3.7.2. 7-Chloro-1-methyl-4-(piperidin-4-ylmethyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione hydrochloride (7b)

Reagents **6b** (1.0 g) and 2 M K_2CO_3 (30 mL) gave **7b** (HCl salt; 0.83 g, 98%) when filtered: mp 245–247 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 1.15–1.42 (2H, quintet, J = 12.4 Hz), 1.60 (1H, d, J = 13.9 Hz), 1.76 (1H, d, J = 14.1 Hz), 1.99 (1H, m), 2.77–2.90 (2H, q, J = 13.0 Hz), 3.19 (3H, s), 3.27–3.34 (4H, q, J = 6.4 Hz); 3.53–3.62 (2H, q, J = 8.8 Hz), 3.64 (1H, d, J = 15.2 Hz), 4.02 (1H, d, J = 15.2 Hz), 7.22 (1H, d, J = 8.8 Hz), 7.45 (1H, dd, J = 8.8, 2.5 Hz), 7.55 (1H, d, J = 2.4 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 25.70, 32.41, 35.56, 44.09, 51.50, 52.60, 124.20, 129.10, 130.50, 131.60, 132.20, 139.80, 168.50, 171.20; Anal. Calcd for $C_{16}H_{21}N_3O_2Cl_2$: C, 53.63; H, 5.92; N, 11.73; Cl, 19.79. Found: C, 53.62; H, 6.14; N; 11.52; Cl, 19.72.

3.7.3. 1-Allyl-4-(piperidin-4-yl)methyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione trifluoroacetate (7c)

Reagents **6c** (1.0 g) and TFA (5 mL) gave **7c** (TFA salt; 0.65 g, 63%): mp 123–126 °C; ^{1}H NMR (400 MHz; DMSO-d_6): δ 1.48 (2H, dquintet, J = 13.6, 4.0 Hz), 1.79–1.92 (2H, d, J = 13.6 Hz), 2.15 (1H, m), 2.99 (2H, dquintet, J = 12.7, 3.0 Hz), 3.38–3.44 (3H, m), 3.76–3.83 (2H, m), 4.16 (1H, d, J = 15.0 Hz), 4.49 (1H, dd, J = 13.6, 5.2 Hz), 4.62 (1H, dd, J = 13.6, 5.3 Hz), 5.14 (2H, t, J = 11.8 Hz), 5.81 (1H, m), 7.38 (1H, dt, J = 7.9, 1.3 Hz), 7.51 (1H, dd, J = 7.5, 0.9 Hz), 7.61 (1H, dt, J = 7.5, 0.9 Hz), 7.77 (1H, dd, J = 7.9, 1.8 Hz); ^{13}C NMR (400 MHz; DMSO-d_6): δ 26.44, 32.46, 43.24, 49.23, 51.77, 52.64, 117.59, 122.39, 126.04, 129.72, 130.78, 132.58, 133.79, 140.13, 167.27, 168.72; Anal. Calcd for $C_{20}H_{26}N_3O_4F_3$: C, 56.20; H, 5.66; N, 9.83. Found: C, 55.61; H, 5.96; N, 9.72.

3.7.4. 1-Allyl-7-chloro-4-(piperidin-4-yl)methyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione trifluoroacetate (7d)

Reagents **6d** (1.0 g) and TFA (5 mL) gave **7d** (TFA salt; 0.92 g, 89%): mp 179–181 °C; ^{1}H NMR (400 MHz; CD_3OD): δ 1.49 (2H, dquintet, J = 11.0, 3.5 Hz), 1.78–1.91 (2H, d, J = 13.6 Hz), 2.15 (1H, m), 2.98 (2H, dquintet, J = 12.3, 3.1 Hz), 3.38–3.50 (3H, m), 3.71 (1H, q, J = 8.3 Hz), 3.81 (1H, d, J = 15.0 Hz), 4.19 (1H, d, J = 15.0 Hz), 4.49 (1H, dd, J = 13.5, 5.3 Hz), 4.59 (1H, dd, J = 13.6, 5.7 Hz), 5.18 (2H, dd, J = 13.6, 1.8 Hz), 5.82 (1H, m), 7.48 (1H, d, J = 8.8 Hz), 7.59 (1H, dd, J = 8.8, 2.2 Hz), 7.74 (1H, dd, J = 7.9, 2.2 Hz); ^{13}C NMR (400 MHz; CD_3OD): δ 26.20, 32.31, 43.38, 48.8, 51.50, 52.50, 117.01, 123.87, 129.61, 130.71, 131.19, 132.16, 132.47, 138.70, 167.01, 168.45; Anal. Calcd for $C_{20}H_{25}N_3O_4F_3Cl$: C, 52.01; H, 5.02; N, 9.10; Cl, 7.68. Found: C, 52.18; H, 5.27; N, 9.16; Cl, 7.72.

3.7.5. 1-Butyl-4-(piperidin-4-yl)methyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione trifluoroacetate (7e)

Reagents **6e** (1.0 g) and TFA (5 mL) gave **7e** (TFA salt; 0.91 g, 88%): mp 152–154 °C; ^{1}H NMR (400 MHz; D_2O): δ 0.68 (3H, t, J = 7.0 Hz), 1.02 (2H, sextet, J = 7.0 Hz), 1.25–1.50 (4H, m), 1.76–1.93 (2H, d, J = 14.5 Hz), 2.10 (1H, m), 2.95 (2H, quintet,

J = 12.8 Hz), 3.43 (3H, m), 3.60–3.75 (3H, m), 4.12 (1H, d, J = 15.0 Hz), 4.26 (1H, quintet, J = 7.0 Hz), 7.39 (1H, t, J = 7.5 Hz), 7.44 (1H, d, J = 8.3 Hz), 7.62 (1H, t, J = 8.3 Hz), 7.69 (1H, d, J = 7.9 Hz); ^{13}C NMR (400 MHz; D_2O): δ 12.87, 19.17, 26.10, 28.94, 32.17, 43.58, 43.67, 46.30, 52.18, 53.21, 123.17, 126.99, 128.93, 129.80, 133.18, 139.01, 169.79, 170.74; Anal. Calcd for $C_{21}H_{28}N_3O_4F_3$: C, 56.88; H, 6.36; N, 9.48. Found: C, 57.09; H, 5.85; N, 9.40.

3.7.6. 1-Butyl-7-chloro-4-(piperidin-4-yl)methyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione trifluoroacetate (7f)

Reagents **6f** (1.0 g) and TFA (5 mL) gave **7f** (TFA salt; 0.75 g, 73%): mp 194–196 °C; ^{1}H NMR (400 MHz; D_2O): δ 0.70 (3H, t, J = 7.5 Hz), 1.01 (2H, sextet, J = 7.5 Hz), 1.34 (2H, quintet, J = 7.5 Hz), 1.41–1.51 (2H, quintet, J = 11.4 Hz), 1.76–1.94 (2H, dd, J = 20.2, 14.5 Hz), 2.11 (1H, m), 2.94 (2H, dquintet, J = 10.5, 2.4 Hz), 3.42 (3H, quintet, J = 6.2 Hz), 3.65–3.71 (2H, m), 3.76 (1H, d, J = 15.0 Hz), 4.16 (1H, d, J = 15.0 Hz), 4.26 (1H, quintet, J = 7.0 Hz), 7.44 (1H, d, J = 8.8 Hz), 7.62 (1H, dd, J = 8.8, 2.2 Hz), 7.72 (1H, d, J = 2.2 Hz); ^{13}C NMR (400 MHz; D_2O): δ 12.88, 19.18, 26.10, 28.91, 32.13, 43.56, 43.66, 46.39, 52.07, 53.31, 124.90, 129.48, 130.39, 131.80, 132.96, 137.83, 168.26, 170.36; Anal. Calcd for $C_{21}H_{27}N_3O_4ClF_3$: C, 52.78; H, 5.69; N, 8.79; Cl, 7.42. Found: C, 52.91; H, 5.74; N, 8.68; Cl, 7.60.

3.7.7. 1-Benzyl-4-(piperidin-4-yl)methyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione trifluoroacetate (7g)

Reagents **6g** (1.0 g) and TFA (5 mL) gave **8g** (TFA salt; 0.85 g, 83%): mp 197–199 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.40–1.59 (3H, m), 1.75 (1H, d, J = 13.2 Hz), 1.98 (1H, m), 2.64 (1H, d, J = 7.9 Hz), 2.78 (1H, d, J = 10.6 Hz), 3.18–3.33 (3H, m), 3.67 (1H, d, J = 14.5 Hz), 3.78 (1H, m), 4.13 (1H, d, J = 14.5 Hz), 4.97 (1H, d, J = 15.5 Hz), 5.08 (1H, d, J = 15.4 Hz), 7.11 (2H, d, J = 6.6 Hz), 7.23–7.30 (5H, m), 7.48 (1H, dt, J = 8.8, 1.3 Hz), 7.81 (1H, dd, J = 7.9, 1.3 Hz), 8.87 (1H, s), 9.37 (1H, s); ^{13}C NMR (400 MHz; $CDCl_3$): δ 26.17, 26.51, 32.88, 43.55, 51.80, 52.51, 53.61, 122.02, 126.47, 127.51, 127.82, 128.82, 129.43, 130.94, 132.55, 136.50, 140.27, 167.57, 168.15; Anal. Calcd for $C_{24}H_{26}N_3O_4F_3$: C, 60.37; H, 5.49; N, 8.80. Found: C, 59.60; H, 4.93; N, 8.55.

3.7.8. 1-Benzyl-7-chloro-4-(piperidin-4-ylmethyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione hydrochloride (7h)

Reagents **6h** (1.0 g) and 2 M K_2CO_3 (30 mL) gave **7h** (HCl salt; 0.72 g, 83%) when filtered: mp 167–170 °C; ^{1}H NMR (270 MHz; CD_3OD): δ 1.14–1.41 (2H, q, J = 12.4 Hz), 1.83 (2H, d, J = 13.4 Hz), 2.05 (1H, m), 2.74 (1H, dt, J = 12.4, 3.2 Hz), 2.93 (1H, dt, J = 12.4, 3.2 Hz), 3.38 (2H, t, J = 7.8 Hz), 3.82 (1H, d, J = 14.9 Hz), 4.20 (1H, d, J = 14.9 Hz), 4.94 (1H, d, J = 15.2 Hz), 5.34 (1H, d, J = 15.2 Hz), 7.11 (2H, dd, J = 7.7, 1.7 Hz), 7.20–7.27 (3H, m), 7.52–7.61 (2H, m), 7.71 (1H, d, J = 2.0 Hz); ^{13}C NMR (270 MHz; CD_3OD): δ 27.40, 27.60, 33.64, 44.87, 51.80, 52.83, 54.14, 126.00, 128.92, 129.00, 129.87, 131.03, 132.20, 132.80, 137.80, 140.50, 168.80, 170.2; Anal. Calcd for $C_{24}H_{25}N_3O_4Cl.H_2O$: C, 58.41; H, 6.02; N, 9.29; Cl, 15.67. Found: C, 57.89; H, 5.94; N, 9.26; Cl, 15.52.

3.7.9. 1-(2-Phenyl)benzyl-4-(piperidin-4-ylmethyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione trifluoroacetate (7i)

Reagents **6i** (1.0 g) and TFA (5 mL) gave **7i** (TFA salt; 0.83 g, 81%) when filtered: mp 108–112 °C; ^{1}H NMR (400 MHz; DMSO-d_6): δ 1.31 (2H, quintet, J = 13.2 Hz), 1.55 (1H, d, J = 13.2 Hz), 1.70 (1H, d, J = 13.2 Hz), 1.96 (1H, m), 2.69–2.83 (2H, m), 3.24 (2H, dd, J = 29.9, 11.9 Hz), 3.44 (2H, d, J = 7.0 Hz), 3.71 (1H, d, J = 14.9 Hz), 4.08 (1H, d, J = 14.9 Hz), 4.87 (1H, d, J = 15.8 Hz), 5.14 (1H, d, J = 16.3 Hz), 7.10–7.44 (12H, m), 7.63 (1H, d, J = 7.5 Hz); ^{13}C NMR (400 MHz; DMSO-d_6): δ 26.51, 32.49, 43.26, 48.19, 51.75, 52.80, 122.17, 125.98, 127.59, 127.73, 127.80, 127.99, 128.90, 129.50, 129.60, 130.53, 130.79, 132.43, 134.69, 140.00, 140.54, 141.56, 167.23, 168.95; Anal. Calcd for $C_{30}H_{30}N_3O_4F_3.H_2O$: C, 63.04: H, 5.64; N, 7.35. Found: C, 62.89; H, 5.54; N, 7.32.

3.7.10. 7-Chloro-1-(2-phenyl)benzyl-4-(piperidin-4-ylmethyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione trifluoroacetate (7j)

Reagents **6j** (1.0 g) and TFA (5 mL) gave **7j** (TFA salt; 0.67 g, 66%) when filtered: mp 120–122 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.50–1.83 (4H, m), 2.00 (1H, m), 2.73–2.87 (2H, sextet, J = 11.4 Hz), 3.25–3.42 (3H, m), 3.66 (2H, m), 4.02 (1H, d, J = 14.5 Hz), 4.89 (1H, d, J = 15.8 Hz), 5.15 (1H, d, J = 15.4 Hz), 6.74 (1H, d, J = 8.8 Hz), 7.16–7.32 (10H, m), 7.69 (1H, d, J = 2.6 Hz), 9.06 (1H, d, J = 8.8 Hz), 9.48 (1H, d, J = 8.8 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 26.29, 26.53, 33.02, 43.48, 48.66, 52.37, 53.65, 123.00, 127.39, 127.85, 128.55, 129.07, 130.50, 131.66, 132.06, 133.24, 138.18, 140.31, 141.79, 166.15, 168.05; Anal. Calcd for $C_{30}H_{29}N_3O_4ClF_3.H_2O$: C, 59.46; H, 5.16; N, 6.93; Cl, 18.85. Found: C, 59.86; H, 4.94; N, 6.98; Cl, 16.02.

3.7.11. 4-(Cyclohexylmethyl)-3,4-dihydro-1*H*-benzo[*e*][1,4] diazepine-2,5-dione (8)

Ceric ammonium nitrate was added to a stirred solution of **5q** (0.5 g) according to the method described by Aquino et al.[9] **8** was isolated as an off white solid (0.14 g, 40%). ^{1}H NMR (270 MHz; $CDCl_3$): δ 0.85–1.76 (11H, m), 3.50 (1H, d, J = 5.5 Hz), 3.85 (2H, s), 7.01 (1H, d, J = 7.5 Hz), 7.22 (1H, m), 7.44 (1H, m), 7.91 (1H, d, J = 7.5 Hz), 9.20 (1H, s); ^{13}C NMR (400 MHz; $CDCl_3$): δ 25.6, 26.3, 30.6, 36.4, 51.5, 55.4, 120.3, 125.2, 126.9, 131.9, 132.3, 135.5, 167.1, 170.5; Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 69.70; H, 7.32; N, 10.13. Found: C, 69.04; H, 7.40, N, 10.00.

3.8. The general method for the synthesis of 3-cyclohexylm ethyl- and 3-(1-Boc-piperidin4-yl)methylquinazoline-2,4-diones 9, 10 and 11

To cyclohexanemethylamine or 1-Boc-4(aminomethyl)piperidine (0.02 mol, 2 equiv) in dry DCM (150 mL) at room temperature was added finely powdered N-substituted isatoic anhydride **4** (0.01 mol, 1 equiv) at such a rate to keep the DCM below reflux temperature. The reaction was stirred until TLC (EtOAc/Hexane 9:1) showed the reaction was complete (1–16 h). The DCM washed with water (2 × 75 mL), separated and returned to the flask was stirred vigorously with 1 M phosphate buffer (150 mL; preparation described above) at 5 °C. Bromoacetylbromide (0.0125 mol, 1.25 equiv) was added dropwise and the reaction monitored by TLC (EtOAc/Hexane 9:1; 1–4 h). The DCM was separated, dried and the solvent removed under reduced pressure. The residue was dissolved in pyridine (10 mL) and refluxed for 4 h. The solvent was removed and the residue triturated with cold HCl (1 M; 20 mL), filtered, washed with water, dried and recrystallised from a suitable solvent.

3.8.1. 3-(Cyclohexylmethyl)-1-methylquinazoline-2,4(1*H*,3*H*)-dione (9a)

Reagents *N*-methyl-isatoic anhydride **4a** (1.77 g), cyclohexanemethylamine (2.26 g) and bromoacetylbromide (2.52 g) gave **9a** (1.77 g, 65%) when recrystallised from ethanol: mp 89–91 °C; ^{1}H NMR (400 MHz; CD_3OD): δ 1.02–1.11 (2H, q, J = 3.6 Hz), 1.16–1.28 (3H, m), 1.64–1.67 (3H, m), 1.72–1.75 (2H, m), 1.79–1.89 (1H, m), 3.60 (3H, s), 3.91 (2H, d, J = 7.2 Hz); 7.22 (1H, t, J = 7.6 Hz), 7.41 (1H, d, J = 8.4 Hz); 7.74 (1H, td, J = 8.8, 1.6 Hz), 8.11 (1H, dd, J = 7.6, 1.6 Hz); ^{13}C NMR (400 MHz; CD_3OD): δ 27.02, 27.52, 31.26, 31.94, 37.85, 48.51, 115.37, 116.42, 124.09, 129.37, 136.54, 142.06, 152.61, 163.78; Anal. Calcd for

$C_{16}H_{20}N_2O_2$: C, 70.55; H, 7.41; N, 10.28. Found: C, 70.42; H, 7.19; N, 10.36.

3.8.2. 6-Chloro-3-(cyclohexylmethyl)-1-methylquinazoline-2,4(1*H*,3*H*)-dione (9b)

Reagents **4b** (2.12 g), cyclohexanemethylamine (2.26 g) and bromoacetylbromide (2.52 g) gave **9b** (1.78 g, 58%) when recrystallised from ethanol: mp 121–123 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.96–1.09 (2H, m), 1.11–1.19 (3H, m), 1.57–1.63 (5H, m), 1.72–1.94 (1H, m), 3.52 (3H, s), 3.86 (2H, d, J = 7.2 Hz), 7.06 (1H, d, J = 8.8 Hz), 7.52 (1H, dd, J = 8.8, 2.4 Hz), 8.31 (1H, d, J = 2.4 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 25.81, 26.31, 30.78, 30.96, 36.45, 47.84, 115.11, 116.71, 128.43, 128.66, 134.91, 139.05, 150.93, 160.99; Anal. Calcd for $C_{16}H_{19}N_2O_2Cl$: C, 62.22; H, 6.87; N, 9.07; Cl, 11.48. Found: C, 62.72; H, 6.40; N, 9.04; Cl, 11.15.

3.8.3. 3-(Cyclohexylmethyl)-1-ethylquinazoline-2,4-(1*H*.3*H*)-dione (9c)

Reagents **4c** (1.91 g), cyclohexanemethylamine (2.26 g) and bromoacetylbromide (2.52 g) gave **9c** (0.86 g, 30%) when recrystallised from ethanol: mp 66–68 °C; ^{1}H NMR (270 MHz; $CDCl_3$); δ 1.06–1.25 (5H, m), 1.35 (3H, t, J = 7.1 Hz), 1.65 (5H, m), 1.87 (1H, m), 3.95 (2H, d, J = 7.2 Hz), 4.18 (2H, q, J = 7.1 Hz), 7.19–7.23 (2H, m), 7.86 (1H, dt, J = 8.5, 1.7 Hz), 8.22 (1H, dd, J = 8.2, 1.4 Hz); ^{13}C NMR (270 MHz; $CDCl_3$); δ 12.76, 26.04, 26.55, 31.05, 36.72, 38.94, 47.73, 113.48, 115.70, 122.81, 129.49, 135.11, 139.80, 150.90, 161.40; Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.29; H 7.76; N 9.78. Found: C, 71.38; H, 7.84; N, 9.87.

3.8.4. 6-Chloro-3-cyclohexylmethyl)-1-ethylquinazoline-2,4(1*H*,3*H*)-dione (9d)

Reagents **4d** (2.26 g), cyclohexanemethylamine (2.26 g) and bromoacetylbromide (2.52 g) gave **9d** (1.89 g, 59%) when recrystallised from ethanol: mp 100–102 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 1.00–1.27 (5H, m), 1.33 (3H, t, J = 7.1 Hz), 1.62 (5H, m), 1.80 (1H, m), 3.92 (2H, d, J = 7.3 Hz), 4.16 (2H, q, J = 7.1 Hz), 7.13 (1H, d, J = 9.0 Hz), 7.58 (1H, dd, J = 9.0, 2.6 Hz), 8.17 (1H, d, J = 2.6 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 12.69, 25.99, 26.49, 30.98, 36.64, 39.20, 47.89, 115.15, 117.20, 128.53, 128.83, 135.07, 138.28, 151.10, 161.40; Anal. Calcd for $C_{17}H_{21}N_2O_2Cl$: C, 63.64; H, 6.61; N, 8.73; Cl, 11.05. Found: C, 63.62; H, 6.74; N, 8.76; Cl 10.87

3.8.5. 1-Butyl-6-chloro-3-(cyclohexylmethyl) quinazoline-2, 4-(1*H*, 3*H*)-dione (9e)

Reagents **4j** (2.54 g), cyclohexanemethylamine (2.26 g) and bromoacetylbromide (2.52 g) gave **9e** (2.06 g, 59%) when recrystallised from ethanol: mp 94–96 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 0.99 (3H, t, J = 7.3 Hz), 1.04–1.27 (4H, m), 1.38–1.52 (2H, quintet, J = 7.6 Hz), 1.62–1.88 (8H, m), 1.85 (1H, m), 3.93 (2H, d, J = 7.3 Hz), 4.09 (2H, t, J = 7.7 Hz), 7.12 (1H, d, J = 9.0 Hz), 7.56 (1H, dd, J = 8.9, 2.6 Hz), 8.17 (1H, d, J = 2.5 Hz); ^{13}C NMR (270 MHz; $CDCl_3$): δ 14.43, 20.69, 26.47, 26.98, 29.95, 31.45, 37.11, 44.44, 48.41, 115.83, 117.70, 129.00, 129.26, 135.50, 138.90, 151.00, 161.30; Anal. Calcd for $C_{19}H_{26}N_2O_2Cl$: C, 65.41; H, 7.24; N, 8.03; Cl, 10.16. Found: C, 65.57; H, 7.38; N, 8.02; Cl, 10.07.

3.8.6. Ethyl-2-(3-(cyclohexylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl)acetate (9f)

Reagents **4k** (2.49 g), cyclohexanemethylamine (2.26 g) and bromoacetylbromide (2.52 g) gave **9f** (1.72 g, 50%) when recrystallised from ethanol: mp 99–100 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.01–1.20 (5H, m), 1.25 (3H, t, J = 7.5 Hz), 1.61–1.67 (5H, m), 1.84 (1H, m), 3.94 (2H, d, J = 7.5 Hz), 4.23 (2H, q, J = 7.0 Hz), 4.88 (2H, s), 6.93 (1H, d, J = 8.3 Hz), 7.25 (1H, t, J = 7.5 Hz), 7.62 (1H, dt, J = 7.0, 1.8 Hz), 8.21 (1H, dd, J = 7.9, 1.8 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 14.19, 25.91, 26.41, 30.86, 36.52, 44.96, 47.83, 62.04, 112.92, 115.73, 123.33, 129.44, 135.16, 139.74, 151.36, 161.94, 167.89; Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.23; H, 7.38; N, 8.20.

3.8.7. Ethyl-2-(6-chloro-3-(cyclohexylmethyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl)acetate (9g)

Reagents **4l** (2.49 g), cyclohexanemethylamine (2.26 g) and bromoacetylbromide (2.52 g) gave **9g** (1.25 g, 50%) when recrystallised from ethanol: mp 99–100 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.01–1.20 (5H, m), 1.25 (3H, t, J = 7.5 Hz), 1.61–1.67 (5H, m), 1.84 (1H, m), 3.94 (2H, d, J = 7.5 Hz), 4.23 (2H, q, J = 7.0 Hz), 4.88 (2H, s), 6.93 (1H, d, J = 8.3 Hz), 7.25 (1H, t, J = 7.5 Hz), 7.62 (1H, dt, J = 7.0, 1.8 Hz), 8.21 (1H, dd, J = 7.9, 1.8 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 14.19, 25.91, 26.41, 30.86, 36.52, 44.96, 47.83, 62.04, 112.92, 115.73, 123.33, 129.44, 135.16, 139.74, 151.36, 161.94, 167.89; Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.23; H, 7.38; N, 8.20.

3.8.8. 1-Benzyl-3-(cyclohexylmethyl)quinazoline-2,4 (1*H*,3*H*)-dione (9h)

Reagents **4o** (2.53 g), cyclohexanemethylamine (2.26 g) and bromoacetylbromide (2.52 g) gave **9h** (1.32 g, 38%) when recrystallised from ethanol: mp 134–136 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.07–1.29 (5H, m), 1.66–1.74 (5H, m), 1.90–2.03 (1H, m), 4.04 (2H, d, J = 7.2 Hz), 5.40 (2H, s), 7.12 (1H, d, J = 8.4 Hz), 7.21–7.37 (6H, m), 7.52 (1H, td, J = 8.4, 1.6 Hz), 8.24 (1H, dd, J = 8.0, 2.4 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 25.87, 26.37, 30.85, 36.50, 47.30, 47.77, 114.31, 115.75, 122.97, 126.44, 127.62, 128.97, 129.10, 134.91, 135.83, 139.96, 151.68, 162.04; Anal. Calcd for $C_{22}H_{22}O_2N_2$: C, 75.83; H, 6.95; N, 8.04. Found: C, 76.03; H, 6.65; N, 7.96.

3.8.9. 1-Benzyl-6-chloro-3-(cyclohexylmethyl)quinazoline-2,4(1*H*,3*H*)-dione (9i)

Reagents **4p** (2.88 g), cyclohexanemethylamine (2.26 g) and bromoacetylbromide (2.52 g) gave **9i** (1.53 g, 40%) when recrystallised from ethanol: mp 140–142 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 1.09–1.25 (5H, m), 1.62–1.72 (5H, m), 1.92 (1H, m), 4.01 (2H, d, J = 7.2 Hz), 5.37 (2H, s), 7.04 (1H, d, J = 8.9 Hz), 7.21–7.38 (5H, m), 7.45 (1H, dd, J = 8.9, 2.6 Hz), 8.19 (1H, dd, J = 2.5 Hz); ^{13}C NMR (270 MHz ; $CDCl_3$): δ 26.01, 26.51, 30.97, 36.61, 47.65, 48.14, 116.18, 117.50, 126.55, 127.99, 128.66, 128.80, 129.25, 135.06, 135.55, 138.80, 151.60, 161.20; Anal. Calcd for $C_{22}H_{21}O_2N_2Cl$: C, 69.01; H, 6.07; N, 7.32; Cl, 9.26. Found: C, 68.76; H, 6.22; N, 7.38; Cl, 9.06.

3.8.10. 3-Cyclohexylmethy-1-(2-phenylbenzyl)quinazoline-2,4(1*H*,3*H*)-dione (9j)

Reagents **4r** (3.29 g), cyclohexanemethylamine (2.26 g) and bromoacetylbromide (2.52 g) gave **9i** (2.29 g, 54%) when recrystallised from ethanol: mp 109–111 °C; ^{1}H NMR (270 MHz; $CDCl_3$): δ 1.07–1.26 (5H, m), 1.66–1.71 (5H, m), 1.90 (1H, m), 3.99 (2H, d, J = 7.3 Hz), 5.31 (2H, s), 6.63 (1H, d, J = 8.4 Hz), 7.02–7.52 (11H, m), 8.16 (1H, dd, J = 7.9, 1.5); ^{13}C NMR (270 MHz; $CDCl_3$): δ 26.51, 27.02, 31.49, 37.12, 46.34, 48.39, 115.02, 116.20, 123.52, 126.19, 128.03, 128.34, 128.75, 129.26, 129.57, 129.74, 130.98, 133.30, 135.42, 140.00, 140.80, 141.50, 151.70, 162.10; Anal. Calcd for $C_{28}H_{26}N_2O_2$: C, 79.21; H, 6.66; N, 6.60. Found: C, 78.97; H, 6.74; N, 6.52.

3.8.11. 6-Chloro-1-(biphenyl-2-yl)methyl-4-cyclohexylmethyl-quinazoline-2,4 (1*H*,3*H*)-dione (9k)

Reagents **4s** (3.64 g), cyclohexanemethylamine (2.26 g) and bromoacetylbromide (2.52 g) gave **9k** (2.40 g, 53%) when recrystallised from ethanol: mp 124–126 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.08–1.28 (5H, m), 1.63–1.74 (5H, m), 1.86–1.93 (1H, m), 4.00

(2H, d, J = 7.2 Hz), 5.32 (2H, s), 6.57 (1H, d, J = 8.8 Hz), 7.05 (1H, d, J = 7.6 Hz), 7.26–7.53 (9H, m), 8.14 (1H, d, J = 2.4 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 25.83, 26.33, 30.79, 36.41, 45.78, 47.92, 116.07, 116.89, 125.67, 127.60, 127.79, 128.19, 128.30, 128.67, 129.07, 130.43, 132.44, 134.74, 138.10, 140.05, 141.00, 151.39, 160.93; Anal. Calcd for $C_{28}H_{25}N_2O_2Cl$: C, 73.26: H, 5.94; N, 6.10; Cl, 7.72. Found: C, 73.10: H, 6.06; N, 6.14; Cl, 7.69.

3.8.12. 6-Chloro-1-(biphenyl-4-yl)methyl-4-cyclohexylmethyl-quinazoline-2,4 (1*H*,3*H*)-dione (9l)

Reagents **4t** (3.64 g), cyclohexanemethylamine (2.26 g) and bromoacetylbromide (2.52 g) gave **9l** (2.40 g, 53%) when recrystallised from ethanol: mp 124–126 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.08–1.28 (5H, m), 1.63–1.74 (5H, m), 1.86–1.93 (1H, m), 4.00 (2H, d, J = 7.2 Hz), 5.32 (2H, s), 6.57 (1H, d, J = 8.8 Hz), 7.05 (1H, d, J = 7.6 Hz), 7.26–7.53 (9H, m), 8.14 (1H, d, J = 2.4 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 25.83, 26.33, 30.79, 36.41, 45.78, 47.92, 116.07, 116.89, 125.67, 127.60, 127.79, 128.19, 128.30, 128.67, 129.07, 130.43, 132.44, 134.74, 138.10, 140.05, 141.00, 151.39, 160.93; Anal. Calcd for $C_{28}H_{25}N_2O_2Cl$: C, 73.26: H, 5.94; N, 6.10; Cl, 7.72. Found: C, 73.10: H, 6.06; N, 6.14; Cl, 7.69.

3.8.13. *tert*-Butyl-4-((1-benzyl-6-chloro-2,4-dioxo-1,2-dihydro-quinazolin-3(4*H*)-yl)methyl)piperidine-1-carboxylate (10a)

Reagents **4p** (1.63 g), 1-Boc-4-(aminomethyl)piperidine (1.39 g) and bromoacetyl bromide (2.52 g) gave **10a** (2.70 g, 56%) when recrystallised from ethanol: mp 142–143 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.32 (2H, qd, J = 12.3, 4.0 Hz), 1.44 (3H, s), 1.61 (2H, d, J = 12.3 Hz), 2.04 (1H, m), 2.64 (2H, t, J = 11.0 Hz), 4.04–4.20 (4H, d, J = 7.5 Hz), 5.34, (2H, s), 7.04 (1H, d, J = 8.8 Hz), 7.19 (2H, d, J = 7.0 Hz), 7.25 (1H, t, J = 7.0 Hz), 7.31 (2H, t, J = 7.9 Hz), 7.45 (1H, dd, J = 8.8, 2.6 Hz), 8.16, (1H, d, J = 2.6 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 28.54, 29.91, 35.14, 43.50, 47.11, 47.63, 79.43, 116.17, 116.89, 126.44, 127.99, 128.56, 129.03, 129.20, 135.18, 135.30, 138.51, 151.35, 154.81, 161.03; Anal. Calcd for $C_{26}H_{31}N_3O_4Cl$: C, 64.52; H, 6.26; N, 8.68; Cl, 7.32. Found: C, 64.43; H, 6.30; N, 8.63; Cl, 7.17.

3.8.14. *tert*-Butyl-4-((1-(2-biphenyl)methyl-2,4-dioxo-1,2-dihydroquinazolin-3(4*H*)-yl)methyl) piperidine-1-carboxylate (10b)

Reagents **4q** (1.86 g), 1-Boc-4-(aminomethyl)piperidine (1.39 g) and bromoacetyl bromide (2.52 g) gave **10b** (0.76 g, 18%) when recrystallised from ethanol: mp 138–141 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.30 (2H, dquintet, J = 12.3, 4.0 Hz); 1.44 (9H, s) 1.62 (2H, d, J = 11.0 Hz), 2.05 (1H, m), 2.66 (2H, t, J = 11.4 Hz), 4.04 (4H, m), 5.30 (2H, s), 6.56 (1H, d, J = 8.8 Hz), 7.01 (1H, d, J = 7.5 Hz), 7.16–7.48 (10H, m), 8.16 (1H, d, J = 7.9 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 28.55, 29.96, 35.17, 43.50, 45.86, 46.90, 79.38, 114.55, 115.60, 123.12, 125.57, 127.55, 127.80, 128.19, 128.71, 129.01, 129.16, 130.49, 132.73, 135.07, 139.72, 140.60, 141.06, 151.74, 154.82, 162.08; Anal. Calcd for $C_{32}H_{36}N_3O_4$: C, 73.12; H, 6.71; N, 7.99. Found: C, 73.30; H, 6.68; N, 8.00.

3.8.15. *tert*-Butyl-4-((1-(2-biphenyl)methyl-6-chloro-2,4-dioxo-1,2-dihydroquinazolin-3(4*H*)-yl)methyl)piperidine-1-carboxy late (10c)

Reagents **4r** (2.06 g), 1-Boc-4-(aminomethyl)piperidine (1.39 g) and bromoacetyl bromide (2.52 g) gave **10c** (1.50 g, 33%) when recrystallised from ethanol: mp 137–139 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.29 (2H, dquintet, J = 12.7, 4.0 Hz), 1.44 (9H, s), 1.62 (2H, d, J = 11.0 Hz), 2.03 (1H, m), 2.63 (2H, t, J = 11.0 Hz), 4.02 (2H, d, J = 7.0 Hz), 4.09 (2H, m), 5.29 (2H, s), 6.56 (1H, d, J = 8.8 Hz), 7.01 (1H, d, J = 7.5 Hz), 7.22–7.49 (9H, m), 8.11 (1H, d, J = 2.6 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 28.55, 29.89, 35.12, 43.50, 45.94, 47.08, 79.43, 116.26, 116.80, 125.69, 127.77, 127.90, 128.29, 128.36, 128.77, 128.93, 129.13, 130.59, 132.37, 135.04, 138.20, 140.00, 141.09, 151.40, 154.81, 160.99; Anal. Calcd for $C_{32}H_{35}N_3O_4Cl$: C, 68.62; H, 6.12; N, 7.50; Cl, 6.33. Found; C, 68.71; H, 5.77; N, 7.48; Cl, 6.15.

3.8.16. *tert*-Butyl-4-((1-(4-biphenyl)methyl-6-chloro-2,4-dioxo-1,2-dihydroquinazolin-3(4*H*)-yl)methyl)piperidine-1-carboxylate (10d)

Reagents **4t** (2.06 g), 1-Boc-4-(aminomethyl)piperidine (1.39 g) and bromoacetyl bromide (2.52 g) gave **10d** (1.50 g, 33%) when recrystallised from ethanol: mp 137–139 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.29 (2H, dquintet, J = 12.7, 4.0 Hz), 1.44 (9H, s), 1.62 (2H, d, J = 11.0 Hz), 2.03 (1H, m), 2.63 (2H, t, J = 11.0 Hz), 4.02 (2H, d, J = 7.0 Hz), 4.09 (2H, m), 5.29 (2H, s), 6.56 (1H, d, J = 8.8 Hz), 7.01 (1H, d, J = 7.5 Hz), 7.22–7.49 (9H, m), 8.11 (1H, d, J = 2.6 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 28.55, 29.89, 35.12, 43.50, 45.94, 47.08, 79.43, 116.26, 116.80, 125.69, 127.77, 127.90, 128.29, 128.36, 128.77, 128.93, 129.13, 130.59, 132.37, 135.04, 138.20, 140.00, 141.09, 151.40, 154.81, 160.99; Anal. Calcd for $C_{32}H_{35}N_3O_4Cl$: C, 68.62; H, 6.12; N, 7.50; Cl, 6.33. Found: C, 68.71; H, 5.77; N, 7.48; Cl, 6.15.

3.8.17. 1-Benzyl-6-chloro-3-(piperidin-4-ylmethyl)quinazoline-2,4(1*H*,3*H*)-dione (11a)

To a solution of **10a** (1 mmol) in anhydrous DCM 5 mL under N_2 was added $AlCl_3$ (1 mmol) in portions at 0 °C. The resulting suspension was stirred vigorously at room temperature and monitored by TLC (EtOAc/Hexane 9:1) until the reaction was complete. The reaction mixture was neutralized with 0.1 M $NaHCO_3$ (30 mL) and the product extracted with EtOAc (3 × 30 mL). The organic extract was dried, filtered and the solvent removed under reduced pressure. The crude product was recrystallised from ethylacetate to yield **11a** (0.41 g, 52%) mp 98–101 °C; ^{1}H NMR (270 MHz; CD_3OD): δ 1.26–1.38 (2H, qd, J = 12.1, 3.8 Hz), 1.64 (2H, d, J = 11.0 Hz), 2.02 (1H, m), 2.52 (2H, td, J = 12.4, 2.5 Hz); 3.01 (2H, d, J = 12.5 Hz), 4.00 (2H, d, J = 7.2 Hz), 5.38 (2H, s), 7.19–7.34 (6H, m), 7.52 (1H, dd, J = 9.0, 2.6 Hz), 8.07 (1H, d, J = 2.5 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 31.33, 35.38, 46.29, 47.60, 47.67, 116.14, 116.95, 126.43, 127.93, 128.55, 128.94, 129.18, 135.08, 135.36, 138.5, 151.38, 161.05; Anal. Calcd for $C_{21}H_{21}N_3O_2Cl.H_2O$: C, 62.76; H, 6.02; N, 10.46; Cl, 8.82. Found: C, 62.83; H, 5.94; N, 10.41; Cl, 8.56.

3.8.18. 1-(2-Biphenyl)methyl-3-(piperidin-4-ylmethyl) quinazoline-2,4(1*H*,3*H*)-dione trifluoroacetate (11b)

Using the general method of TFA deprotection described earlier.[7]

Reagents **10b** (1.0 g) and 2 M K_2CO_3 (30 mL) gave **11b** (TFA salt; 1.22 g, 96%) when filtered: mp 205–207 °C; ^{1}H NMR (400 MHz; DMSO-d_6): δ 1.39 (2H, q, J = 11.4 Hz), 1.75 (2H, d, J = 12.3 Hz), 2.06 (1H, m), 2.82 (2H, t, J = 12.7 Hz), 3.27–3.38 (2H, d, J = 12.3 Hz), 3.88 (2H, d, J = 7.0 Hz), 5.22 (2H, s), 6.94 (1H, d, J = 8.4 Hz), 7.04 (1H, d, J = 7.5 Hz), 7.26–7.65 (9H, m), 8.05 (1H, dd, J = 7.9, 1.3 Hz), 8.60 (2H, s); ^{13}C NMR (400 MHz; DMSO-d_6): δ 26.88, 32.76, 43.39, 46.08, 46.17, 115.19, 115.59, 123.50, 125.92, 127.86, 128.17, 128.48, 128.63, 129.14, 129.60, 130.66, 133.65, 135.86, 140.40, 141.13, 151.40, 160.00; Anal. Calcd for $C_{29}H_{29}N_3O_4F_3$: C, 64.56; H, 5.23; N, 7.79. Found: C, 64.63; H, 5.13; N, 7.67.

3.8.19. 6-Chloro-1-(2-biphenylmethyl)-3-(piperidin-4-yl) methyl)quinazoline-2,4(1*H*,3*H*)-dione trifluoroacetate (11c)

Reagents **10c** (1.0 g) and 2 M K_2CO_3 (30 mL) gave **11c** (TFA salt; 1.13 g, 90%) when filtered: mp 187–189 °C; ^{1}H NMR (400 MHz; DMSO-d_6): δ 1.37 (2H, q, J = 11.4 Hz), 1.74 (2H, d, J = 11.9 Hz), 2.04 (1H, m), 2.81 (2H, t, J = 12.7 Hz), 3.24–3.41 (2H, d, J = 12.3 Hz), 3.85 (2H, d, J = 7.0 Hz), 5.20 (2H, s), 7.01 (1H, d, J = 8.8 Hz), 7.09 (1H, d, J = 7.5 Hz), 7.26–7.52 (8H, m), 7.69 (1H,

dd, J = 8.8, 2.6 Hz), 7.98 (1H, d, J = 2.6 Hz), 8.60 (2H, s); ^{13}C NMR (400 MHz; DMSO-d_6): δ 26.82, 32.68, 43.36, 46.38, 117.63, 118.03, 125.96, 127.68, 127.86, 127.92, 128.16, 128.49, 129.13, 129.56, 130.69, 133.36, 135.80, 139.40, 140.36, 141.13, 151.08, 160.04; Anal. Calcd for $C_{29}H_{27}N_3O_4ClF_3$: C, 60.98; H, 4.74; N, 7.32; Cl, 6.18. Found: C, 61.27; H, 4.80; N, 7.10; Cl, 6.12.

3.8.20. 6-Chloro-1-(4-biphenylmethyl)-3-(piperidin-4-yl) methyl)quinazoline-2,4(1*H*,3*H*)-dione trifluoroacetate (11d)

Reagents **10d** (1.0 g) and 2 M K_2CO_3 (30 mL) gave **11d** (TFA salt; 1.13 g, 90%) when filtered: mp 187–189 °C; ^{1}H NMR (400 MHz; DMSO-d_6): δ 1.37 (2H, q, J = 11.4 Hz), 1.74 (2H, d, J = 11.9 Hz), 2.04 (1H, m), 2.81 (2H, t, J = 12.7 Hz), 3.24–3.41 (2H, d, J = 12.3 Hz), 3.85 (2H, d, J = 7.0 Hz), 5.20 (2H, s), 7.01 (1H, d, J = 8.8 Hz), 7.09 (1H, d, J = 7.5 Hz), 7.26–7.52 (8H, m), 7.69 (1H, dd, J = 8.8, 2.6 Hz), 7.98 (1H, d, J = 2.6 Hz), 8.60 (2H, s); ^{13}C NMR (400 MHz; DMSO-d_6): δ 26.82, 32.68, 43.36, 46.38, 117.63, 118.03, 125.96, 127.68, 127.86, 127.92, 128.16, 128.49, 129.13, 129.56, 130.69, 133.36, 135.80, 139.40, 140.36, 141.13, 151.08, 160.04; Anal. Calcd for $C_{29}H_{27}N_3O_4ClF_3$: C, 60.68; H, 4.74; N, 7.32; Cl, 6.18. Found: C, 61.27; H, 4.80; N, 7.10; Cl, 6.12.

Acknowledgements

This work was supported by the University of Strathclyde and the EPSRC for a Ph.D. studentship (to R.LC.), The Ghana Foundation for a Ph.D. studentship (to G.O.D) and the University of Greenwich for a Ph.D. studentship (to R.P.R).

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