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# A continuous-flow synthesis of 1,4-benzodiazepin-5-ones, privileged scaffolds for drug discovery

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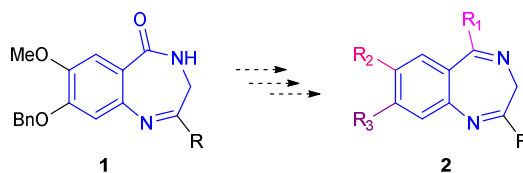
## Abstract

An efficient and gram-scale continuous-flow protocol for the synthesis of the privileged structure 3,4-dihydro-5*H*-benzo[e][1,4]diazepin-5-one is reported. If compared to the traditional metal mediated non-catalytic reduction procedure, this approach is high yielding and does not require purification steps and therefore could be conveniently used for the generation of compound libraries for drug discovery.

## Introduction

The design and synthesis of small molecules libraries have become a crucial aspect of drug discovery and chemical biology programs. Of particular interest in the hit discovery and the hit-to-lead processes are compound collections based on ‘privileged structures’,<sup>1, 2</sup> molecular frameworks which are able to provide useful ligands for more than one type of biological targets. The term, first coined by Evans in the late 1980s,<sup>3</sup> was originally referring to the 1,4-benzodiazepine nucleus and, indeed, numerous 1,4-benzodiazepine derivatives endowed with selective activities against a variety of enzymes and receptors have been identified thus far.<sup>4, 5</sup> Being interested in the development of small-molecule modulators of epigenetic targets,<sup>6, 7</sup> we planned the synthesis of the 3,4-dihydro-5*H*-benzo[e][1,4]diazepin-5-one

scaffold (**1**) which could be easily manipulated to provide a number of highly functionalized potential ligands (**2**) (Figure 1).



**Figure 1.** General structure of potential ligands (**2**) of epigenetic targets, containing 1,4-benzodiazepin-5-one scaffold (**1**).

Despite the impressive diversity of 1,3-dihydro-benzo[e][1,4]diazepin-2-ones prepared to date, the corresponding 3,4-dihydro-5*H*-benzo[e][1,4]diazepin-5-one isomer has been only rarely explored. The synthetic strategies for the preparation of such moiety basically rely on the ring closure of properly substituted keto anthranilamides, which can be obtained by reduction of the corresponding nitro derivatives,<sup>8-10</sup> or on the reaction of isatoic anhydride with appropriate  $\alpha$ -aminoketones.<sup>11, 12</sup> Both methods are affected by the formation of undesired byproducts and/or by low to moderate yields. Moreover, the need for impractical and costly purifications procedures makes these approaches inadequate to be run on larger scales.

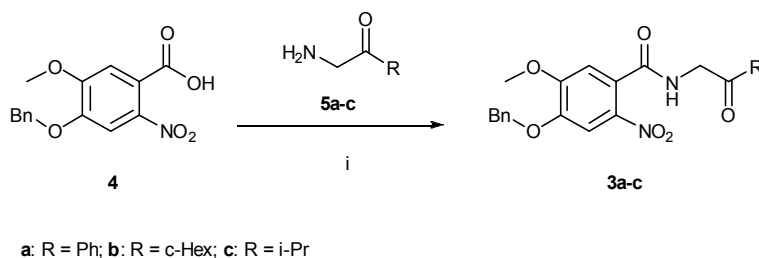
In this paper, we are pleased to report the concise and scalable synthesis of 3,4-dihydro-5*H*-benzo[e][1,4]diazepin-5-ones from 2-nitro benzamides under continuous flow catalytic hydrogenation conditions. The same reaction was also run under batch conditions as well as using non-catalytic reducing metals, and the results were analyzed and compared.

## Results and Discussion

To study the reduction-cyclization procedure, as model substrates we chose three differently substituted 2-nitro benzamides **3a–c**, prepared from 4-(benzyloxy)-5-methoxy-2-nitrobenzoic acid **4** and

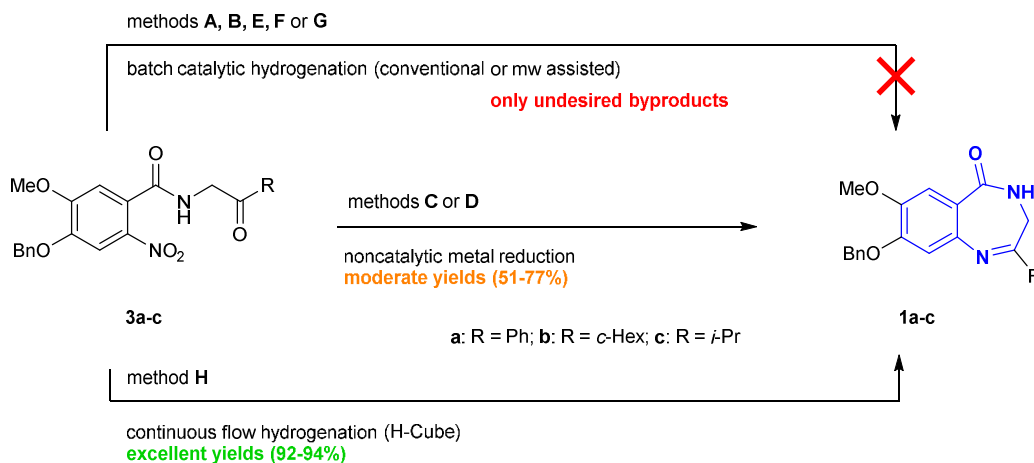
aminoethanones **5a-c** following standard coupling procedures as reported in Scheme 1. The general synthetic route to the target scaffold is depicted in Scheme 2 and the detailed results are reported in Tables 1 and 2.

### Scheme 1. Preparation of nitro benzamide intermediates **3a-c**.



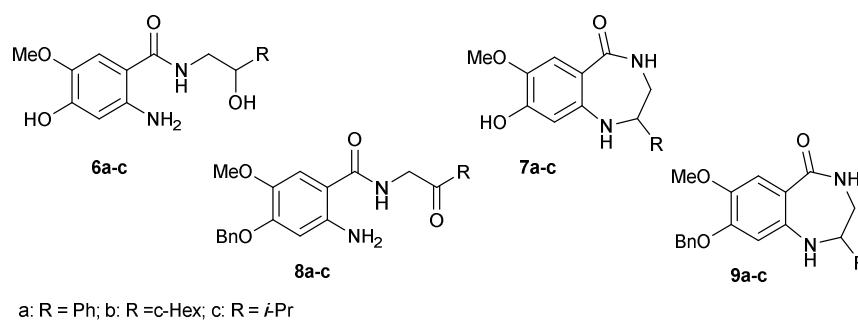
i) HOBt, HBTU, DIPEA, THF/DMF dry 4:1, 0 °C to r.t., 12 h (70-85%).

### Scheme 2. General synthetic route to 1,4-benzodiazepin-5-one derivatives **1a-c**



The catalytic hydrogenation (palladium on carbon) of the 2-nitro benzamides always resulted in the removal of the benzyl group, yet it yielded only undesired byproducts (Figure 2) depending on the substrate. In fact, the treatment of substrate **3a** afforded derivative **6a**, in which both the nitro and the keto groups were reduced (Table 1, entry 1), whereas the main product of catalytic hydrogenation of

nitro benzamide **3b** was the tetrahydrobenzodiazepinone **7b** (Table 1, entry 2). The reduction of the imine of the 3,4-dihydro-5*H*-benzo[*e*][1,4]diazepin-5-one core was unexpected as it has been reported to occur only in presence of LAH.<sup>8</sup> A similar result was also obtained under microwave-assisted catalytic transfer hydrogenation conditions.<sup>13</sup> The reaction of phenyl derivative **3a** gave tetrahydrobenzodiazepinone **7a** as main byproduct (Table 1, entry 3). On the other hand, the traditional non-catalytic reduction of the substrates with iron sulfate heptahydrate gave the desired 3,4-dihydro-5*H*-benzo[*e*][1,4]diazepin-5-ones **1a-c**, although in moderate yields (53–61%, Table 1, entries 4–6). A slight improvement was observed with iron powder in acetic acid only for derivative **1a** (Table 1, entry 7).



**Figure 2.** Main byproducts obtained from reduction of 2-nitro benzamides **3** under conventional batch conditions.

**Table 1. Reduction of 2-nitro benzamides 3a–c under different batch conditions.**

entry	R	method <sup>a</sup>	time	Yield <b>1</b> <sup>b</sup> (%)	Main product <sup>b</sup> (%)
1	Ph	A	1 h	-	<b>6a</b> (54)
2	<i>c</i> -Hex	A	1 h	-	<b>7b</b> (88)
3	Ph	B	10 min	-	<b>7a</b> (67) <sup>c</sup>
4	Ph	C	8 h	53	-
5	<i>c</i> -Hex	C	16 h	55	-
6	<i>i</i> -Pr	C	2 h	61	-
7	Ph	D	2 h	77	-

<b>8</b>	<i>c</i> -Hex	D	2 h	51	-
<b>9</b>	<i>i</i> -Pr	D	2 h	63	-
<b>10</b>	Ph	E	18 h	-	<b>3a</b> (98)
<b>11</b>	Ph	F	10 h	-	<b>3a</b> (95)
<b>12</b>	Ph	G	18 h	-	<b>3a</b> (98)

<sup>a</sup>Reaction conditions: A) H<sub>2</sub>, Pd/C (10%, 0.1 eq.), EtOAc:EtOH 2:1 (0.03 M), 20 °C, 1 atm; B) 1,4-Cyclohexadiene (6 eq.) Microwave mode, Pd/C (10%, 0.05 eq.) MeOH (0.1 M), 120 °C; C) FeSO<sub>4</sub>·7H<sub>2</sub>O (10 eq.), NH<sub>4</sub>OH, EtOH, reflux; D) Fe (20 eq.), AcOH (0.1 M), 70 °C; E) H<sub>2</sub>, Ru/C (5%, 0.02 eq.), THF (0.03 M), 20 °C, 1 atm; F) H<sub>2</sub>, Ru/C (5%, 0.02 eq.), THF (0.03 M), reflux, 1 atm; G) H<sub>2</sub>, Ru/C (5%, 0.04 eq.), THF (0.03 M), 20 °C, 1 atm. <sup>b</sup>Isolated yield after chromatographic purification; <sup>c</sup>Debenzylated nitro compound (22%) was also recovered.

Besides the inadequate yields, the metal mediated non-catalytic methods suffer from various practical drawbacks, such as the generation of a large amount of waste and bothersome purification procedures, thus being not suitable for the preparation of the 3,4-dihydro-5*H*-benzo[e][1,4]diazepin-5-ones as scaffolds for library synthesis.

Following our interest in exploiting modern synthetic technologies to improve classical organic reactions,<sup>14</sup> we, therefore, explored the possibility of taking advantage of the continuous-flow technology to develop a practical method to prepare the 3,4-dihydro-5*H*-benzo[e][1,4]diazepin-5-ones **1a-c** that could be easily scalable to gram-scale. To this aim, we investigated a continuous-flow hydrogenation protocol employing a fixed-bed catalyst (H-Cube Pro, Thales Nanotechnology Inc.) and performed a thorough screening of different catalysts and reaction conditions in order to identify the suitable method for the reduction and concomitant cyclization of substrates **3**.

At first, the flow hydrogenation of 2-nitro benzamide **3a** was optimized using a 0.03 M solution of substrate (0.30 mmol) in EtOAc/EtOH (10 mL), 1.0 mL/min as flow rate, 10 bar of pressure at 30 °C in full-H<sub>2</sub> mode. In analogy to the results obtained under batch conditions, the employment of catalyst cartridges filled with 10% Pd/C furnished only the debenzylated anilino alcohol **6a** (Table 2, entry 1). The same result was obtained using 5% Rh/C as catalyst and 50 bar of pressure (entry 2).

5% Pt/C gave more encouraging results providing the desired benzodiazepin-5-one **1a** even if in very low yield (12%). This was primarily due to ineffective cyclization step, as the intermediate anthranilamide **8a** was recovered as main product (entry 3). This issue was addressed using THF, a more appropriate solvent for cyclization (entry 4), and raising the temperature to 80 °C (entry 5). In this case, the partial conversion negatively affected the yields. We attempted to obtain an efficient cyclodehydration step without the support of a dehydrating agent placed in-line. Therefore, the pressure was raised to increase conversion and the flow rate was slowed down to promote ring closure (entry 6). Nevertheless, again the obtained yield was moderate, probably due to the incomplete cyclization and to the reduction of the imine since the 3,4-dihydro-5*H*-benzo[e][1,4]diazepin-5-one **9a** was also recovered as main byproduct. Hence we resolved to switch to ruthenium, an uncommon metal in heterogeneous catalysis, but reported to be selective for preferential hydrogenation of aromatic nitro groups.<sup>15</sup> We were delighted to find out that, using the improved reaction conditions disclosed (THF as solvent, 0.3 mL/min as flow rate and 50 bar of pressure at 80 °C) the reaction gave exclusively the desired 3,4-dihydro-5*H*-benzo[e][1,4]diazepin-5-one **1a** in excellent 94% yield and without the need for further purification, as the yield remained substantially the same after flash chromatography (entry 7). Satisfied with these conditions, we applied the procedure also to the substrates **3b** and **3c** and obtained derivatives **1b** and **1c** in comparable high yields (entries 8 and 9).

In order to more accurately compare the good results obtained following the continuous flow hydrogenation protocol with those obtained under the traditional batch conditions, we performed the

catalytic hydrogenation of the 2-nitro benzamide **3a** using ruthenium on carbon as catalyst. As reported in Table 1, using the same molar substrate-to-catalyst ratio used in the continuous flow protocol, no reduction was detected at room temperature or at higher temperature (entries 10-11). The same detrimental outcome was obtained doubling the molar catalyst-to-substrate ratio (entry 12).

Finally, to evaluate the applicability of the continuous flow protocol to the preparation of useful scaffolds for drug discovery, the same reaction conditions were applied to prepare **1a** on gram scale (1.3 g), equally scaling the amounts of substrate and solvent. The desired product was isolated with high purity and in excellent yield, without the need of multiple operator intervention. It is noteworthy that the efficiency of the cartridge is long-lasting. In fact the conversion percentage and the reaction yield obtained employing a “used” (after a gram scale single run) or a new cartridge were the same.

**Table 2. Reduction of 2-nitro benzamides **3** under continuous-flow conditions<sup>a</sup>.**

Entry	R	Catalyst	T (°C)	Solvent	Flow rate (mL/min)	Pressure (bar)	Conversion (%) <sup>b</sup>	Yield <b>1</b> <sup>c</sup> (%)	Main byproduct <sup>c</sup> (%)
<b>1</b>	Ph	10% Pd/C	30	EtOAc:EtOH 2:1	1.0	10	>99	-	<b>6a</b> (>98)
<b>2</b>	Ph	5% Rh/C	30	EtOAc:EtOH 2:1	1.0	50	>99	-	<b>6a</b> (>98)
<b>3</b>	Ph	5% Pt/C	30	EtOAc:EtOH 2:1	1.0	10	94	12	<b>8a</b> (82)
<b>4</b>	Ph	5% Pt/C	30	THF	1.0	10	54	21	<b>8a</b> (33)
<b>5</b>	Ph	5% Pt/C	80	THF	1.0	10	60	50	<b>8a</b> (10)
<b>6</b>	Ph	5% Pt/C	80	THF	0.3	50	>99	52	<b>8a</b> (18) + <b>9a</b> (25)
<b>7</b>	Ph	5% Ru/C	80	THF	0.3	50	>99	94 (93) <sup>c</sup>	-
<b>8</b>	<i>i</i> -Pr	5% Ru/C	80	THF	0.3	50	>99	94 (92) <sup>c</sup>	-
<b>9</b>	<i>c</i> -Hex	5% Ru/C	80	THF	0.3	50	>99	92 (91) <sup>c</sup>	-

<sup>a</sup>H-Cube Pro, Full-H<sub>2</sub> mode, 30 mm × 4 mm i.d. catalyst cartridge, ~ 150 mg of catalyst; <sup>b</sup>Calculated as 100 – % of residual nitroderivative **3** as determined by HPLC; <sup>c</sup>Determined by HPLC; <sup>d</sup>Isolated yield after chromatographic purification.



## Conclusions

In conclusion, we have developed an improved continuous-flow synthetic protocol for the preparation of 3,4-dihydro-5*H*-benzo[e][1,4]diazepin-5-ones derivatives. Even if the continuous-flow approach has been successfully used for the preparation of several heterocycles,<sup>16</sup> until recently it was never applied to the synthesis of the benzodiazepine moiety. Only during the preparation of this manuscript, Baumann *et al.* reported on a continuous flow protocol to obtain dibenzodiazepines.<sup>17</sup> Yet, the described procedure was plagued by the requirement of assisting cyclodehydration by placing in-line, after the flow cartridge, a glass Omnifit column packed with anhydrous MgSO<sub>4</sub> and the need of a final chromatographic purification step.

The protocol herein described is highly preferable over traditional metal mediated non-catalytic reduction procedure, due to its efficiency, high yielding, and ease in scale-up. As no purification steps are required, it could be successfully exploited for the rapid construction of the 3,4-dihydro-5*H*-benzo[e][1,4]diazepin-5-one privileged structures, useful for the generation of compound libraries for drug discovery.

## Experimental

### General information

All chemicals were purchased from Aldrich Chimica (Milan, Italy) and were of the highest purity. All solvents were reagent grade. Reactions were routinely monitored by TLC performed on aluminum-backed silica gel plates (Merck DC, Alufolien Kieselgel 60 F254) with spots visualized by UV light ( $\lambda = 254, 365$  nm). Solvents were removed using a rotary evaporator operating at a reduced pressure of  $\sim 10$  Torr. Organic solutions were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Chromatographic purification was done on

an automated flash-chromatography system (Isolera<sup>TM</sup>One, Biotage) using cartridges packed with KP-SIL, 60 Å (40-63 µm particle size) and dichloromethane/methanol mixtures as eluents.

High performance liquid chromatography (HPLC) was performed on a Shimadzu SPD 20A UV/VIS detector ( $\lambda = 215$  nm) using C-18 column Phenomenex Synergi Fusion – RP 80A (75 × 4.60 mm; 4 µm) at 25 °C using a mobile phase A (water + 0.1% trifluoroacetic acid (TFA)) and B (MeCN + 0.1% TFA) at a flow rate of 1 mL/min. The following gradient was applied: isocratic elution for 1 min at 10% of solvent B, linear increase from 10% to 95% of solvent B over 10 min, hold at 95% solvent B for 3 min.

Melting points were determined on a Stuart SMP30 melting point apparatus in open capillary tubes and are uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 300 MHz and 75 MHz respectively with a Bruker Avance 300 spectrometer. Chemical shifts are reported in  $\delta$  (ppm) relative to the internal reference tetramethylsilane (TMS). Mass spectra were recorded on a Finnigan LCQ DECA TermoQuest (San Jose, CA) mass spectrometer in electrospray positive and negative ionization modes (ESI-MS). Elemental analyses (C, H, N) were performed on a Perkin-Elmer 2400 CHN elemental analyzer at the laboratory of microanalysis of the Department of Chemistry and Biology, University of Salerno (Italy). When the elemental analysis is not included, compounds were used in the next step without further purification. The amino ketone **5a** was commercially available while 4-(benzyloxy)-5-methoxy-2-nitrobenzoic acid **4**<sup>18</sup> and amino ketones **5b**<sup>19</sup> and **5c**<sup>20</sup> were synthesized following reported procedures.

#### **4-(Benzyloxy)-5-methoxy-2-nitro-N-(2-oxo-2-phenylethyl)benzamide (3a)**

To an ice cooled suspension of 4-(benzyloxy)-5-methoxy-2-nitrobenzoic acid **4** (1.30 g, 4.29 mmol), HOBt·H<sub>2</sub>O (1.58 g, 10.3 mmol), HBTU (3.91 g, 10.3 mmol) in THF:DMF 4:1 (100 mL), N,N-diisopropylethylamine (DIPEA) (3.59 mL, 20.6 mmol) was added. The reaction mixture was stirred under a nitrogen atmosphere for 15 min and then 2-amino-1-phenylethan-1-one hydrochloride **5a** (0.88 g, 5.15 mmol) was added. After stirring at room temperature for 12 h, the mixture was concentrated in

vacuo and EtOAc (60 mL) was added. The organic layer was washed with NaHCO<sub>3</sub> saturated solution (3 x 20 mL), dried, and concentrated in vacuo. Recrystallization from ethanol provided the title compound as white solid (1.51 g, 84%). M.p. 166–168 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 8.95 (t, J = 5.5 Hz, 1H exchangeable with D<sub>2</sub>O), 8.06 – 8.04 (m, 2H), 7.73 – 7.67 (m, 2H), 7.60 – 7.55 (m, 2H), 7.49 – 7.31 (m, 5H), 7.15 (s, 1H), 5.26 (s, 2H), 4.79 (d, J = 5.5 Hz, 2H), 3.94 (s, 3H); MS (ESI) *m/z*: 421 (M + H)<sup>+</sup>.

#### **4-(Benzyloxy)-*N*-(2-cyclohexyl-2-oxoethyl)-5-methoxy-2-nitrobenzamide (3b)**

Prepared using 2-amino-1-cyclohexylethan-1-one hydrochloride **5b** according to the procedure described for **3a**. White solid (1.28 g, 70%). M.p. 178–180 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 8.80 (t, J = 5.6 Hz, 1H exchangeable with D<sub>2</sub>O), 7.72 (s, 1H), 7.49 – 7.35 (m, 5H), 7.13 (s, 1H), 5.25 (s, 2H), 4.15 (d, J = 5.6 Hz, 2H), 3.93 (s, 3H), 2.62 – 2.56 (m, 1H), 1.84 – 1.61 (m, 5H), 1.36 – 1.13 (m, 5H); MS (ESI) *m/z*: 427 (M + H)<sup>+</sup>.

#### **4-(Benzyloxy)-5-methoxy-*N*-(3-methyl-2-oxobutyl)-2-nitrobenzamide (3c)**

Prepared using 1-amino-3-methylbutan-2-one hydrochloride **5c** according to the procedure described for **3a**. White solid (1.41 g, 85%). M.p. 154–156 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 8.80 (t, J = 5.5 Hz, 1H exchangeable with D<sub>2</sub>O), 7.72 (s, 1H), 7.48 – 7.34 (m, 5H), 7.12 (s, 1H), 5.25 (s, 2H), 4.18 (d, J = 5.5 Hz, 2H), 3.92 (s, 3H), 2.89 – 2.73 (m, 1H), 1.05 (d, J = 7.0 Hz, 6H); MS (ESI) *m/z*: 387 (M + H)<sup>+</sup>.

**General procedure for the reduction of 2-nitro benzamides **3** under conventional batch conditions.**

**Methods A, E, F and G.** The proper catalyst was added to a solution of the appropriate 2-nitro benzamide **3** (0.60 mmol) in a suitable solvent (20 mL) and the reaction was stirred under H<sub>2</sub> (1 atm, balloon) at the indicated temperature. The reaction mixture was filtered, concentrated and the residue was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH).

**Method B.** A 10 mL CEM microwave process vial with a stir bar was charged with the appropriate 2-nitro benzamide **3** (0.10 mmol), 10 wt. % Pd/C (0.05 eq), and methanol (1 mL). 1,4-Cyclohexadiene (57  $\mu$ L, 0.60 mmol) was added. The vessel was capped and heated under microwave conditions at 120 °C for 10 min. The reaction was filtered through Celite, concentrated and the residue was purified by silica gel chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ).

**Method C.** A boiling solution of the appropriate 2-nitro benzamide **3** (0.60 mmol) in ethanol (3 mL) was added to a suspension of iron (II) sulfate heptahydrate (1.67 g, 6.00 mmol) in water (3 mL) and 32 % ammonium hydroxide (0.30 mL). The reaction mixture was heated under reflux until the disappearance of the starting material (TLC analysis) while 32 % ammonium hydroxide was dropped (3 mL). The hot mixture was then filtered, concentrated and  $\text{CHCl}_3$  (50 mL) was added. The organic layer was washed with  $\text{H}_2\text{O}$  ( $3 \times 20$  mL) and brine ( $1 \times 50$  mL), dried, and concentrated in vacuo. The residue was purified by silica gel chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ).

**Method D.** Iron powder (0.67 g, 60.0 mg-atom) was added to a solution of the appropriate 2-nitro benzamide **3** (0.60 mmol) in acetic acid (6 mL). The reaction mixture was heated at 70 °C until the disappearance of the starting material (TLC analysis). The mixture was diluted with  $\text{H}_2\text{O}$  (20 mL) and  $\text{CHCl}_3$  (20 mL) and filtered through a small pad of Celite. After separation of the two phases, the aqueous layer was extracted with  $\text{CHCl}_3$  ( $2 \times 20$  mL). The organic phase was then washed with  $\text{H}_2\text{O}$  ( $3 \times 20$  mL),  $\text{NaHCO}_3$  saturated solution ( $1 \times 20$  mL) and brine ( $1 \times 20$  mL), dried and concentrated in vacuo. The residue was purified by silica gel chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ).

**Continuous flow processing for the reduction of 2-nitro benzamides **3** using the H-Cube Pro hydrogenator (Method H).**

A 10 mL stock solution of the appropriate 2-nitro benzamide **3** with a 0.03 M concentration in THF was prepared in a glass vial. The reaction parameters (Full- $\text{H}_2$  mode, 80 °C, 50 bar and 0.3 mL/min flow

rate) were selected on the H-Cube-Pro<sup>TM</sup> hydrogenator. The instrument was fitted with a 30 mm Ru/C CatCart and the processing was started, whereby initially only pure solvent was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing. At that point, the sample inlet line was switched to the vial containing the substrate. A total reaction volume of 15 mL was collected and the cartridge subsequently washed with pure solvent for 5 min to remove any substrate/product still adsorbed on the catalyst. Evaporation of the solvent afforded the desired 3,4-dihydro-5*H*-benzo[*e*][1,4]diazepin-5-ones **1a–c** (99% crude yield), which were purified by flash chromatography to provide pure compounds (91–93%).

**8-(Benzyloxy)-7-methoxy-2-phenyl-3,4-dihydro-5*H*-benzo[*e*][1,4]diazepin-5-one (1a).** White solid; M.p. 195-197 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*6): δ 8.41 (t, *J* = 5.8 Hz, 1H exchangeable with D<sub>2</sub>O), 8.06 – 8.03 (m, 2H), 7.55 – 7.33 (m, 9H), 7.02 (s, 1H), 5.21 (s, 2H), 3.94 (d, *J* = 5.8 Hz, 2H), 3.85 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, DMSO-*d*6): δ 167.6, 165.3, 150.4, 147.0, 141.2, 136.6, 136.4, 131.0, 128.7, 128.5, 128.0, 127.9, 127.7, 119.0, 111.5, 110.8, 69.9, 55.7, 38.6; MS (ESI) *m/z*: 373 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>23</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.29; H, 5.42; N, 7.50.

**8-(Benzyloxy)-2-cyclohexyl-7-methoxy-3,4-dihydro-5*H*-benzo[*e*][1,4]diazepin-5-one (1b).** White solid; M.p. 199-201 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*6): δ 8.26 (t, *J* = 5.6 Hz, 1H exchangeable with D<sub>2</sub>O), 7.47 – 7.34 (m, 5H), 7.29 (s, 1H), 6.82 (s, 1H), 5.15 (s, 2H), 3.81 (s, 3H), 3.40 (d, *J* = 5.6 Hz, 2H), 2.45 – 2.36 (m, 1H), 1.93 – 1.65 (m, 5H), 1.42 – 1.17 (m, 5H). <sup>13</sup>C NMR (75.5 MHz, DMSO-*d*6): δ 175.0, 167.4, 150.2, 146.4, 140.9, 136.6, 128.4, 127.9, 127.8, 118.9, 111.3, 110.4, 69.8, 55.6, 46.7, 38.7, 29.5, 25.4; MS (ESI) *m/z*: 379 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.75; H, 6.94; N, 7.42.

**8-(Benzyloxy)-2-isopropyl-7-methoxy-3,4-dihydro-5*H*-benzo[*e*][1,4]diazepin-5-one (1c).** White solid; M.p. 187-189 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*6): δ 8.31 (t, *J* = 5.6 Hz, 1H exchangeable with D<sub>2</sub>O), 7.48 – 7.35 (m, 5H), 7.31 (s, 1H), 6.85 (s, 1H), 5.17 (s, 2H), 3.82 (s, 3H), 3.41 (d, *J* = 5.6 Hz,

2H), 2.83 – 2.70 (m, 1H), 1.18 (d,  $J = 6.8$  Hz, 6H);  $^{13}\text{C}$  NMR (75.5 MHz, DMSO-*d*6):  $\delta$  175.9, 167.5, 150.2, 146.5, 140.8, 136.6, 128.4, 128.0, 127.8, 118.9, 111.4, 110.4, 69.9, 55.6, 39.0, 37.1, 19.5; MS (ESI)  $m/z$ : 339 (M + H) $^+$ . Anal. Calcd for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.84; H, 6.53; N, 8.31.

**2-Amino-4-hydroxy-*N*-(2-hydroxy-2-phenylethyl)-5-methoxybenzamide (6a).** Yellow oil.  $^1\text{H}$  NMR (300 MHz, DMSO-*d*6)  $\delta$  9.28 (br s, 1H exchangeable with D<sub>2</sub>O), 8.02 (t,  $J = 5.7$  Hz, 1H exchangeable with D<sub>2</sub>O), 7.38 – 7.22 (m, 5H), 7.05 (s, 1H), 6.14 – 6.13 (m, 3H, 2H exchangeable with D<sub>2</sub>O), 5.50 (d,  $J = 4.2$  Hz, 1H exchangeable with D<sub>2</sub>O), 4.77 – 4.71 (m, 1H), 3.67 (s, 3H), 3.25 – 3.17 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz, DMSO-*d*6)  $\delta$  168.9, 150.9, 146.2, 144.0, 138.4, 128.0, 126.9, 126.0, 113.2, 105.1, 103.1, 71.4, 56.8, 47.5; MS (ESI)  $m/z$ : 303 (M + H) $^+$ . Anal. Calcd for C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.71; H, 5.99; N, 9.29.

**8-Hydroxy-7-methoxy-2-phenyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (7a).** White solid. M.p. 218–220 °C (dec.);  $^1\text{H}$  NMR (300 MHz, DMSO-*d*6)  $\delta$  9.37 (br s, 1H exchangeable with D<sub>2</sub>O), 7.66 (t,  $J = 5.7$  Hz, 1H exchangeable with D<sub>2</sub>O), 7.37 – 7.26 (m, 5H), 7.15 (s, 1H), 6.35 (s, 1H), 5.75 (s, 1H exchangeable with D<sub>2</sub>O), 4.66 (t,  $J = 5.7$  Hz, 1H), 3.69 (s, 3H), 3.37 – 3.33 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz, DMSO-*d*6)  $\delta$  171.4, 151.9, 144.8, 143.2, 141.6, 129.4, 128.1, 128.0, 116.0, 111.4, 106.4, 63.6, 57.2, 47.2; MS (ESI)  $m/z$ : 285 (M + H) $^+$ . Anal. Calcd for C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.38; H, 5.69; N, 9.83.

**2-Cyclohexyl-8-hydroxy-7-methoxy-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (7b).** White solid. M.p. 221–223 °C (dec);  $^1\text{H}$  NMR (300 MHz, DMSO-*d*6)  $\delta$  9.23 (br s, 1H exchangeable with D<sub>2</sub>O), 7.68 (t,  $J = 5.8$  Hz, 1H exchangeable with D<sub>2</sub>O), 7.16 (s, 1H), 6.21 (s, 1H), 5.86 (d,  $J = 4.5$  Hz, 1H exchangeable with D<sub>2</sub>O), 3.64 (s, 3H), 3.21 – 3.10 (m, 2H), 3.03 – 3.00 (m, 1H), 1.77 – 1.62 (m, 5H), 1.45 – 1.36 (m, 1H), 1.23 – 0.87 (m, 5H);  $^{13}\text{C}$  NMR (75 MHz, DMSO-*d*6)  $\delta$  170.4, 151.1, 142.7,

139.8, 115.2, 108.0, 104.6, 62.3, 56.2, 41.9, 29.5, 27.8, 26.0; MS (ESI)  $m/z$ : 291 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.36; H, 7.62; N, 9.62.

**2-Amino-4-(benzyloxy)-5-methoxy-N-(2-oxo-2-phenylethyl)benzamide (8a).** Yellow oil. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  8.40 (t, J = 5.8 Hz, 1H exchangeable with D<sub>2</sub>O), 8.06 – 8.03 (m, 2H) 7.55 – 7.33 (m, 11H, 2H exchangeable with D<sub>2</sub>O), 7.02 (s, 1H), 5.21 (s, 2H), 3.95 (d, J = 5.8 Hz, 2H), 3.85 (s, 3H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  195.9, 168.6, 146.3, 136.7, 135.3, 133.4, 128.8, 128.4, 127.9, 127.8, 112.7, 109.1, 101.2, 69.4, 56.7, 46.0; MS (ESI)  $m/z$ : 391 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>23</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>: C, 70.75; H, 5.68; N, 7.18. Found: C, 70.98; H, 5.66; N, 7.15.

**8-(Benzyloxy)-7-methoxy-2-phenyl-1,2,3,4-tetrahydro-5H-benzo[*e*][1,4]diazepin-5-one (9a).** White solid. M.p. 180–182 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.73 (t, J = 5.5 Hz, 1H, exchangeable with D<sub>2</sub>O), 7.48 – 7.26 (m, 10H), 7.20 (s, 1H), 6.61 (s, 1H), 6.22 (d, J = 3.6 Hz, 1H, exchangeable with D<sub>2</sub>O), 5.04 (s, 2H), 4.69 – 4.67 (m, 1H), 3.69 (s, 3H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  171.0, 152.7, 144.5, 143.2, 142.2, 137.8, 129.6, 129.4, 129.1, 128.2, 127.9, 115.8, 111.4, 104.4, 70.7, 63.6, 57.1, 47.2; MS (ESI)  $m/z$ : 375 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>23</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.54; H, 5.93; N, 7.50.

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**Electronic Supplementary Information (ESI) available:** Copies of <sup>1</sup>H, <sup>13</sup>C NMR spectra of synthesized compounds. See DOI:

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