Rapid Synthesis of Benzodiazepines by Ring Expansion of Aziridines with Anthranilic Acids by Using a Grinding Technique

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Abstract: A grinding-induced, atom-economic, rapid, efficient, one-pot protocol was developed for the synthesis of pharmaceutically relevant benzo-1,4-diazepin-5-ones in excellent yields (72–91%) and high regioselectivities. The method involves a ring-opening–ring-closure cascade of aziridines with anthranilic acids by grinding the neat reactants at room temperature in the presence of lithium bromide as a mild catalyst. Among the advantages of this protocol are its economic viability, the ability to recycle the catalyst, and the formation of water as the only byproduct.

Key words: heterocycles, cyclizations, solid-phase synthesis, cascade reactions, benzodiazepines

The generation of complex molecular systems by cascade reactions by following green chemistry protocols is an area that is of current interest to organic chemists.[1] In the last decade, cascade reactions have become powerful tools in organic chemistry, not only because they offer significant potential to reduce byproduct formation, waste production, energy costs, and materials consumption, to mitigate hazards, and to use nonrenewable resources, but also because they open the way to the development of new methods for preparing previously unobtainable materials.[2] Recently, the initiation of solvent-free organic reactions by grinding has attracted considerable interest, and it has been found to provide several excellent methods for performing aldol condensations,[3] Grignard reactions,[4] Reformatsky reactions,[5] Dieckmann condensations,[6] Knoevenagel condensations,[7] reductions,[8] and other organic reactions.[9] Most of these reactions are carried out at room temperature under neat conditions using only a pestle and mortar.

In general, the chemistry of seven-membered heterocycles has been far less extensively studied than that of five- or six-membered heterocycles or that of inherently strained small-ring heterocycles. The synthesis of heterocycles with seven- to eleven-membered rings is difficult for enthalpic and entropic reasons.[10] In recent decades, the synthesis of heterocycles with ring sizes in the range from seven to eleven has received a great deal of attention because of the abundance of oxygen- and nitrogen-containing seven-membered and other medium-sized rings in natural products,[11] drug candidates,[12] functional materials,[13] and catalysts.[14] Among the seven-membered heterocycles, those with two heteroatoms in the 1- and 4-positions, especially benzodiazepines, are important scaffolds in medicinal chemistry, and many biologically active compounds contain such cores.[15] Benzodiazepines are widely used as drugs of the central nervous system. For example, diazepam, lorazepam, parazepam, and oxazepam are used as anxiolytics; flurazepam is a hypnotic; clonazepan is an antiepileptic;[15c] triflubazam (**A**) and clobazam (**B**)[16] are anxiolytic agents; anthramycin (**C**)[17] is a naturally occurring antitumor antibiotic, and other analogues such as the pyrrolobenzodiazepine **D**[18] display antileishmanial activity (Figure 1). In addition, some benzodiazepine derivatives are potent inhibitors of HIV-1 reverse transcriptase.[19]

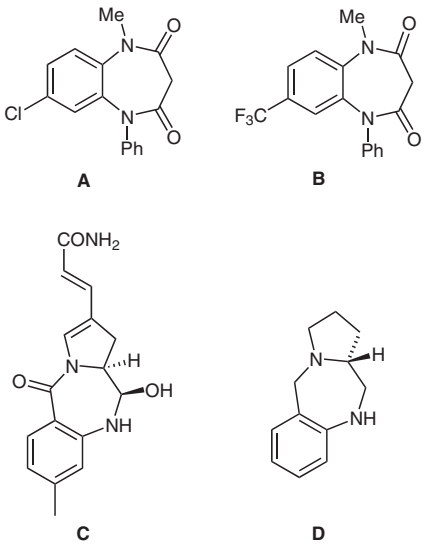

Figure 1 Some medicinally important 1,4-benzodiazepine derivatives

The widespread occurrence and medicinal applications of benzodiazepines make these compounds attractive as targets for synthesis. Benzodiazepines are generally synthesized by acid-catalyzed condensation of a benzene-1,2-diamine with a ketone. This transformation is catalyzed by many reagents including boron trifluoride etherate,[20a] sodium borohydride,[20b] magnesium oxide–phosphoryl trichloride,[20c] alumina–phosphorus pentoxide,[20d] acetic acid (with microwave heating),[20e] diiodine,[20f] silver heteropolyphosphotungstate ($Ag_3PW_{12}O_{40}$),[20g] indium(III) bromide,[20h] bromo(dimethyl)sulfonium bromide,[20i] cerium(IV) ammonium nitrate,[20j] silver nitrate,[20k] triflates,[20l,m]

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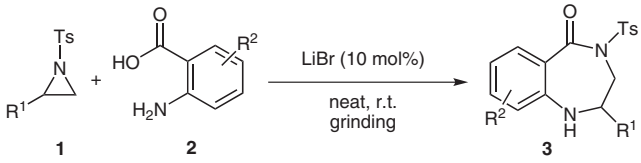
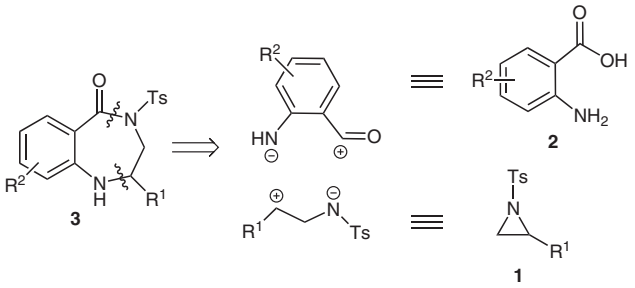
palladium,[20n] or ionic liquids.[20o] Corral and co-workers synthesized benzodiazepines by the addition of methyl anthranilate to ethyl enimines with subsequent intramolecular cyclization of the resulting intermediates.[21] However, most methodologies for the synthesis of benzodiazepines have disadvantages such as long reaction times, high temperatures, harsh reaction conditions, the use of expensive reagents, or the use of toxic or hazardous organic solvents. There is therefore a need to develop economical and environmentally benign methods for the synthesis of these compounds.

In continuation of our ongoing efforts to develop new cyclization processes,[22] we have devised an efficient, regioselective, one-pot synthesis of pharmacologically relevant benzo-1,4-diazepin-5-ones **3**. Our protocol involves ring expansion of an aziridine **1** with an anthranilic acid **2** (Scheme 1).



Scheme 1 Ring expansion of aziridines to benzo-1,4-diazepin-5-ones

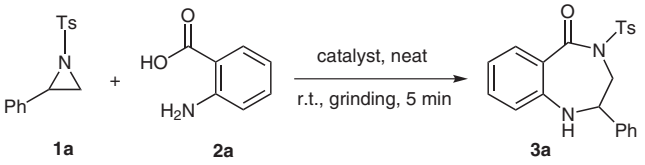
We selected the *N*-tosylaziridine **1** and the anthranilic acid **2** as reactants on the basis of the disconnection approach shown in Scheme 2.



Scheme 2 Disconnection approach for the target compounds **3**

Here, we report a lithium bromide-catalyzed reaction involving regioselective cleavage of the aziridine ring in **1** by the amino group of the anthranilic acid **2**, followed by cyclization to afford the 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one **3** (Scheme 1). In general, the efficiency of a synthetic process can be enhanced by increasing the concentration of the reactants and by the use of a suitable catalyst. To realize our idea, we initially examined the synthesis of 2-phenyl-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (**3a**) by the reaction of 2-phenyl-1-tosylaziridine (**1a**) with 2-aminobenzoic acid (**2a**; anthranilic acid) in the presence of several Lewis acid catalysts that should efficiently catalyze both steps of the ring-opening–ring-closing cascade of the aziridine with the anthranilic acid. The best results were obtained by using lithium bromide (Table 1, entries 2–4). Significantly lower yields of benzodiazepine **3a** were obtained with the other catalysts (Table 1, entries 1 and 5–10).

Table 1 Optimization of the Catalyst for the Synthesis of 2-Phenyl-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (**3a**)



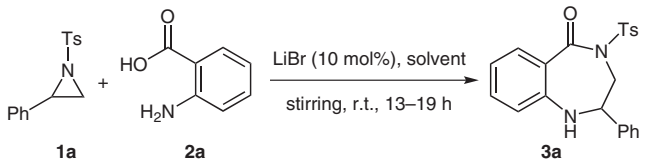
Entry	Catalyst (mol%)	Yield (%)[a]
1	LiI (10)	60[b]
2	LiBr (10)	85
3	LiBr (5)	76
4	LiBr (15)	85
5	LiCl (10)	62
6	$AlCl_3$ (10)	53
7	$AlBr_3$ (10)	55
8	NaCl (10)	21
9	NaBr (10)	26
10	$CuCl_2$ (10)	33
11	$CuBr_2$ (10)	35
12	$FeCl_3$ (10)	49
13	$FeBr_3$ (10)	53

[a] Isolated yield of purified product **3a**.
[b] *N*-(2-iodo-2-phenylethyl)-4-methylbenzenesulfonamide was also isolated in 24% yield.

No appreciable amount of product **3a** was formed from aziridine **1a** and anthranilic acid **2a** in the absence of lithium bromide after grinding for five minutes at room temperature, showing that lithium bromide is an effective catalyst. For comparison, we also performed the reaction in various solvents with lithium bromide as the catalyst, but we obtained significantly lower yields of **3a** in relatively longer reaction times (13–19 hours; Table 2).

Of the solvents tested, dichloromethane was the best in terms of the yield and reaction time (Table 2, entry 3). Having optimized the reaction conditions, we then proceeded to examine the scope of our grinding method. A wide range of benzo-1,4-diazepin-5-ones **3** were rapidly synthesized in excellent yields and complete regioselectivity (Table 3). The reaction therefore permits the introduction of a considerable degree of molecular diversity under mild reaction conditions. The regioselectivity of the reaction was ascertained by recording the ^{1}H NMR spectra of the crude samples, and we found that the regioisomer **3** was formed exclusively. The regioselective cleavage of the aziridine ring at the benzylic position is

Table 2 Optimization of the Solvent for the Synthesis of 2-Phenyl-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (**3a**)



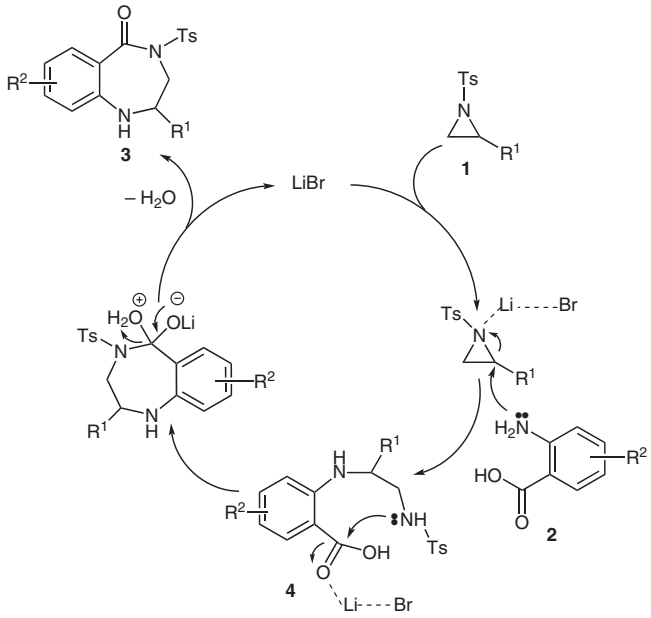
1a 2a 3a

Entry	Solvent	Time (h)	Yield (%)[a]
1	THF	15	71
2	1,4-dioxane	17	73
3	CH_2Cl_2	13	75
4	EtOH	16	69
5	toluene	19	62
6	$CHCl_3$	14	70

[a] Isolated yield of purified product **3a**.

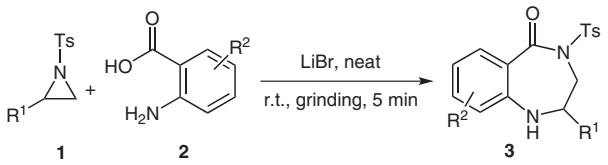
easily understandable. The regioselective ring opening of the alkyl aziridines at the secondary position is in agreement with reactivity–selectivity arguments reported in the literature.[23] Therefore, the amino group of the anthranilic acid preferentially attacks the 2-alkyl-1-tosylaziridine at the 2-position, which has a partial positive charge, rather than at the 3-position.

The important feature of this procedure is the compatibility of the reaction conditions with a broad range of functional groups, including ether, nitro, and chloro groups. Anthranilic acids **2** bearing an electron-withdrawing group give slightly lower yields (Table 3, entries 6–10, 18, and 19) than those bearing electron-donating groups (Table 3, entries 11–15). On the basis of our experimental results, we proposed the mechanism for the formation of benzo-1,4-diazepin-5-ones **3** that is shown in Scheme 3. Lithium bromide activates the aziridine ring by coordinating with the nitrogen atom, thereby facilitating regioselective nucleophilic ring cleavage by the amino group of anthranilic acid **2** to form intermediate **4**. Intramolecular dehydrative cyclization of **4** affords the benzo-1,4-diazepin-5-ones **3** and liberates lithium bromide to complete the catalytic cycle (Scheme 3).



Scheme 3 A plausible mechanism and catalytic cycle for ring expansion of aziridines

Table 3 Synthesis of 1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepin-5-ones **3**



1 2 3

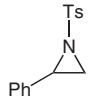
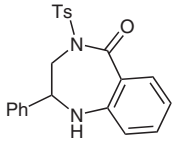
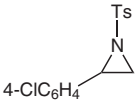
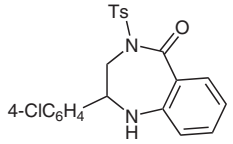
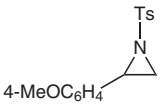
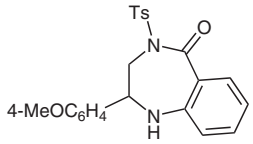
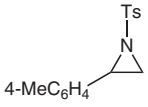
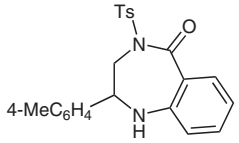
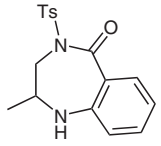
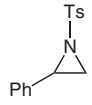
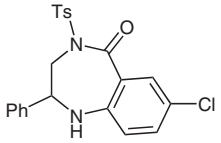
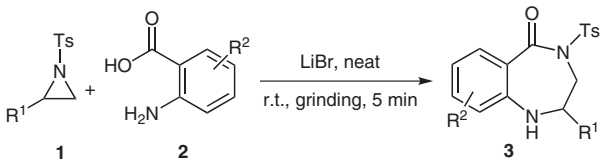
Entry	Aziridine **1**	R^2	Product	Yield (%)[a,b]
1		H	 **3a**	85
2		H	 **3b**	89
3		H	 **3c**	88
4		H	 **3d**	86
5		H	 **3e**	77
6		5-Cl	 **3f**	82

Table 3 Synthesis of 1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepin-5-ones **3** (continued)



1 2 3

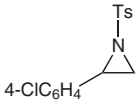
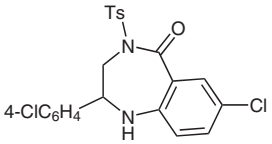
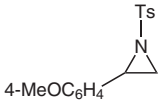
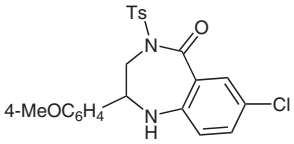
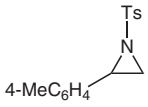
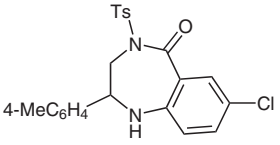
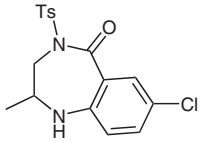
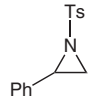
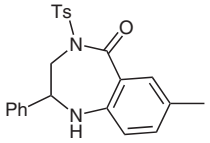
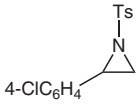
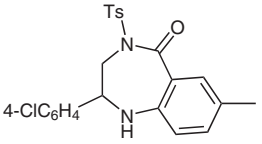
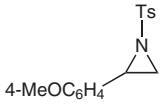
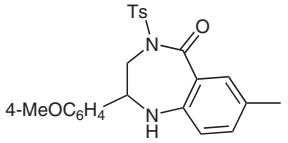
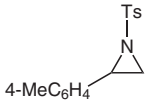
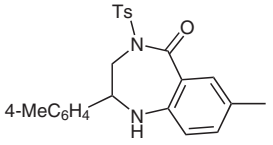
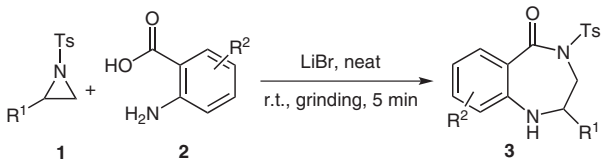
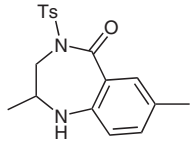
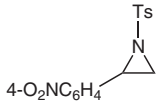
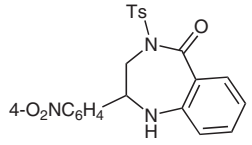
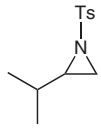
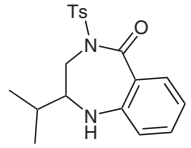
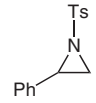
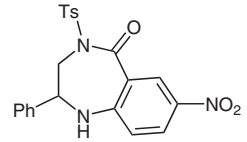
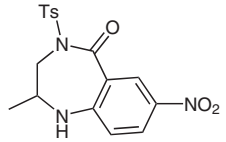
Entry	Aziridine **1**	R^2	Product	Yield (%)[a,b]
7		5-Cl	 **3g**	86
8		5-Cl	 **3h**	84
9		5-Cl	 **3i**	87
10		5-Cl	 **3j**	76
11		5-Me	 **3k**	84
12		5-Me	 **3l**	88
13		5-Me	 **3m**	87
14		5-Me	 **3n**	91

Table 3 Synthesis of 1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepin-5-ones **3** (continued)



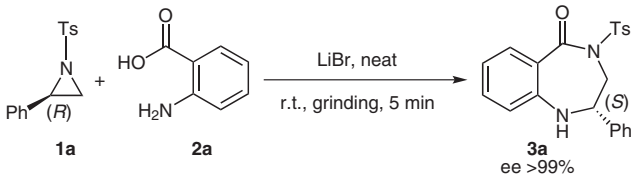
1 2 3

Entry	Aziridine **1**	R^2	Product	Yield (%)[a,b]
15		5-Me	 **3o**	78
16		H	 **3p**	85
17		H	 **3q**	81
18		5-NO_2	 **3r**	77
19		5-NO_2	 **3s**	72

[a] Isolated yield of purified product **3**.

[b] All the products were solids and showed the expected IR, ^{1}H NMR, ^{13}C NMR, and EIMS spectra. Their C, H, and N analyses were within ±0.36% of the expected values.

In a pilot study of the one-pot enantioselective synthesis of the benzo-1,4-diazepin-5-one (*S*)-**3a** (Scheme 4), a mixture of aziridine (*R*)-**1a** (1 mmol), anthranilic acid **2a** (1 mmol), and lithium bromide (10 mol%) was ground in a mortar with a pestle at room temperature for five minutes to give the (*S*)-benzo-1,4-diazepin-5-one (*S*)-**3a** in 87% yield with an enantiomeric excess (ee) of about 99%, as determined by chiral HPLC using a chiral Eurocel column [250 × 4.6 mm, 5 ; λ = 225 nm; *i*-PrOH–hexane (10:90), 1 mL/min; t_R = 6.4 min (minor), 7.6 min (major)]; $[\alpha]_D^{20}$ +94 (*c* 0.90, THF). This shows that the ring opening of the optically active aziridine (*R*)-**1a** with anthranilic acid **2a** proceeds by an S_N2-type pathway.



Scheme 4 Enantioselective synthesis of (2*S*)-2-Phenyl-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one [(*S*)-**3a**]

In summary, we have developed a simple and highly efficient one-pot green protocol for the synthesis of pharmaceutically relevant benzo-1,4-diazepine derivatives by means of a lithium bromide-catalyzed regioselective ring expansion of an aziridine with an anthranilic acid. This rapid synthesis is performed within five minutes at room temperature under neat conditions by the application of grinding. Moreover, the protocol has the advantages in terms of sustainability, economic viability, recycling of the catalyst, atom economy, high yield, and formation of water as the sole byproduct, making it one of the most convenient and efficient methods for the synthesis of this class of compounds.

IR spectra in KBr were recorded on a Perkin-Elmer 993 IR spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance II (400 MHz) Fourier-transform spectrometer in $CDCl_3$ with TMS as the internal reference. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz in $CDCl_3$ with TMS as internal reference. Mass (EI) spectra were recorded on a JEOL D-300 mass spectrometer. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen, and nitrogen analyzer. All chemicals were of reagent grade and were used as received without further purification. Silica gel-G was used for TLC.

1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepin-5-one 3; General Procedure

Aziridine **1** (1 mmol), anthranilic acid **2** (1 mmol), and LiBr (10 mol%) were thoroughly ground with a pestle and mortar for 5 min at r.t. When the reaction was complete [TLC, EtOAc–hexane (2:3)], H_2O (5 mL) was added and the mixture was extracted with EtOAc (3×5 mL). The combined organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography [silica gel, EtOAc–hexane (1:3)]. After isolation of the product, the remaining aqueous layer containing LiBr was washed with Et_2O (2×5 mL) to remove any organic impurities and dried under reduced pressure to afford LiBr, which was reused in subsequent runs without further purification and with no loss of efficiency.

2-Phenyl-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (3a)

Yellowish solid; yield: 333 mg (85%); mp 175–177 °C.

IR (KBr): 3340, 1700, 1600, 1323, 1159, 810 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 3.22 (dd, *J* = 12.1, 5.4 Hz, 1 H), 3.46 (dd, *J* = 12.1, 7.6 Hz, 1 H), 4.55 (dd, *J* = 7.6, 5.4 Hz, 1 H), 5.36 (br s, 1 H, NH, exchanges with D_2O), 6.32 (dd, *J* = 8.3, 1.3 Hz, 1 H, H_{arom}), 6.62 (m, 1 H, H_{arom}), 7.16–7.31 (m, 6 H, H_{arom}), 7.33 (d, *J* = 8.2 Hz, 2 H, H_{arom}), 7.71 (d, *J* = 8.2 Hz, 2 H, H_{arom}), 7.97 (dd, *J* = 8.3, 1.3 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7, 47.8, 62.3, 112.6, 115.5, 117.8, 125.8, 127.1, 127.5, 128.5, 129.2, 129.9, 133.5, 137.3, 141.9, 143.0, 147.8, 168.4.

MS (EI): *m/z* = 392 [M]$^+$.

Anal. Calcd for $C_{22}H_{20}N_2O_3S$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.62; H, 5.50; N, 7.09.

2-(4-Chlorophenyl)-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (3b)

Yellowish solid; yield: 379 mg (89%); mp 184–186 °C.

IR (KBr): 3326, 1702, 1603, 1326, 1158, 840 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 3.20 (dd, *J* = 12.2, 5.3 Hz, 1 H), 3.45 (dd, *J* = 12.2, 7.5 Hz, 1 H), 4.57 (dd, *J* = 7.5, 5.3 Hz, 1 H), 5.34 (br s, 1 H, NH, exchanges with D_2O), 6.33 (dd, *J* = 8.1, 1.0 Hz, 1 H, H_{arom}), 6.65 (m, 1 H, H_{arom}), 7.30 (d, *J* = 8.1 Hz, 2 H, H_{arom}), 7.33–7.36 (m, 1 H, H_{arom}), 7.65–7.70 (m, 2 H, H_{arom}), 7.71 (d, *J* = 8.1 Hz, 2 H, H_{arom}), 8.00 (dd, *J* = 8.2, 1.0 Hz, 1 H, H_{arom}), 8.10–8.17 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.9, 47.9, 62.5, 112.6, 115.8, 117.9, 127.7, 128.6, 128.7, 128.9, 130.0, 132.5, 133.4, 137.8, 141.8, 142.1, 147.9, 168.6.

MS (EI): *m/z* = 426 [M]$^+$.

Anal. Calcd for $C_{22}H_{19}ClN_2O_3S$: C, 61.89; H, 4.49; N, 6.56. Found: C, 62.17; H, 4.24; N, 6.69.

2-(4-Methoxyphenyl)-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (3c)

Yellowish solid; yield: 371 mg (88%); mp 161–162 °C.

IR (KBr): 3328, 1705, 1598, 1328, 1159, 860 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 3.21 (dd, *J* = 12.3, 5.2 Hz, 1 H), 3.46 (dd, *J* = 12.3, 7.7 Hz, 1 H), 3.85 (s, 3 H), 4.52 (dd, *J* = 7.7, 5.2 Hz, 1 H), 5.34 (br s, 1 H, NH, exchanges with D_2O), 6.30 (dd, *J* = 8.0, 1.2 Hz, 1 H, H_{arom}), 6.61 (m, 1 H, H_{arom}), 7.31 (d, *J* = 8.2 Hz, 2 H, H_{arom}), 7.35–7.37 (m, 1 H, H_{arom}), 7.67–7.69 (m, 2 H, H_{arom}), 7.71 (d, *J* = 8.2 Hz, 2 H, H_{arom}), 7.94 (dd, *J* = 8.0, 1.2 Hz, 1 H, H_{arom}), 8.01–8.03 (m, 2 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 47.3, 55.6, 62.0, 112.1, 114.6, 115.4, 117.3, 127.1, 127.8, 128.3, 129.1, 133.2, 136.0, 137.9, 141.4, 147.5, 159.2, 168.0.

MS (EI): *m/z* = 422 [M]$^+$.

Anal. Calcd for $C_{23}H_{22}N_2O_4S$: C, 65.38; H, 5.25; N, 6.63. Found: C, 65.07; H, 5.51; N, 6.41.

2-(4-Tolyl)-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (3d)

Yellowish solid; yield: 349 mg (86%); mp 154–155 °C.

IR (KBr): 3330, 1701, 1600, 1336, 1157, 855 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 2.36 (s, 3 H), 3.19 (dd, *J* = 12.0, 5.3 Hz, 1 H), 3.42 (dd, *J* = 12.0, 7.4 Hz, 1 H), 4.52 (dd, *J* = 7.4, 5.3 Hz, 1 H), 5.32 (br s, 1 H, NH, exchanges with D_2O), 6.30 (dd, *J* = 8.0, 1.1 Hz, 1 H, H_{arom}), 6.62 (m, 1 H, H_{arom}), 7.10–7.36 (m, 5 H, H_{arom}), 7.32 (d, *J* = 8.2 Hz, 2 H, H_{arom}), 7.70 (d, *J* = 8.2 Hz, 2 H, H_{arom}), 7.93 (dd, *J* = 8.0, 1.1 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 24.9, 47.4, 62.5, 112.7, 115.2, 117.1, 126.8, 127.3, 128.2, 129.0, 129.4, 133.4, 136.2, 137.0, 140.7, 141.7, 147.5, 168.2.

MS (EI): *m/z* = 406 [M]$^+$.

Anal. Calcd for $C_{23}H_{22}N_2O_3S$: C, 67.96; H, 5.46; N, 6.89. Found: C, 67.80; H, 5.79; N, 6.61.

2-Methyl-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (3e)

Yellowish solid; yield: 254 mg (77%); mp 93–94 °C.

IR (KBr): 3332, 1704, 1601, 1329, 1158, 850 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 7.0 Hz, 3 H), 2.32 (s, 3 H), 3.00–3.32 (m, 1 H), 3.86 (dd, *J* = 12.3, 5.4 Hz, 1 H), 4.58 (dd, *J* = 12.3, 7.8 Hz, 1 H), 5.30 (br s, 1 H, NH, exchanges with D_2O), 6.31 (dd, *J* = 8.2, 0.9 Hz, 1 H, H_{arom}), 6.60 (m, 1 H, H_{arom}), 7.30 (d, *J* = 8.1 Hz, 2 H, H_{arom}), 7.34–7.36 (m, 1 H, H_{arom}), 7.72 (d, *J* = 8.1 Hz, 2 H, H_{arom}), 8.00 (dd, *J* = 8.2, 0.9 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 24.8, 48.2, 52.3, 113.1, 115.8, 117.0, 127.5, 127.9, 129.1, 132.8, 136.6, 141.7, 147.8, 168.1.

MS (EI): *m/z* = 330 $[M]^+$.

Anal. Calcd for $C_{17}H_{18}N_2O_3S$: C, 61.80; H, 5.49; N, 8.48. Found: C, 61.99; H, 5.80; N, 8.18.

7-Chloro-2-phenyl-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (3f)

Yellowish solid; yield: 349 mg (82%); mp 179–181 °C.

IR (KBr): 3345, 1705, 1603, 1323, 1160, 835 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 3.23 (dd, *J* = 12.3, 5.5 Hz, 1 H), 3.47 (dd, *J* = 12.3, 7.7 Hz, 1 H), 4.58 (dd, *J* = 7.7, 5.5 Hz, 1 H), 5.38 (br s, 1 H, NH, exchanges with D_2O), 6.78 (d, *J* = 8.6 Hz, 1 H, H_{arom}), 7.16–7.31 (m, 5 H, H_{arom}), 7.35 (d, *J* = 8.3 Hz, 2 H, H_{arom}), 7.38 (dd, *J* = 8.6, 1.8 Hz, 1 H, H_{arom}), 7.74 (d, *J* = 8.3 Hz, 2 H, H_{arom}), 8.26 (d, *J* = 1.8 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.9, 47.9, 62.5, 115.3, 116.9, 123.1, 126.5, 127.3, 127.5, 128.3, 128.8, 129.6, 133.6, 137.4, 141.8, 143.9, 145.8, 168.4.

MS (EI): *m/z* = 426 $[M]^+$.

Anal. Calcd for $C_{22}H_{19}ClN_2O_3S$: C, 61.89; H, 4.49; N, 6.56. Found: C, 61.63; H, 4.34; N, 6.88.

7-Chloro-2-(4-chlorophenyl)-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (3g)

Yellowish solid; yield: 396 mg (86%); mp 198–200 °C.

IR (KBr): 3342, 1703, 1598, 1332, 1156, 840 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 3.24 (dd, *J* = 12.3, 5.4 Hz, 1 H), 3.48 (dd, *J* = 12.3, 7.6 Hz, 1 H), 4.58 (dd, *J* = 7.6, 5.3 Hz, 1 H), 5.38 (br s, 1 H, NH, exchanges with D_2O), 6.80 (d, *J* = 8.5 Hz, 1 H, H_{arom}), 7.32 (d, *J* = 8.2 Hz, 2 H, H_{arom}), 7.39 (dd, *J* = 8.5, 1.7 Hz, 1 H, H_{arom}), 7.65–7.72 (m, 2 H, H_{arom}), 7.73 (d, *J* = 8.2 Hz, 2 H, H_{arom}), 8.12–8.19 (m, 2 H, H_{arom}), 8.27 (d, *J* = 1.7 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7, 48.1, 62.6, 114.7, 116.6, 122.9, 127.9, 128.5, 128.7, 128.9, 129.8, 132.9, 133.8, 137.9, 141.9, 142.2, 145.0, 168.7.

MS (EI): *m/z* = 460 $[M]^+$.

Anal. Calcd for $C_{22}H_{18}C_{l2}N_2O_3S$: C, 57.27; H, 3.93; N, 6.07. Found: C, 57.49; H, 3.65; N, 6.26.

7-Chloro-2-(4-methoxyphenyl)-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (3h)

Yellowish solid; yield: 383 mg (84%); mp 168–170 °C.

IR (KBr): 3338, 1703, 1602, 1326, 1158, 820 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 3.23 (dd, *J* = 12.5, 5.4 Hz, 1 H), 3.46 (dd, *J* = 12.5, 7.6 Hz, 1 H), 3.75 (s, 3 H), 4.50 (dd, *J* = 7.6, 5.4 Hz, 1 H), 5.36 (br s, 1 H, NH, exchanges with D_2O), 6.74 (d, *J* = 8.6 Hz, 1 H, H_{arom}), 7.31 (d, *J* = 8.3 Hz, 2 H, H_{arom}), 7.40 (dd, *J* = 8.6, 1.6 Hz, 1 H, H_{arom}), 7.68–7.70 (m, 2 H, H_{arom}), 7.72 (d, *J* = 8.3 Hz, 2 H, H_{arom}), 8.02–8.04 (m, 2 H, H_{arom}), 8.28 (d, *J* = 1.6 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.9, 47.5, 55.5, 62.0, 114.4, 115.1, 116.7, 123.1, 127.6, 128.1, 128.5, 129.2, 133.2, 135.9, 136.9, 141.5, 145.7, 158.9, 168.5.

MS (EI): *m/z* = 456 $[M]^+$.

Anal. Calcd for $C_{23}H_{21}ClN_2O_4S$: C, 60.46; H, 4.63; N, 6.13. Found: C, 60.16; H, 4.81; N, 6.48.

7-Chloro-2-(4-tolyl)-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (3i)

Yellowish solid; yield: 383 mg (87%); mp 159–161 °C.

IR (KBr): 3342, 1704, 1600, 1328, 1157, 834 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 2.36 (s, 3 H), 3.20 (dd, *J* = 12.2, 5.2 Hz, 1 H), 3.40 (dd, *J* = 12.2, 7.4 Hz, 1 H), 4.49 (dd, *J* = 7.4, 5.2 Hz, 1 H), 5.31 (br s, 1 H, NH, exchanges with D_2O), 6.72 (d, *J* = 8.4 Hz, 1 H, H_{arom}), 7.12–7.35 (m, 4 H, H_{arom}), 7.32 (d, *J* = 8.2 Hz, 2 H, H_{arom}), 7.38 (dd, *J* = 8.4, 1.5 Hz, 1 H, H_{arom}), 7.71 (d, *J* = 8.2 Hz, 2 H, H_{arom}), 8.23 (d, *J* = 1.5 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 24.8, 47.3, 62.6, 114.8, 116.2, 122.8, 127.0, 127.5, 128.8, 129.2, 129.5, 133.6, 136.3, 137.9, 140.4, 141.8, 145.6, 168.3.

MS (EI): *m/z* = 440 $[M]^+$.

Anal. Calcd for $C_{23}H_{21}ClN_2O_3S$: C, 62.65; H, 4.80; N, 6.35. Found: C, 62.75; H, 4.58; N, 6.65.

7-Chloro-2-methyl-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (3j)

Yellowish solid; yield: 277 mg (76%); mp 100–101 °C.

IR (KBr): 3335, 1702, 1605, 1320, 1159, 838 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 7.1 Hz, 3 H), 2.32 (s, 3 H), 3.08–3.36 (m, 1 H), 3.88 (dd, *J* = 12.4, 5.6 Hz, 1 H), 4.59 (dd, *J* = 12.4, 7.9 Hz, 1 H), 5.33 (br s, 1 H, NH, exchanges with D_2O), 6.74 (d, *J* = 8.6 Hz, 1 H, H_{arom}), 7.34 (d, *J* = 8.2 Hz, 2 H, H_{arom}), 7.40 (dd, *J* = 8.6, 1.6 Hz, 1 H, H_{arom}), 7.73 (d, *J* = 8.2 Hz, 2 H, H_{arom}), 8.22 (d, *J* = 1.6 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 24.7, 48.4, 51.8, 115.4, 116.9, 123.1, 127.6, 128.9, 129.3, 133.2, 136.3, 141.9, 145.8, 168.3.

MS (EI): *m/z* = 364 $[M]^+$.

Anal. Calcd for $C_{17}H_{17}ClN_2O_3S$: C, 55.96; H, 4.70; N, 7.68. Found: C, 55.71; H, 4.99; N, 7.81.

7-Methyl-2-phenyl-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (3k)

Yellowish solid; yield: 341 mg (84%); mp 171–172 °C.

IR (KBr): 3343, 1702, 1595, 1319, 1157, 805 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 2.32 (s, 3 H), 3.20 (dd, *J* = 12.1, 5.4 Hz, 1 H), 3.43 (dd, *J* = 12.1, 7.6 Hz, 1 H), 4.54 (dd, *J* = 7.6, 5.4 Hz, 1 H), 5.32 (br s, 1 H, NH, exchanges with D_2O), 6.75 (d, *J* = 8.5 Hz, 1 H, H_{arom}), 7.12–7.30 (m, 5 H, H_{arom}), 7.32 (d, *J* = 8.4 Hz, 2 H, H_{arom}), 7.35 (dd, *J* = 8.5, 1.6 Hz, 1 H, H_{arom}), 7.74 (d, *J* = 8.3 Hz, 2 H, H_{arom}), 8.24 (d, *J* = 1.6 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 24.7, 47.6, 62.3, 112.5, 115.2, 126.6, 126.9, 127.2, 127.5, 128.7, 128.9, 129.6, 133.2, 137.7, 141.7, 143.2, 144.2, 168.1.

MS (EI): *m/z* = 406 $[M]^+$.

Anal. Calcd for $C_{23}H_{22}N_2O_3S$: C, 67.96; H, 5.46; N, 6.89. Found: C, 67.64; H, 5.98; N, 6.63.

2-(4-Chlorophenyl)-7-methyl-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (3l)

Yellowish solid; yield: 387 mg (88%); mp 179–182 °C.

IR (KBr): 3345, 1700, 1600,1324, 1158, 824 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 2.34 (s, 3 H), 3.23 (dd, *J* = 12.1, 5.2 Hz, 1 H), 3.46 (dd, *J* = 12.1, 7.6 Hz, 1 H), 4.58

(dd, *J* = 7.6, 5.2 Hz, 1 H), 5.33 (br s, 1 H, NH, exchanges with D_2O), 6.78 (d, *J* = 8.3 Hz, 1 H, H_{arom}), 7.31 (d, *J* = 8.3 Hz, 2 H, H_{arom}), 7.38 (dd, *J* = 8.3, 1.7 Hz, 1 H, H_{arom}), 7.61–7.70 (m, 2 H, H_{arom}), 7.71 (d, *J* = 8.3 Hz, 2 H, H_{arom}), 8.09–8.16 (m, 2 H, H_{arom}), 8.26 (d, *J* = 1.5 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.7, 24.6, 47.8, 62.1, 113.1, 115.7, 126.6, 127.4, 128.3, 128.6, 128.9, 129.6, 132.7, 133.5, 137.2, 141.8, 142.1, 145.6, 168.3.

MS (EI): *m/z* = 440 $[M]^+$.

Anal. Calcd for $C_{23}H_{21}ClN_2O_3S$: C, 62.65; H, 4.80; N, 6.35. Found: C, 62.87; H, 4.92; N, 6.04.

2-(4-Methoxyphenyl)-7-methyl-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (3m)

Yellowish solid; yield: 379 mg (87%); mp 151–152 °C.

IR (KBr): 3342, 1705, 1598, 1326, 1159, 835 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 2.34 (s, 3 H), 3.22 (dd, *J* = 12.3, 5.1 Hz, 1 H), 3.44 (dd, *J* = 12.3, 7.3 Hz, 1 H), 3.73 (s, 3 H), 4.53 (dd, *J* = 7.3, 5.1 Hz, 1 H), 5.35 (br s, 1 H, NH, exchanges with D_2O), 6.74 (d, *J* = 8.5 Hz, 1 H, H_{arom}), 7.30 (d, *J* = 8.1 Hz, 2 H, H_{arom}), 7.38 (dd, *J* = 8.5, 1.6 Hz, 1 H, H_{arom}), 7.65–7.67 (m, 2 H, H_{arom}), 7.71 (d, *J* = 8.1 Hz, 2 H, H_{arom}), 8.00–8.03 (m, 2 H, H_{arom}), 8.25 (d, *J* = 1.4 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 24.7, 47.3, 55.3, 62.3, 113.2, 115.3, 115.6, 126.4, 127.3, 128.1, 128.9, 129.4, 132.8, 136.1, 137.2, 141.3, 144.8, 159.3, 168.4.

MS (EI): *m/z* = 436 $[M]^+$.

Anal. Calcd for $C_{24}H_{24}N_2O_4S$: C, 66.03; H, 5.54; N, 6.42. Found: C, 65.94; H, 5.37; N, 6.78.

7-Methyl-2-(4-tolyl)-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one(3n)

Yellowish solid; yield: 382 mg (91%); mp 145–146 °C.

IR (KBr): 3340, 1700, 1603, 1321, 1158, 810 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 2.37 (s, 3 H), 2.72 (s, 3 H), 3.18 (dd, *J* = 12.1, 5.4 Hz, 1 H), 3.39 (dd, *J* = 12.1, 7.3 Hz, 1 H), 4.45 (dd, *J* = 7.3, 5.4 Hz, 1 H), 5.27 (br s, 1 H, NH, exchanges with D_2O), 6.70 (d, *J* = 8.3 Hz, 1 H, H_{arom}), 7.10–7.32 (m, 4 H, H_{arom}), 7.30 (d, *J* = 8.1 Hz, 2 H, H_{arom}), 7.35 (dd, *J* = 8.3, 1.3 Hz, 1 H, H_{arom}), 7.70 (d, *J* = 8.1 Hz, 2 H, H_{arom}), 8.20 (d, *J* = 1.3 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4, 24.6, 24.8, 47.8, 62.6, 112.3, 115.6, 126.6, 126.9, 127.5, 128.5, 129.1, 129.3, 133.2, 136.5, 137.2, 140.8, 141.4, 144.9, 168.3.

MS (EI): *m/z* = 420 $[M]^+$.

Anal. Calcd for $C_{24}H_{24}N_2O_3S$: C, 68.55; H, 5.75; N, 6.66. Found: C, 68.28; H, 6.04; N, 6.53.

2,7-Dimethyl-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (3o)

Yellowish solid; yield: 268 mg (78%); mp 97–98 °C.

IR (KBr): 3339, 1703, 1604, 1322, 1159, 827 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 7.3 Hz, 3 H), 2.31 (s, 3 H), 2.36 (s, 3 H), 3.12–3.38 (m, 1 H), 3.89 (dd, *J* = 12.3, 5.4 Hz, 1 H), 4.61 (dd, *J* = 12.3, 8.0 Hz, 1 H), 5.35 (br s, 1 H, NH, exchanges with D_2O), 6.73 (d, *J* = 8.5 Hz, 1 H, H_{arom}), 7.32 (d, *J* = 8.1 Hz, 2 H, H_{arom}), 7.42 (dd, *J* = 8.5, 1.5 Hz, 1 H, H_{arom}), 7.70 (d, *J* = 8.1 Hz, 2 H, H_{arom}), 8.23 (d, *J* = 1.5 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 24.2, 24.8, 48.3, 52.0, 112.8, 115.5, 126.8, 127.2, 127.6, 129.3, 132.7, 136.3, 141.3, 145.3, 168.0.

MS (EI): *m/z* = 344 $[M]^+$.

Anal. Calcd for $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13. Found: C, 62.85; H, 5.67; N, 8.37.

2-(4-nitrophenyl)-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (3p)

Yellowish solid; yield: 372 mg (85%); mp 215–217 °C.

IR (KBr): 3329, 1703, 1600, 1324, 1159, 826 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 3.25 (dd, *J* = 12.1, 5.4 Hz, 1 H), 3.48 (dd, *J* = 12.1, 7.6 Hz, 1 H), 4.62 (dd, *J* = 7.6, 5.4 Hz, 1 H), 5.40 (br s, 1 H, NH, exchanges with D_2O), 6.34 (dd, *J* = 8.3, 1.0 Hz, 1 H, H_{arom}), 6.67 (m, 1 H, H_{arom}), 7.30 (d, *J* = 8.1 Hz, 2 H, H_{arom}), 7.34–7.38 (m, 1 H, H_{arom}), 7.66–7.68 (m, 2 H, H_{arom}), 7.72 (d, *J* = 8.2 Hz, 2 H, H_{arom}), 8.02 (dd, *J* = 8.2, 1.0 Hz, 1 H, H_{arom}), 8.15–8.19 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3, 48.1, 62.6, 112.8, 115.9, 118.0, 121.3, 127.8, 128.1, 128.9, 129.6, 133.5, 136.9, 141.4, 141.8, 146.9, 149.7, 168.7.

MS (EI): *m/z* = 437 $[M]^+$.

Anal. Calcd for $C_{22}H_{19}N_3O_5S$: C, 60.40; H, 4.38; N, 9.61. Found: C, 60.72; H, 4.11; N, 9.74.

2-Isopropyl-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (3q)

Yellowish solid; yield: 290 mg (81%); mp 65–66 °C.

IR (KBr): 3331, 1702, 1600, 1326, 1158, 833 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 6.7 Hz, 3 H), 1.25 (d, *J* = 6.5 Hz, 3 H), 1.34–1.43 (m, 1 H), 2.32 (s, 3 H), 2.94–3.30 (m, 1 H), 3.84 (dd, *J* = 12.1, 5.5 Hz, 1 H), 4.52 (dd, *J* = 12.1, 7.6 Hz, 1 H), 5.28 (br s, 1 H, NH, exchanges with D_2O), 6.30 (dd, *J* = 8.3, 0.9 Hz, 1 H, H_{arom}), 6.60 (m, 1 H, H_{arom}), 7.31 (d, *J* = 8.2 Hz, 2 H, H_{arom}), 7.35–7.37 (m, 1 H, H_{arom}), 7.70 (d, *J* = 8.2 Hz, 2 H, H_{arom}), 8.02 (dd, *J* = 8.3, 0.9 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.8, 19.6, 25.2, 31.6, 43.5, 61.9, 112.9, 115.9, 117.6, 127.2, 128.8, 129.6, 133.2, 136.9, 141.4, 147.9, 168.4.

MS (EI): *m/z* = 358 $[M]^+$.

Anal. Calcd for $C_{19}H_{22}N_2O_3S$: C, 63.66; H, 6.19; N, 7.82. Found: C, 63.89; H, 6.36; N, 7.50.

7-Nitro-2-phenyl-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (3r)

Yellowish solid; yield: 337 mg (77%); mp 224–226 °C.

IR (KBr): 3344, 1702, 1604, 1328, 1159, 845 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 3.28 (dd, *J* = 12.5, 5.6 Hz, 1 H), 3.49 (dd, *J* = 12.5, 7.6 Hz, 1 H), 4.61 (dd, *J* = 7.6, 5.6 Hz, 1 H), 5.39 (br s, 1 H, NH, exchanges with D_2O), 6.92 (d, *J* = 8.7 Hz, 1 H, H_{arom}), 7.19–7.34 (m, 5 H, H_{arom}), 7.36 (d, *J* = 8.4 Hz, 2 H, H_{arom}), 7.76 (d, *J* = 8.4 Hz, 2 H, H_{arom}), 8.13 (d, *J* = 1.9, 8.7 Hz, 1 H, H_{arom}), 8.53 (dd, *J* = 1.9 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8, 47.9, 62.7, 114.8, 117.1, 123.5, 125.9, 126.7, 127.4, 127.8, 128.8, 129.7, 137.3, 137.8, 141.9, 144.2, 153.8, 168.5.

MS (EI): *m/z* = 437 $[M]^+$.

Anal. Calcd for $C_{22}H_{19}N_3O_5S$: C, 60.40; H, 4.38; N, 9.61. Found: C, 60.28; H, 4.70; N, 9.79.

2-Methyl-7-nitro-4-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (3s)

Yellowish solid; yield: 270 mg (72%); mp 59–60 °C.

IR (KBr): 3338, 1701, 1602, 1325, 1158, 840 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 7.3 Hz, 3 H), 2.33 (s, 3 H), 3.10–3.39 (m, 1 H), 3.89 (dd, *J* = 12.5, 5.8 Hz, 1 H), 4.61 (dd, *J* = 12.5, 8.0 Hz, 1 H), 5.37 (br s, 1 H, NH, exchanges with D_2O), 6.87 (d, *J* = 8.7 Hz, 1 H, H_{arom}), 7.32 (d, *J* = 8.1 Hz, 2 H, H_{arom}), 7.72 (d, *J* = 8.2 Hz, 2 H, H_{arom}), 8.10 (dd, *J* = 8.7, 1.8 Hz, 1 H, H_{arom}), 8.56 (d, *J* = 1.8 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 24.9, 48.8, 52.9, 114.5, 116.5, 123.7, 125.5, 127.7, 129.5, 136.2, 137.4, 141.7, 153.5, 168.4.

MS (EI): *m/z* = 375 $[M]^+$.

Anal. Calcd for $C_{17}H_{17}N_3O_5S$: C, 54.39; H, 4.56; N, 11.19. Found: C, 54.16; H, 4.42; N, 11.47.

2-Phenyl-4-tosyl-1,2,3,4-Tetrahydro-2-phenyl-4-tosylbenzo[*e*][tetrahydro-5*H*-1,4]-benzodiazepin-5-one (3a): Solution-Phase Syntheses; General Procedure

A mixture of aziridine **1a** (1 mmol), anthranilic acid **2a** (1 mmol), and LiBr (10 mol%) in the selected solvent (1 mL) was stirred at r.t. for 13 h. When the reaction was complete [TLC, EtOAc–hexane (2:3)], H_2O (5 mL) was added and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography [silica gel, EtOAc–hexane (1:3)] to give an analytically pure product**.** After isolation of the product, the remaining aqueous layer containing LiBr was washed with Et_2O (2 × 5 mL) to remove any organic impurity and dried under reduced pressure to afford LiBr, which was reused in subsequent runs without further purification or any loss of efficiency.

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