Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 6895

A one-pot synthetic strategy for construction of the dibenzodiazepine skeleton *via* a transition metal-free process†

Shuai Fang,[a] Xiaoyi Niu,[a] Zeyuan Zhang,[a] Yan Sun,[a] Xiaomeng Si,[a] Cuicui Shan,[a] Lei Wei,[a] Aiqing Xu,[a] Lei Feng[a] and Chen Ma*[a,b]

Received 30th April 2014,
Accepted 13th July 2014

DOI: 10.1039/c4ob00871e

www.rsc.org/obc

A one-pot transition metal-free methodology for constructing pharmacologically active dibenzodiazepine derivatives was developed. Fluoro-, bromo- and nitro-substituted aryl aldehydes were applied to this reaction efficiently.

Introduction

In the past 50 years, dibenzodiazepines and their structural analogues have attracted significant attention because of their efficient pharmacological activity. Clozapine **1** has been a listed drug for treating schizophrenia since 1982.[1] Compounds **2** and **3** exhibited good affinity to the D_1-like subtype of dopamine receptors.[2,3] Compound **4** revealed a high RXR antagonistic activity and good pharmacokinetic properties (Fig. 1).[4] Other pharmacologically active dibenzodiazepine derivatives were also reported abundantly in previous literature.[5]

Since the first synthesis of dibenzodiazepine derivatives by Schmutz in 1964,[6] limited progress has been made. Traditional paths universally depended on lactam or amide intermediates,[7,8] and dibenzodiazepines and their structural analogues were obtained through multi-step or metal-catalysed reactions (Scheme 1). In recent years, a few novel methods have been established. Buchwald developed a skilful method that contained two steps of palladium-catalysed cross-coupling reaction and subsequent intramolecular condensation.[9] However, the reactant is difficult to prepare, and utilization of a metal catalyst and ligand is not economical. Yin and Liang also developed synthetic methods to obtain dibenzodiazepines, respectively.[10,11] Similarly, transition metal catalysts played key roles in their systems. Thus, it is necessary to provide a concise, general and efficient protocol for combining dibenzodiazepine derivatives.

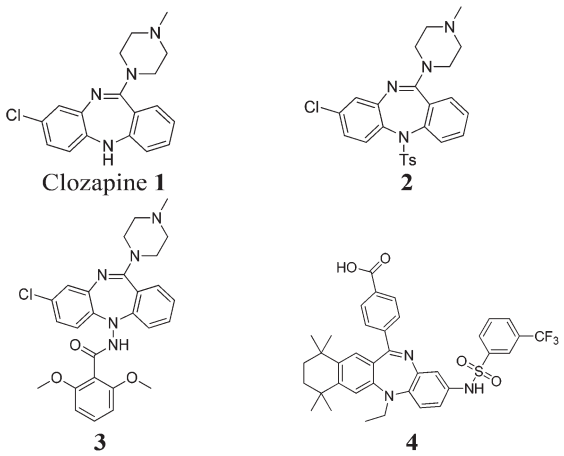
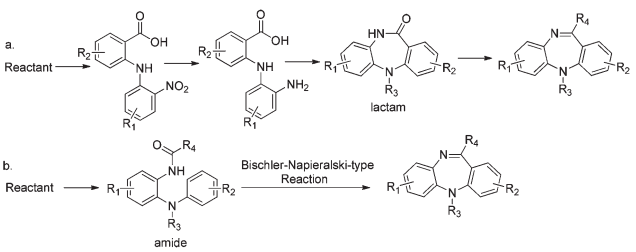


Fig. 1 Pharmacologically active dibenzodiazepine derivatives.



Scheme 1 Traditional methods for preparing dibenzodiazepine derivatives.

Herein, we report a one-pot, transition metal-free method to produce dibenzodiazepine derivatives. *N*-(2-Aminophenyl)-4-methylbenzenesulfonamide derivatives and 2-fluorobenzaldehyde derivatives acted as substrates.

[a]*Key Laboratory of Special Functional Aggregated Materials, Ministry of Education, School of Chemistry and Chemical Engineering, Shandong University, Jinan, 250100, P. R. China*

[b]*State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100050, P. R. China. E-mail: chenma@sdu.edu.cn*

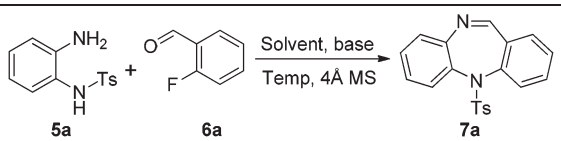
†Electronic supplementary information (ESI) available: The NMR spectra of all synthesized new compounds. See DOI: 10.1039/c4ob00871e

Results and discussion

N-(2-Aminophenyl)-4-methylbenzenesulfonamide **5a** was prepared according to literature procedures.[12] To optimize the reaction conditions, *N*-(2-aminophenyl)-4-methylbenzenesulfonamide **5a** and 2-fluorobenzaldehyde **6a** were used as model substrates (Table 1). The effect of bases was investigated, and Cs_2CO_3 showed the best efficiency in this reaction (entry 6). K_2CO_3 was equally efficient as Cs_2CO_3 (entry 5) but a stronger base like NaOH did not favor the reaction (entry 2). Higher yields were obtained with the increase of temperature (entries 4–6). The solvents were screened as well. NMP and DMSO generated moderate yields, but the reaction in toluene failed to form the product (entries 8–10). Molecular sieves 4 Å had a strong effect on the reactions (entries 6 and 7). Herein, entry 6 was the best condition.

With the optimized conditions in hand, the scope of the reaction was tested. Initially, the reaction of *N*-(2-aminophenyl)-4-methylbenzenesulfonamide **5a** and 2-fluorobenzaldehyde derivatives **6** was investigated (Table 2). A variety of electron deficient 2-halo- and 2-nitro-substituted aryl aldehydes were detected and discovered to work efficiently (Table 2, entries 1–3). To our delight, the coupling of 2-bromobenzaldehyde derivatives with **5a** took place in the absence of a transition metal (entries 2, 10).[13] Although the nitro group has rarely been utilized as a leaving group,[14] a moderate yield was obtained from the reaction of *N*-(2-aminophenyl)-4-methylbenzenesulfonamide **5a** and 2-nitrobenzaldehyde **6c** (entries 3, 11). All substrates worked well with moderate yields. Moreover, 2-fluorobenzaldehyde **6** with electron-withdrawing groups (entries 4–8, 12–15 and 18) generated better yields than those with electron-donating groups (entries 16, 19). Subsequently, the scope of *N*-(2-aminophenyl)-4-methylbenzenesulfonamide derivatives **5** was screened. *N*-(2-Amino-4,5-

Table 1 Optimization of reaction conditions[a]

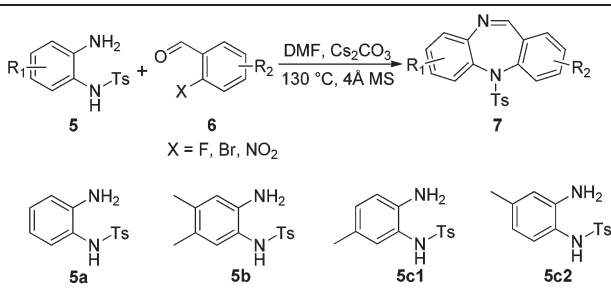


5a **6a** **7a**

Entry	Solvent	Base	*T*/°C	Time/h	Yield[b]/%
1	DMF	Cs_2CO_3	120	2	57
2	DMF	NaOH	120	2	41
3	DMF	K_2CO_3	120	2	55
4	DMF	Cs_2CO_3	130	2	64
5	DMF	K_2CO_3	130	3	70
6	**DMF**	Cs_2CO_3	**130**	**3**	**75**
7	DMF	Cs_2CO_3	130	3	63[c]
8	NMP	Cs_2CO_3	130	3	58
9	Toluene	K_2CO_3	Reflux	3	Trace
10	DMSO	Cs_2CO_3	130	3	65

[a] Reaction conditions: *N*-(2-aminophenyl)-4-methylbenzenesulfonamide **5a** (1.0 equiv.), 2-fluorobenzaldehyde **6a** (1.3 equiv.) and a base (3.0 equiv.), under a nitrogen atmosphere, 4 Å molecular sieves. [b] Isolated yields. [c] Reaction without 4 Å molecular sieves.

Table 2 The reaction of *N*-(2-aminophenyl)-4-methylbenzenesulfonamide derivatives **5** and 2-substituted aryl aldehydes **6**[a]



5 **6** **7**

X = F, Br, NO_2

5a **5b** **5c1** **5c2**

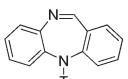
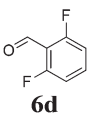
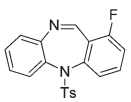
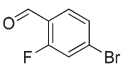
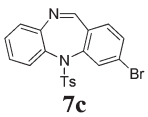
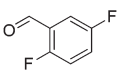
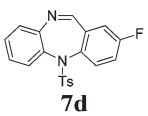
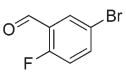
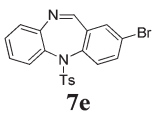
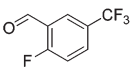
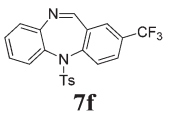
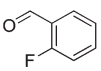
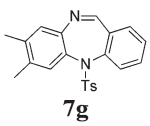
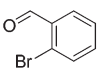
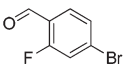
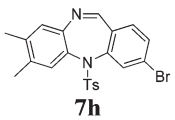
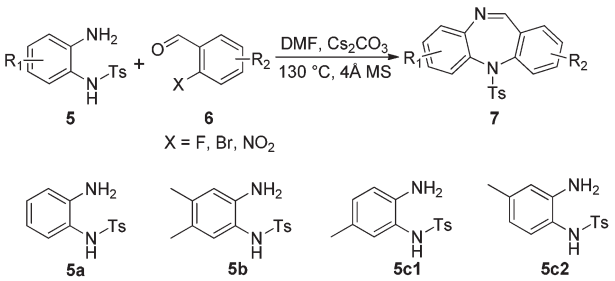
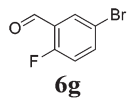
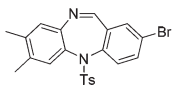
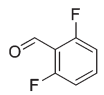
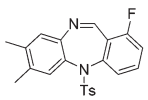
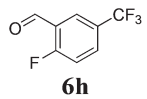
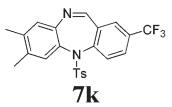
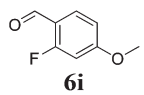
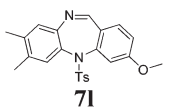
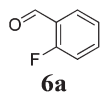
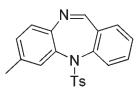
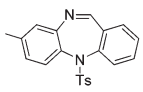
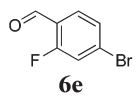
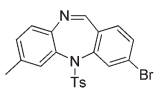
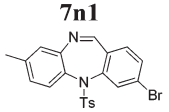
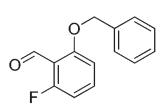
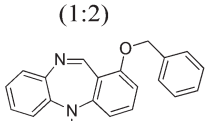
Entry	Substrate 5	Substrate 6	Product	Yield[b]/%
1	**5a**	 **6a**	 **7a**	75
2	**5a**	 **6b**	**7a**	54[c]
3	**5a**	 **6c**	**7a**	63
4	**5a**	 **6d**	 **7b**	74
5	**5a**	 **6e**	 **7c**	69
6	**5a**	 **6f**	 **7d**	72
7	**5a**	 **6g**	 **7e**	67
8	**5a**	 **6h**	 **7f**	81
9	**5b**	 **6a**	 **7g**	72
10	**5b**	 **6b**	**7g**	45[c]
11	**5b**	 **6c**	**7g**	69
12	**5b**	 **6e**	 **7h**	63

Table 2 *(Contd.)*



Entry	Substrate 5	Substrate 6	Product	Yield[b]/%
13	**5b**	 **6g**	 **7i**	69
14	**5b**	 **6d**	 **7j**	73
15	**5b**	 **6h**	 **7k**	78
16	**5b**	 **6i**	 **7l**	40
17	**5c1**, **5c2**	 **6a**	 **7m1**  **7m2** (1:2)	73[d]
18	**5c1**, **5c2**	 **6e**	 **7n1**  **7n2** (1:2)	67[d]
19	**5a**	 **6j**	 **7o**	35[e]

[a] Reaction conditions: **5** (1.0 equiv.), **6** (1.3 equiv.) and a base (3.0 equiv.), under a nitrogen atmosphere. [b] Isolated yields. [c] Reaction conditions: Cs_2CO_3, DMF, 145 °C, 4 Å molecular sieves, 3 h. [d] The ratios were obtained using NMR. [e] Reaction time: 4 h.

dimethylphenyl)-4-methylbenzenesulfonamide **5b** and *N*-(2-amino-5-methylphenyl)-4-methylbenzenesulfonamide **5c1** were also applicable to this reaction. The ratio of isomers **7m** and **7n** is in accordance with the ratio of reactants **5c1** and **5c2**.

Conclusions

We provide a one-pot synthetic strategy to construct dibenzodiazepine derivatives *via* a transition metal-free procedure. This tandem process could work well with a wide range of 2-fluoro-, 2-bromo- and 2-nitro-substituted aryl aldehydes. The application of this reaction system in pharmaceuticals and industry is in progress.

Experimental

General information

N-(2-Aminophenyl)-4-methylbenzenesulfonamide **5a**, *N*-(2-amino-4,5-dimethylphenyl)-4-methylbenzenesulfonamide **5b** and *N*-(2-amino-5-methylphenyl)-4-methylbenzenesulfonamide **5c1** were prepared according to literature procedures.[12] Other chemicals were commercially available and were used without further purification. All reactions were monitored by thin-layer chromatography (TLC). ^{1}H NMR spectra were recorded on a Bruker Avance 400 or 300 spectrometer at 400 or 300 MHz, using DMSO-d_6 as the solvent and tetramethylsilane (TMS) as the internal standard. ^{13}C NMR spectra were run on the same instrument at 100 or 75 MHz. Melting points were determined on an XD-4 digital micro melting point apparatus. HRMS spectra were determined on a Q-TOF6510 spectrograph (Agilent).

General experimental procedure for starting material 5a

1,2-Phenylenediamine (54 mmol) was dissolved in dry DCM, cooled to 0 °C and Et_3N (50 mmol) was added followed by *p*-toluenesulphonyl chloride (50 mmol). The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 3 h. The reaction was quenched by the addition of water, the organic matter was extracted with $CHCl_3$ (50 mL × 2), dried and concentrated to obtain the crude product, which was further purified by a short pad silica gel column chromatography to obtain *N*-tosylated *o*-phenylenediamine (ref. 12). A similar procedure was employed for *N*-(2-amino-4,5-dimethylphenyl)-4-methylbenzenesulfonamide **5b** and *N*-(2-amino-5-methylphenyl)-4-methylbenzenesulfonamide **5c2**.

General experimental procedure for 7a

A mixture of *N*-(2-aminophenyl)-4-methylbenzenesulfonamide **5a** (1.0 mmol), 2-fluorobenzaldehyde **6a** (1.3 mmol), Cs_2CO_3 (3 mmol) and 4 Å molecular sieves in DMF (6 mL) was stirred at 130 °C under a nitrogen atmosphere, and TLC monitored the end of the reaction. After the mixture was cooled, water was added. The solution was extracted with ethyl acetate (20 ml × 3). The combined organic phase was dried with

$MgSO_4$ and the solvent was removed *in vacuo* to obtain the residue. The residue was purified by column chromatography on silica gel to afford **7a**.

5-Tosyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine (7a). White solid (75%). Mp 155–157 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.03 (s, 1H), 7.75–7.70 (m, 1H), 7.61–7.53 (m, 3H), 7.50–7.41 (m, 3H), 7.32–7.26 (m, 3H), 7.18 (d, J = 9.0 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.94, 144.02, 143.97, 140.81, 136.06, 133.35, 132.99, 131.05, 131.00, 130.46, 130.08, 129.75, 129.41, 129.18, 128.50, 128.32, 127.09, 21.04; HRMS calcd for $C_{20}H_{16}N_2O_2S$ $(M + H)^+$ 349.0932; found: 349.0994.

1-Fluoro-5-tosyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine (7b). White solid (74%). Mp 160–162 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.14 (s, 1H), 7.78–7.73 (m, 1H), 7.48–7.38 (m, 5H), 7.34–7.25 (m, 5H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.64 (d, J = 252.0 Hz, 1C), 152.65 (d, J = 7.0 Hz, 1C), 144.79, 144.45, 143.58 (d, J = 4.0 Hz, 1C), 136.44, 135.03 (d, J = 10.0 Hz, 1C), 133.64, 131.49, 130.41, 130.19, 129.13, 128.81, 127.61, 126.68 (d, J = 3.0 Hz, 1C), 119.24 (d, J = 12.0 Hz, 1C), 116.83 (d, J = 21.0 Hz, 1C), 21.55; HRMS calcd for $C_{20}H_{15}FN_2O_2S$ $(M + H)^+$ 367.0838; found: 367.0895.

3-Bromo-5-tosyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine (7c). White solid (69%). Mp 166–167 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.99 (s, 1H), 7.84–7.81 (m, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.52–7.42 (m, 3H), 7.33–7.26 (m, 3H), 7.19 (d, J = 8.1 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.92, 144.22, 143.89, 141.63, 135.74, 132.89, 132.76, 132.34, 132.03, 131.27, 130.11, 129.86, 129.69, 128.58, 128.55, 127.13, 125.74, 21.05; HRMS calcd for $C_{20}H_{15}N_2O_3S$ $(M + H)^+$ 427.0038; found: 427.0066.

2-Fluoro-5-tosyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine (7d). White solid (72%). Mp 173–175 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (s, 1H), 7.58–7.56 (m, 2H), 7.50–7.42 (m, 4H), 7.32–7.26 (m, 3H), 7.19 (d, J = 8.3 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.08 (d, J = 273.0 Hz, 1C), 157.92, 144.60, 144.28, 137.64 (d, J = 3.0 Hz, 1C), 136.32, 133.76, 133.19 (d, J = 8.0 Hz, 1C), 133.10 (d, J = 9.0 Hz, 1C), 131.62, 130.34, 130.06, 129.12, 127.63, 120.56 (d, J = 23.0 Hz, 1C), 117.15(d, J = 24.0 Hz, 1C), 21.54; HRMS calcd for $C_{20}H_{15}FN_2O_2S$ $(M + H)^+$ 367.0838; found: 367.0848.

2-Bromo-5-tosyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine (7e). White solid (67%). Mp 195–197 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.97 (s, 1H), 7.93–7.87 (m, 2H), 7.50–7.43 (m, 4H), 7.33 (d, J = 8.1 Hz, 2H), 7.29–7.26 (m, 1H), 7.19 (d, J = 8.4 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.37, 144.17, 143.75, 140.05, 135.80, 135.73, 133.02, 132.62, 132.17, 131.09, 129.88, 129.62, 128.63, 127.12, 122.11, 21.06; HRMS calcd for $C_{20}H_{15}BrN_2O_2S$ $(M + H)^+$ 427.0038; found: 427.0027.

5-Tosyl-2-(trifluoromethyl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine (7f). White solid (81%). Mp 181–183 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15 (s, 1H), 8.08 (d, J = 5.9 Hz, 2H), 7.75 (d, J = 8.9 Hz, 1H), 7.50–7.45 (m, 3H), 7.34–7.28 (m, 3H), 7.22 (d, J = 8.3 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.20, 144.82, 144.67, 144.28, 136.32, 133.37, 131.99, 131.83, 131.57, 130.43, 130.28, 130.03 (q, J = 3.0, 33.0 Hz, 1C), 129.28, 129.16, 128.29 (d, J = 4.0 Hz, 1C), 127.61, 123.94 (d, J = 271.0 Hz, 1C), 21.54; HRMS calcd for $C_{21}H_{15}F_3N_2O_2S$ $(M + H)^+$ 417.0806; found: 417.0883.

7,8-Dimethyl-5-tosyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine (7g). Pale yellow solid (72%). Mp 164–167 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.09 (s, 1H), 7.70–7.67 (m, 1H), 7.54 (d, J = 4.2 Hz, 2H), 7.49 (d, J = 7.9 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.24 (s, 1H), 7.14 (d, J = 8.2 Hz, 2H), 7.03 (s, 1H), 2.38 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.52, 144.31, 142.18, 141.21, 138.37, 137.49, 136.63, 133.21, 131.86, 131.69, 131.20, 130.81, 130.55, 130.14, 129.57, 129.48, 127.62, 21.53, 19.31, 19.25; HRMS calcd for $C_{22}H_{20}N_2O_2S$ $(M + H)^+$ 377.1245; found: 377.1382.

3-Bromo-7,8-dimethyl-5-tosyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine (7h). Pale yellow solid (63%). Mp 164–167 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88 (s, 1H), 7.79–7.77 (m, 1H), 7.71 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.30–7.25 (t, 3H), 7.17 (d, J = 8.1 Hz, 2H), 7.04 (s, 1H), 2.38 (s, 3H), 2.24 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.46, 144.57, 142.03, 138.71, 137.79, 136.27, 133.20, 132.63, 132.41, 132.04, 130.78, 130.70, 130.26, 129.65, 127.65, 125.93, 21.54, 19.32, 19.28; HRMS calcd for $C_{22}H_{19}BrN_2O_2S$ $(M + H)^+$ 455.0423; found: 455.0487.

2-Bromo-7,8-dimethyl-5-tosyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine (7i). Pale yellow solid (69%). Mp 266–267 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88 (d, J = 2.3 Hz, 1H), 7.87 (s, 1H), 7.82 (d, J = 2.3 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 8.2 Hz, 1H), 7.24 (s, 1H), 7.18–7.16 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 8.1 Hz, 2H), 7.04 (s, 1H), 2.38 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.90, 144.51, 141.90, 140.42, 138.64, 137.90, 136.34, 135.95, 133.37, 133.32, 132.66, 131.89, 130.84, 130.27, 129.71, 127.64, 122.42, 21.54, 19.30, 19.28; HRMS calcd for $C_{22}H_{19}BrN_2O_2S$ $(M + H)^+$ 455.0423; found: 455.0486.

1-Fluoro-7,8-dimethyl-5-tosyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine (7j). Pale yellow solid (73%). Mp 179–181 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (s, 1H), 7.75–7.71 (m, 1H), 7.43 (t, J = 9.2 Hz, 1H), 7.36–7.31 (m, 3H), 7.22 (d, J = 7.8 Hz, 3H), 7.05 (s, 1H), 2.39 (s, 3H), 2.25 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.58 (d, J = 251.0 Hz, 1C), 151.63 (d, J = 8.0 Hz, 1C), 144.66, 143.49, 142.07, 138.79, 137.93, 136.49, 134.77 (d, J = 10.0 Hz, 1C), 131.77, 130.98, 130.33, 129.33, 127.63, 126.67 (d, J = 3.0 Hz, 1C), 119.38 (d, J = 12.0 Hz, 1C), 116.64 (d, J = 20.0 Hz, 1C), 21.55, 19.32, 19.27; HRMS calcd for $C_{22}H_{19}FN_2O_2S$ $(M + H)^+$ 395.1151; found: 395.1123.

7,8-Dimethyl-5-tosyl-2-(trifluoromethyl)-5*H*-dibenzo[*b*,*e*][1,4]-diazepine (7k). Pale yellow solid (78%). Mp 188–190 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07–8.03 (m, 3H), 7.71 (d, J = 8.2 Hz, 1H), 7.32–7.28 (m, 3H), 7.19 (d, J = 8.1 Hz, 2H), 7.07 (s, 1H), 2.39 (s, 3H), 2.26 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.24, 144.67, 144.52, 141.89, 138.88, 138.11, 136.30, 132.15, 131.89 (d, J = 3.0 Hz, 1C), 130.64, 130.37, 129.75 (q, 1C), 129.71, 128.25, 127.63, 124.00 (d, J = 269.0 Hz, 1C), 21.55, 19.32, 19.29; HRMS calcd for $C_{23}H_{19}F_3N_2O_2S$ $(M + H)^+$ 445.1119; found: 445.1202.

3-Methoxy-7,8-dimethyl-5-tosyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine (7l). Pale yellow solid (40%). Mp 137–138 °C. ^{1}H NMR

(400 MHz, DMSO-d_6): δ 7.80 (s, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.28 (d, J = 8.2 Hz, 2H), 7.22 (s, 1H), 7.14 (d, J = 8.9 Hz, 2H), 7.13–7.10 (m, 1H), 7.01 (s, 1H), 7.00 (s, 1H), 3.85 (s, 3H), 2.37 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.13, 157.91, 144.28, 142.54, 142.52, 138.34, 137.10, 136.49, 132.36, 132.01, 130.71, 130.08, 129.52, 127.69, 124.74, 115.45, 56.32, 21.54, 19.35, 19.27; HRMS calcd for $C_{23}H_{22}N_2O_3S$ $(M + H)^+$ 407.1424; found: 407.1484.

7-Methyl-5-tosyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine (7m1) and 8-methyl-5-tosyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine (7m2) (1 : 2). Pale yellow solid (73%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99, 7.95 (d, 1H), 7.70 (m, 1H), 7.56–7.50 (m, 3H), 7.34–7.28 (m, 3H), 7.22–7.16 (m, 3H), 7.06 (s, 1H), 2.37, 2.34 (d, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.63, 158.61, 144.42, 144.39, 144.18, 142.11, 141.37, 141.07, 139.64, 138.75, 136.61, 136.57, 133.49, 133.38, 133.32, 131.63, 131.58, 131.39, 131.19, 130.91, 130.85, 130.60, 130.50, 130.21, 129.61, 129.56, 129.52, 129.17, 128.81, 127.59, 21.53, 20.89, 20.76; HRMS calcd for $C_{21}H_{18}N_2O_2S$ $(M + H)^+$ 363.1162; found: 363.1192.

2-Bromo-7-methyl-5-tosyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine (7n1) and 2-bromo-8-methyl-5-tosyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine (7n2) (1 : 2). Pale yellow solid (67%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.96, 7.92 (d, 1H), 7.81–7.74 (m, 2H), 7.55–7.52 (m, 1H), 7.37–7.30 (m, 3H), 7.25–7.15 (m, 3H), 7.08 (s, 1H), 2.39, 2.36 (d, 3H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.78, 157.05, 144.15, 144.12, 143.55, 141.71, 141.49, 141.41, 139.46, 138.52, 135.79, 135.76, 132.76, 132.67, 132.52, 132.20, 131.99, 131.92, 131.34, 130.91, 130.89, 130.42, 130.36, 130.24, 130.19, 129.24, 128.77, 128.40, 127.14, 125.60, 125.54, 21.04, 20.40, 20.28; HRMS calcd for $C_{21}H_{17}BrN_2O_2S$ $(M + H)^+$ 441.0267; found: 441.0294.

1-(Benzyloxy)-5-tosyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine (7o). Pale yellow solid (35%). Mp 155–157 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.16 (s, 1H), 7.64 (t, J = 8.2 Hz, 1H), 7.44–7.10 (m, 14H), 7.09 (d, J = 8.0 Hz, 1H), 5.26–5.17 (m, J = 25.48, 12.0 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.08, 155.82, 145.08, 144.47, 143.89, 136.98, 136.69, 134.34, 134.11, 131.14, 130.21, 129.87, 129.01, 128.57, 127.37, 128.19, 128.07, 127.61, 122.16, 119.85, 113.78, 70.78, 21.53; HRMS calcd for $C_{27}H_{22}N_2O_3S$ $(M + H)^+$ 455.1424; found: 455.1474.

Acknowledgements

We are grateful to the National Science Foundation of China (no. 21172131) and State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College (no. GTZK201405) for financial support of this research.

Notes and references

1 M. Rowley, L. J. Bristow and P. H. Hutson, *J. Med. Chem.*, 2001, **44**, 477–501.
2 J. Su, H. Tang, B. A. McKittrick, D. A. Burnett, H. Zhang, A. Smith-Torhan, A. Fawzi and J. Lachowicz, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4548–4553.
3 T. K. Sasikumar, D. A. Burnett, H. Zhang, A. Smith-Torhan, A. Fawzi and J. E. Lachowicz, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4543–4547.
4 J. Sakaki, K. Konishi, M. Kishida, H. Gunji, T. Kanazawa, H. Uchiyama, H. Fukaya, H. Mitani and M. Kimura, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4808–4811.
5 For recent reviews of the pharmacological activity of dibenzodiazepines, see: (*a*) A. V. Joshua, S. K. Sharma, A. Strelkov, J. R. Scott, M. T. Martin-Iverson, D. N. Abrams, P. H. Silverstone and A. J. McEwan, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4066–4069; (*b*) M. Ebisawa, H. Umemiya, K. Ohta, H. Fukasawa, E. Kawachi, G. Christoffel, H. Gronemeyer, M. Tsuji, Y. Hashimoto, K. Shudo and H. Kagechika, *Chem. Pharm. Bull.*, 1999, **47**, 1778–1786; (*c*) F. M. McRobb, I. T. Crosby, E. Yuriev, J. R. Lane and B. Capuano, *J. Med. Chem.*, 2012, **55**, 1622–1634; (*d*) H. Umemiya, H. Fukasawa, M. Ebisawa, L. Eyrolles, E. Kawachi, G. Eisenmann, H. Gronemeyer, Y. Hashimoto, K. Shudo and H. Kagechika, *J. Med. Chem.*, 1997, **40**, 4222–4234.
6 (*a*) F. Hunziker, F. Künzle, O. Schindler and J. Schmutz, *Helv. Chim. Acta*, 1964, **47**, 1163–1172; (*b*) F. Hunziker, F. Künzle and J. Schmutz, *Helv. Chim. Acta*, 1966, **49**, 244–249; (*c*) F. Hunziker, E. Fischer and J. Schmutz, *Helv. Chim. Acta*, 1967, **50**, 1588–1599.
7 For reviews of the synthesis of dibenzodiazepines (and their derivatives) *via* lactam intermediates, see: (*a*) R. A. Smits, H. D. Lim, B. Stegink, R. A. Bakker, I. J. P. de Esch and R. Leurs, *J. Med. Chem.*, 2006, **49**, 4512–4516; (*b*) L. Wang, G. M. Sullivan, L. A. Hexamer, L. A. Hasvold, R. Thalji, M. Przytulinska, Z.-F. Tao, G. Li, Z. Chen, Z. Xiao, W.-Z. Gu, J. Xue, M.-H. Bui, P. Merta, P. Kovar, J. J. Bouska, H. Zhang, C. Park, K. D. Stewart, H. L. Sham, T. J. Sowin, S. H. Rosenberg and N.-H. Lin, *J. Med. Chem.*, 2007, **50**, 4162–4176; (*c*) Y. Liao, B. J. Venhuis, N. Rodenhuis, W. Timmerman, H. Wikström, E. Meier, G. D. Bartoszyk, H. Böttcher, C. A. Seyfried and S. Sundell, *J. Med. Chem.*, 1999, **42**, 2235–2244; (*d*) R. S. Kalhapure, B. P. Patil, M. N. Jadhav, L. A. Kawle and S. B. Wagh, *Eur. J. Chem.*, 2011, **8**, 1747–1749.
8 For reviews of the synthesis of dibenzodiazepines (and their derivatives) *via* amide intermediates, see: (*a*) J. Cairns, T. R. Clarkson, J. A. M. Hamersma and D. R. Rae, *Tetrahedron Lett.*, 2002, **43**, 1583–1585; (*b*) X. Xu, S. Guo, Q. Dang, J. Chen and X. Bai, *J. Comb. Chem.*, 2007, **9**, 773–782; (*c*) F. Shi, X. Xu, L. Zheng, Q. Dang and X. Bai, *J. Comb. Chem.*, 2008, **10**, 158–161; (*d*) H. Umemiya, H. Fukasawa, M. Ebisawa, L. Eyrolles, E. Kawachi, G. Eisenmann, H. Gronemeyer, Y. Hashimoto, K. Shudo and H. Kagechika, *J. Med. Chem.*, 1997, **40**, 4222–4234; (*e*) J. Yang, X. Che, Q. Dang, Z. Wei, S. Gao and X. Bai, *Org. Lett.*, 2005, **7**, 1541–1543; (*f*) X. Jiang, G. T. Lee, K. Prasad and O. Repič, *Org. Process Res. Dev.*, 2008, **12**, 1137–1141.

9 D. Tsvelikhovsky and S. L. Buchwald, *J. Am. Chem. Soc.*, 2011, **133**, 14228–14231.
10 X.-J. Wang, Y.-L. Tian, Q.-Y. Zhang, J.-G. Qi and D.-L. Yin, *Chin. Chem. Lett.*, 2013, **24**, 743–746.
11 G. Huang, M. Yang, L. Wu, D. She, H. Hui, Q. Zhao, M. Chen and Y. Liang, *Synlett*, 2008, **3**, 448–452.
12 S. Saha and J. N. Moorthy, *Tetrahedron Lett.*, 2010, **51**, 912–916.
13 (*a*) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6954–6971; (*b*) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359–1470.
14 (*a*) Y. Li, C. Zhan, B. Yang, X. Cao and C. Ma, *Synthesis*, 2013, 111–117; (*b*) X. Zhang, J. Jia and C. Ma, *Org. Biomol. Chem.*, 2012, **10**, 7944–7948.