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PAPER

One pot synthesis of *cis*-bispyrimidodiazepinone derivatives *via* low-valent titanium reagent ($TiCl_4$/Sm)†

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An efficient and convenient method for the preparation of *cis*-bispyrimidodiazepinone derivatives has been described. A variety of substrates can participate in the process with good yields, making this methodology suitable for library synthesis in drug discovery efforts. The mechanistic course of the reaction suggests the involvement of reduction, coupling which determine the products' configuration and cyclization by one-pot.

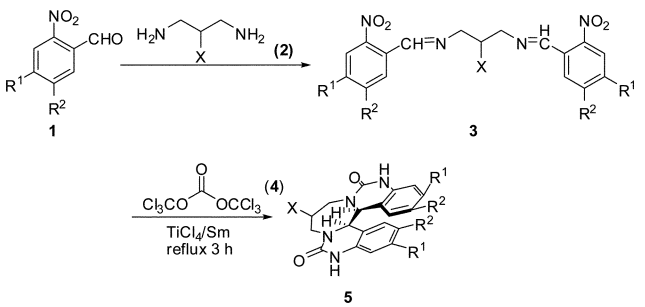
Introduction

Seven-membered rings such as the diazepines and tropolones are uncommon natural products. The 1,4-diazepine system is considered today a relevant pharmacophore in a wide range of biological activitivies.[1,2] Recently, analogues possessing pyrimidine ring attracted attention since they showed to be promising pharmacophores, and some of them found to be specially active against different cancer types.[3–6]

Israel *et al.*[7] and Senda *et al.*[8] reported the synthesis of some pyrimido[4,5-*b*][1,4]diazepines, and a few reported syntheses of pyrimido[4,5-*e*][1,4]diazepines.[9] Recently, some efforts have been directed toward preparation of pyrimidodiazepinones. Ohmoto reported the synthesis of pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-one derivatives which were prepared by condensation of 2-cyano-5-((4-methoxyphenylamino)methyl)-4-(neopentylamino)pyrimidine with chloroacetyl chloride.[10] Novel racemic indeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-diones were synthesized from the reaction of 5,6-diamino-3,4-dihydropyrimidin-4-ones and 2-aryldeneindandione in absolute ethanol and acetic acid for 6-8 h.[11] Bai developed a practical and efficient method for the synthesis of 4,6,8,9-tetrasubstituted 8.9-dihydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-7(6*H*)-ones from 4,6-dicholorpyrimidine aldehyde, N-substituted amino acid esters, and amines in five steps.[12] Despite pyrimidodiazepinones have been attracted more attentions, bispyrimidodiazepinones have not been synthesized now.

On the other hand, low-valent titanium reagent has attracted substantial attention in recent years.[13–15] The application of low-valent titanium reagent in organic synthesis provides some chemical processes with attributes such as enhanced reaction rates, higher yields of products and easier workup.

As part of our ongoing efforts to prepare libraries of novel heterocycles,[16–21] we envisioned that bispyrimidodiazepinone derivatives could be readily prepared by the reaction of bis(2-nitrobenzylidene)propane-1,3-diamines **3** which can be obtained from the reaction of 2-nitrobenzaldehydes **1** and 1,3-diamines **2** easily and triphosgene **4** *via* low-valent titanium reagent (Scheme 1). Herein, the details of these studies are presented.



Scheme 1

Results and discussion

We performed the reaction of a variety of bis(2-nitrobenzylidene)propane-1,3-diamines **3** and triphosgene **4** *via* low-valent titanium reagent ($TiCl_4$/Sm). Since nitro group needs to be reduced in this reaction, so the quantity of low-valent titanium reagent is 4 equivalents, and the reaction time must be about 3 h. Table 1 summarizes our results on the cyclization of **3** and **4**.

As shown in Table 1, we found that this reaction can be performed on a multigram scale under the simple conditions described above. And we also pleased to find that 2-nitrobiimines which contain hydroxyl can reacted with triphosgene well and the corresponding products were also obtained in good yields (**5e** and **5f**, Table 1).

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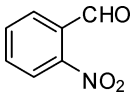
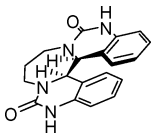
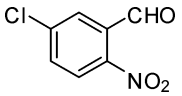
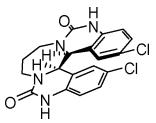
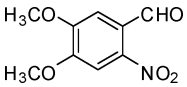
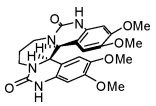
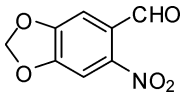
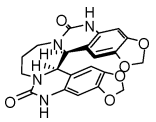
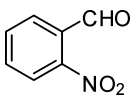
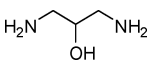
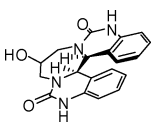
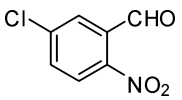
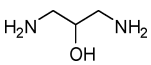
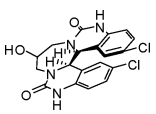
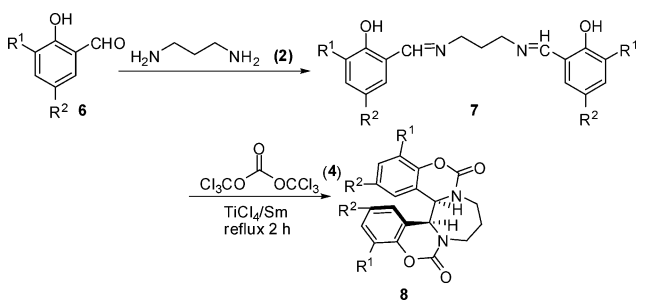
† Electronic supplementary information (ESI) available. CCDC reference number 826748. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05791j

Table 1 Preparation of products **5**

Entry	Aldehyde	1,3-Diamine	Product	**5**	Yield/%
1				**5a**	72
2				**5b**	68
3				**5c**	75
4				**5d**	74
5				**5e**	65
6				**5f**	63

Encouraged by these results, we next focused our attention on the synthesis of oxazinodiazepinones.

In order to demonstrate the efficiency and the applicability of the present method, we performed the reaction of triphosgene **4** and bis(2-hydroxybenzylidene)propane-1,3-diamines **7** which is synthesized from 2-hydroxybenzaldehyde **6** and propane-1,3-diamine **2** (Scheme 2).

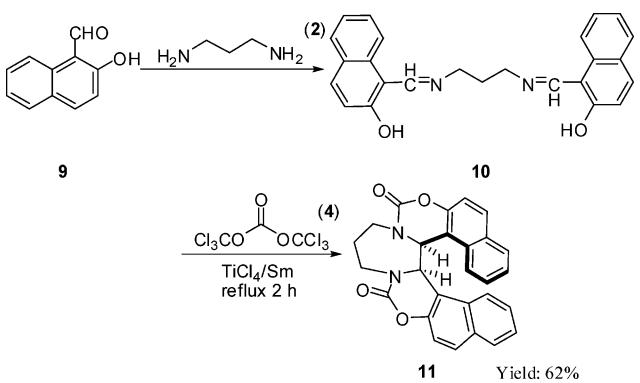


Scheme 2

When triphosgene **4** and bis(2-hydroxybenzylidene)propane-1,3-diamines **7** which is synthesized from 2-hydroxybenzaldehyde **6** and propane-1,3-diamine **2** were treated with the low-valent titanium reagent prepared from titanium(IV) chloride and samarium powder in anhydrous tetrahydrofuran at room temperature under a nitrogen atmosphere, the coupling cyclization products **8** were obtained and purified by recrystallization from DMF. Table 2 summarizes our results on the synthesis of oxazinodiazepinones.

From Table 2, it can be seen that this protocol can be applied not only to the aromatic aldehydes with electron-withdrawing groups (such as halide groups) but also to aromatic aldehydes with electron-donating groups (such as alkyl and alkoxyl groups).

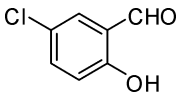
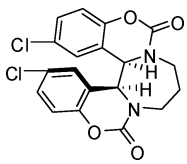
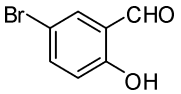
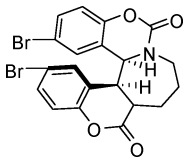
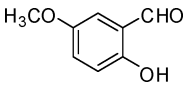
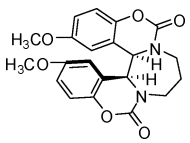
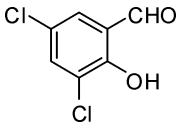
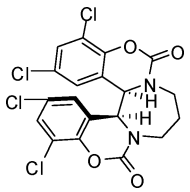
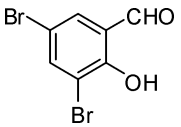
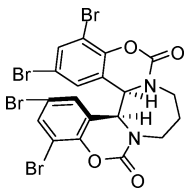
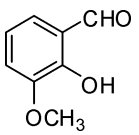
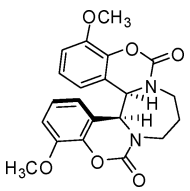
The method was next extended to conjoin 1,1′-((1*E*, 1′*E*)-(ethane-1,2-diylbis(azanylylidene))bis(methanylylidene))bis-(naphthalene-2-ol) **10** with triphosgene **4** (Scheme 3).



Scheme 3

All the products were characterized by NMR, IR and HRMS spectra. Furthermore, the structure of product **8c** has been

Table 2 Preparation of products **8**

Entry	Aldehyde	Product	8	Yield/%
1			**8a**	67
2			**8b**	73
3			**8c**	68
4			**8d**	74
5			**8e**	53
6			**8f**	67

confirmed by X-ray analysis. The molecular structure of the product **8c** is shown in Fig. 1.

From Fig. 1, we found that the H of C13 and C14 was *cis*. The conformation of diazepine ring is chairconformation. With the use of Discrete Fourier Transformation (DFT) and computer programme, B3LYP/6-31G,[22] a geometrical optimization of product **5c** was obtained. The optimized geometry of **5c** was shown in Fig. 2. From Fig. 2, we found the H of C13 and C14 was also *cis* and the diazepine ring was also chair conformation.

Although the mechanism of the reaction is presently unclear, a few possible sequences of events are outlined in Scheme 4. First of all, $TiCl_4$ is reduced by Sm dust to give low-valent titanium species. The diimines were first reduced to radical anions, which then coupled to form C–C. The configuration of the products can be determined by this step. The transition states of this synthetic method are seven member rings which are chairconformation (see

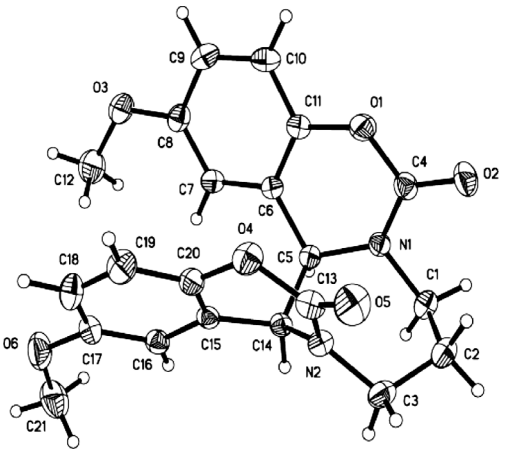


Fig. 1 Molecular structure of product **5c**.

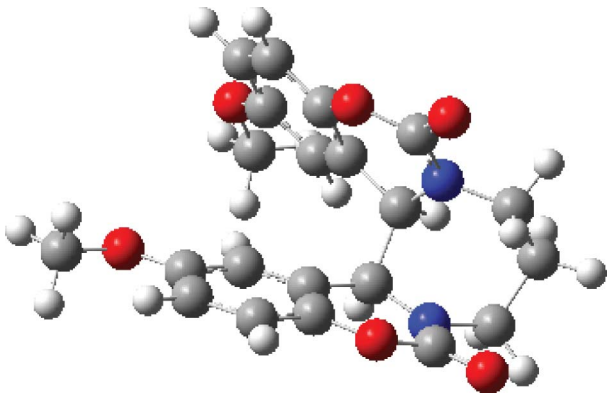


Fig. 2 Optimized geometry of **5c**.

C in Scheme 4), so the two hydrogen atoms of the new formed CH–CH are *cis* which determine the products' configurations.

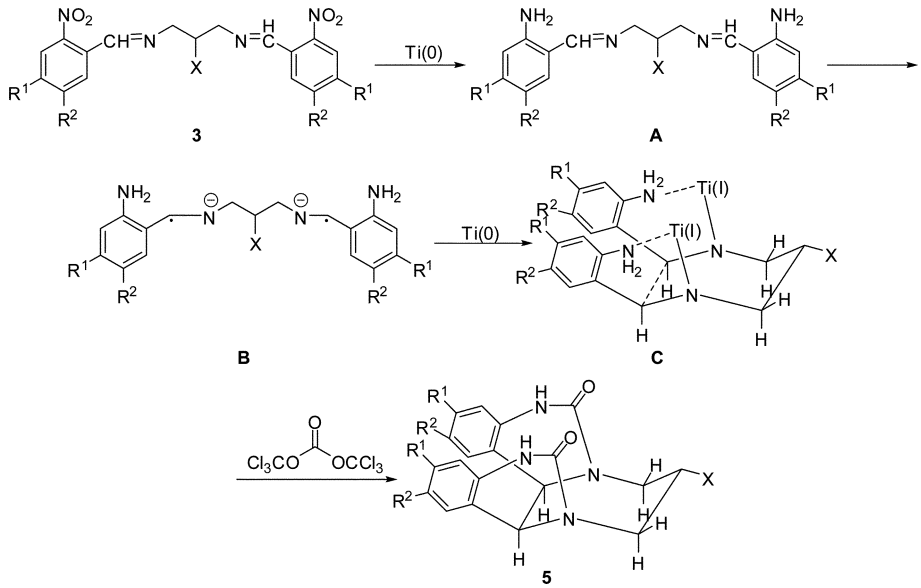
Conclusion

In conclusion, we have developed an efficient and convenient method for the preparation of *cis*-bispyrimidodiazepinone derivatives. The process was carried out in THF *via* $TiCl_4$/Sm. A variety of substrates can participate in the process with good yields. The procedure used commmericially available *o*-nitrobenzaldehydes or *o*-hydroxylbenzaldehydes, propane-1,3-diamines and triphosgene. In particular, the product could easily be collected by recrystallization. The short reaction times and easily-available materials render this method particularly attractive for the efficient preparation of biologically and medicinally interesting molecules. Importantly, all the compounds synthesized in this paper are first reported.

Experimental

General

THF was distilled from sodium-benzophenone immediately prior to use. All reactions were conducted under N_2 atmosphere. Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm^{-1}. ^1H NMR was determined on NMRststem-300 MHz spectrometer in DMSO-d_6 solution. *J* values are in Hz. Chemical shifts are expressed in ppm



Scheme 4

downfield from internal standard TMS. X-Ray diffractions were recorded on a Siemens P4 diffractometer.

Preparation of compounds 5

$TiCl_4$ (0.9 mL, 8 mmol) was added dropwise using a syringe to a stirred suspension of samarium powder (1.2 g, 8 mmol) in freshly distilled anhydrous THF (5 mL) at r.t. under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to r.t. and a solution of 2-hydroxyldiimines (1 mmol) and triphosgene (2 mmol) in THF (5 mL) was added dropwise. The reaction mixture was then refluxed for 2 h under N_2 atmosphere. After this period, the TLC analysis of the mixture showed the completion of this reaction. The mixture was then quenched with 5% HCl (30 mL) and extracted with $ClCH_2CH_2Cl$ (3 × 50 mL). The extracts were washed with water (3 × 50 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude products were purified by recrystallization from 95% ethanol and DMF.

5a: White solid, mp: >300 °C; IR (KBr): ν 3202, 3129, 3059, 2905, 2757, 2698, 1672, 1603, 1468, 1420, 1374, 1336, 1321, 1295, 1265, 1221, 1157, 1109, 1049, 936, 864, 754, 701 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.48 (s, 1H, NH), 8.94 (s, 1H, NH), 7.15 (t, J = 5.7 Hz, 1H, ArH), 6.89–6.84 (m, 2H, ArH), 6.71–6.69 (m, 1H, ArH), 6.58–6.49 (m, 2H, ArH), 6.46–6.43 (m, 1H, ArH), 5.84 (d, J = 5.7 Hz, 1H, ArH), 5.12 (s, 1H, CH), 4.36 (s, 1H, CH), 4.16–4.00 (m, 2H, CH_2), 2.99–2.86 (m, 2H, CH_2), 2.28–2.27 (m, 1H, CH), 1.63–1.57 (m, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.32, 152.36, 137.83, 137.44, 128.58, 128.51, 127.68, 127.43, 119.69, 119.45, 117.50, 117.29, 113.08, 112.66, 65.78, 64.48, 46.77, 45.59, 23.82; HRMS [Found: m/z 334.1432 (M^+), calcd for $C_{19}H_{18}N_4O_2$: M, 334.1430]

5b: White solid, mp: >300 °C; IR (KBr): ν 3185, 3083, 3037, 2918, 2749, 1672, 1601, 1499, 1464, 1424, 1398, 1291, 1262, 1156, 1090, 1017, 822, 757 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.67 (s, 2H, 2 × NH), 7.24–7.27 (m, 2H, ArH), 6.91–6.88 (m, 2H, ArH), 5.89 (s, 2H, ArH), 4.44 (s, 2H, 2 × CH), 4.04–3.99 (m, 2H, CH_2), 2.89–2.84 (m, 2H, CH_2), 2.26–2.24 (m, 2H, CH_2); HRMS [Found: m/z 402.0652 (M^+), calcd for $C_{19}H_{16}N_4O_2{}^{35}Cl_2$: M, 402.0650]

5c: White solid, mp: >300 °C; IR (KBr): ν 3196, 3083, 2937, 2886, 1670, 1624, 1526, 1464, 1389, 1292, 1257, 1240, 1209, 1140, 1097, 1010, 969, 853, 774 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.14 (s, 2H, 2 × NH), 6.48 (s, 2H, ArH), 5.44 (s, 2H, ArH), 4.13 (s, 2H, 2 × CH), 3.77–3.73 (m, 4H, 2 × CH_2), 3.65 (s, 6H, 2 × CH_3O), 3.22 (s, 6H, 2 × CH_3O), 2.19–2.16 (m, 2H, CH_2); HRMS [Found: m/z 454.1855 (M^+), calcd for $C_{23}H_{26}N_4O_6$: M, 454.1852]

5d: White solid, mp: >300 °C; IR (KBr): ν 3210, 3123, 2905, 1718, 1661, 1502, 1462, 1340, 1264, 1229, 1039, 935, 846, 776, 758 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.20 (s, 1H, NH), 8.05 (s, 1H, NH), 7.18–7.17 (m, 1H, ArH), 6.91–6.83 (m, 1H, ArH), 6.59–6.56 (m, 1H, ArH), 6.44 (s, 1H, ArH), 6.07 (s, 2H, CH_2), 5.91 (s, 1H, CH), 5.87 (s, 1H, CH), 5.77 (s, 1H, CH), 5.51 (s, 1H, CH), 4.29–4.26 (m, 1H, CH), 4.17 (s, 1H, CH), 3.86–3.84 (m, 1H, CH), 2.78–2.74 (m, 1H, CH), 2.18–2.12 (m, 2H, CH_2); HRMS [Found: m/z 422.1226 (M^+), calcd for $C_{21}H_{18}N_4O_6$: M, 422.1226]

5e: White solid, mp: >300 °C; IR (KBr): ν 3197, 3124, 3053, 2913, 1674, 1602, 1465, 1260, 1110, 1051, 814, 751 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.98 (s, 1H, NH), 9.56 (s, 1H, NH), 7.21–7.13 (m, 2H, ArH), 6.94–6.86 (m, 2H, ArH), 6.65–6.54 (m, 21H, ArH), 5.89–5.84 (m, 2H, ArH), 5.38–5.35 (m, 1H, OH), 4.57–4.37 (m, 4H, 2 × CH_2), 4.13–4.03 (m, 3H, 3 × CH); HRMS [Found: m/z 350.1380 (M^+), calcd for $C_{19}H_{18}N_4O_3$: M, 350.1379]

5f: White solid, mp: >300 °C; IR (KBr): ν 3185, 3083, 3037, 2918, 2749, 1672, 1601, 1499, 1464, 1398, 1336, 1291, 1262, 1156, 1090, 1017, 822, 757 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.08 (s, 1H, NH), 9.69 (s, 1H, NH), 7.31–7.24 (m, 3H, ArH), 6.96–6.88 (m, 3H, ArH), 5.93–5.89 (m, 2H, CH_2), 4.64–4.61 (m, 1H, OH), 4.53–4.45 (m, 2H, 2 × CH), 4.17–4.13 (m, 3H, CH_2 + CH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.46, 152.59, 136.67, 136.04, 128.62, 128.52, 128.25, 124.20, 123.52, 118.86, 118.17, 115.20,

114.83, 109.37, 69.53, 65.21, 65.12, 54.66, 52.90; HRMS [Found: *m/z* 418.0595 (M^+), calcd for $C_{19}H_{16}N_4O_3{}^{35}Cl_2$: M, 418.0599]

Preparation of compounds 8 and 11

$TiCl_4$ (0.66 mL, 6 mmol) was added dropwise using a syringe to a stirred suspension of samarium powder (0.9 g, 6 mmol) in freshly distilled anhydrous THF (5 mL) at r.t. under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to r.t. and a solution of 2-hydroxyldiimines (1 mmol) and triphosgene (2 mmol) in THF (5 mL) was added dropwise. The reaction mixture was then refluxed for 2 h under N_2 atmosphere. After this period, the TLC analysis of the mixture showed the completion of this reaction. The mixture was then quenched with 5% HCl (30 mL) and extracted with $ClCH_2CH_2Cl$ (3 × 50 mL). The extracts were washed with water (3 × 50 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude products were purified by recrystallization from 95% ethanol and DMF.

8a: White solid, mp: >300 °C; IR (KBr): *ν* 2926, 2834, 1736, 1492, 1458, 1430, 1412, 1373, 1274, 1212, 1102, 1044, 1082, 882, 829, 754 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *δ* 7.20–7.15 (m, 4H, ArH), 6.82 (d, *J* = 8.4 Hz, 2H, ArH), 5.35 (s, 2H, 2 × CH), 4.11–4.09 (m, 2H, CH_2), 3.29–3.17 (m, 4H, 2 × CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 148.67, 148.14, 129.04, 127.89, 127.42, 120.57, 117.07, 62.27, 49.67, 21.89; HRMS [Found: *m/z* 471.9554 (M^+), calcd for $C_{22}H_{18}N_2O_4{}^{35}Cl_2$: M, 471.9551]

8b: White solid, mp: >300 °C; IR (KBr): *ν* 2947, 1730, 1485, 1428, 1407, 1273, 1233, 1209, 1129, 945, 884 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *δ* 7.63–7.59 (m, 1H, ArH), 7.34–7.29 (m, 2H, ArH), 7.20–7.17 (m, 1H, ArH), 6.79–6.76 (m, 1H, ArH), 6.32–6.31 (m, 1H, ArH), 5.36 (s, 1H, CH), 4.81 (s, 1H, CH), 4.12–4.01 (m, 2H, CH_2), 3.26–3.09 (m, 4H, 2 × CH_2); HRMS [Found: *m/z* 491.9317 (M^+), calcd for $C_{22}H_{18}N_2O_4{}^{35}Cl_2$: M, 491.9320]

8c: White solid, mp: >300 °C; IR (KBr): *ν* 2936, 2836, 1719, 1613, 1504, 1459, 1431, 1376, 1321, 1287, 1219, 1162, 1127, 1033, 951, 897, 833, 817, 779, 747, 681 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *δ* 7.13–7.11 (m, 1H, ArH), 6.96–6.94 (m, 1H, ArH), 6.72–6.66 (m, 4H, ArH), 5.69 (s, 1H, CH), 5.29 (s, 1H, CH), 4.67 (s, 1H, CH), 4.11–3.99(m, 2H, CH_2), 3.59 (s, 3H, CH_3O), 3.47 (s, 3H, CH_3O), 3.25–3.15 (m, 2H, CH_2), 1.72–1.69 (m, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 154.78, 154.38, 150.11, 149.56, 144.00, 143.39, 119.38, 118.91, 116.76, 116.13, 115.98, 115.38, 113.17, 112.27, 65.67, 62.64, 55.47, 55.24, 49.05, 46.89, 22.12; HRMS [Found: *m/z* 396.1322 (M^+), calcd for $C_{21}H_{20}N_2O_6$: M, 396.1321]

8d: White solid, mp: >300 °C; IR (KBr): *ν* 3079, 2974, 1730, 1602, 1471, 1429, 1405, 1372, 1314, 1264, 1251, 1206, 1185, 1109, 1039, 977, 940, 895, 863, 846, 810, 753, 695 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *δ* 7.53–7.52 (m, 2H, ArH), 7.23–7.22 (m, 2H, ArH), 5.42 (s, 2H, 2 × CH), 4.13–4.09 (m, 2H, CH_2), 3.25–3.21 (m, 4H, 2 × CH_2); HRMS [Found: *m/z* 471.9554 (M^+), calcd for $C_{19}H_{12}N_2O_4{}^{35}Cl_4$: M, 471.9551]

8e: White solid, mp: >300 °C; IR (KBr): *ν* 3072, 2946, 1734, 1461, 1427, 1399, 1371, 1248, 1207, 1175, 1104, 1038, 962, 865, 831, 776 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *δ* 7.73 (d, *J* = 2.0 Hz, 2H, ArH), 7.38 (d, *J* = 2.0 Hz, 2H, ArH), 5.39 (s, 2H, 2 × CH), 4.13–4.09 (m, 2H, CH_2), 3.28–3.22 (m, 3H, CH_2 + CH), 1.73–1.69 (m, 1H, CH); HRMS [Found: *m/z* 647.7533 (M^+), calcd for $C_{19}H_{12}N_2O_4{}^{79}Br_4$: M, 647.7531]

8f: White solid, mp: >300 °C; IR (KBr): *ν* 2979, 2944, 1734, 1718, 1624, 1496, 1462, 1433, 1370, 1329, 1274, 1218, 1203, 1126, 1080, 1040, 950, 760, 728, 696 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *δ* 6.82 (d, *J* = 4.4 Hz, 4H, ArH), 6.53 (t, *J* = 5.2 Hz, 2H, ArH), 5.35 (s, 2H, 2 × CH), 4.11–4.08 (m, 2H, CH_2), 3.68 (s, 6H, 2 × CH_3O), 3.38–3.22 (m, 3H, CH_2 + CH), 1.76–1.72 (m, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 149.24, 146.19, 138.71, 123.34, 119.59, 119.32, 112.05, 62.40, 55.96, 48.90, 22.07; HRMS [Found: *m/z* 396.1322 (M^+), calcd for $C_{21}H_{20}N_2O_6$: M, 396.1321]

11: White solid, mp: >300 °C; IR (KBr): *ν* 3031, 2941, 1725, 1631, 1518, 1457, 1374, 1339, 1220, 1076, 998, 816, 747 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): *δ* 7.73 (d, *J* = 8.8 Hz, 2H, ArH), 7.38 (d, *J* = 8.0 Hz, 2H, ArH), 7.33 (d, *J* = 8.8 Hz, 2H, ArH), 6.91 (t, *J* = 7.2 Hz, 2H, ArH), 6.73–6.65 (m, 4H, ArH), 5.67 (s, 2H, 2 × CH), 4.13–4.07 (m, 2H, CH_2), 3.62–3.54 (m, 2H, CH), 2.45–2.38 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 150.15, 148.63, 130.49, 129.56, 129.33, 127.30, 125.21, 124.04, 120.79, 115.43, 112.52, 62.23, 46.76, 22.87; HRMS [Found: *m/z* 476.1737 (M^+), calcd for $C_{30}H_{24}N_2O_4$: M, 476.1736]

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References

1 J. K. Landquist, In *Comprehensive Heterocyclic Chemistry*; A. R. Katritzky, C. W. Rees (ed.); Pergamon: Oxford, 1984, p 166.
2 H. Schutz, *Benzodiazepines*; Springer: Heidelberg, 1982.
3 B. Insuasty, M. Ramos, J. Quiroga, A. Sanchez, M. Nogueras, N. Hanold and H. J. Meier, *J. Heterocycl. Chem.*, 1994, **31**, 61–64.
4 T. A. Kelly, D. W. McNeil, J. M. Rose, E. David, C. K. Shih and P. M. Grob, *J. Med. Chem.*, 1977, **440**, 2430–2433 and references therein.
5 (*a*) S. Seto, A. Tanioka, M. Ikeda and S. Izawa, *Bioorg. Med. Chem.*, 2005, **13**, 5717–5732; (*b*) S. Seto, A. Tanioka, M. Ikeda, S. Izawa Patent EP1496059, 2005.
6 D. H. Kim, A. A. Santilli Patent US3535310, 1970.
7 M. Israel, S. K. Tinter, D. H. Trites and E. J. J. Modest, *J. Heterocycl. Chem.*, 1970, **7**, 1029–1035.
8 S. Senda, K. Hirota, T. Asao and K. Maruhashi, *J. Am. Chem. Soc.*, 1977, **99**, 7358–7359.
9 (*a*) F. Heaney, C. Burke, D. Cunningham and P. McArdle, *J. Chem. Soc., Perkin Trans. 1*, 2001, 622–632; (*b*) N. E. Huddleston, J. L. Harris, H. L. Nguyen and P. S. Ray, *Heterocycl. Commun.*, 2004, **10**, 405–406.
10 K. Ohmoto, K. Hisaichi, M. Okuma, M. Tanaka, N. Kawada Patent US20070197510, 2007.
11 B. Insuasty, F. Orozco, C. Lizarazo, J. Quiroga, R. Abonia, M. Hursthouse, M. Nogueras and J. Cobo, *Bioorg. Med. Chem.*, 2008, **16**, 8492–8500.
12 J. B. Xiang, D. S. Wen, H. X. Xie, Q. Dang and X. Bai, *J. Comb. Chem.*, 2010, **12**, 503–509.
13 (*a*) J. E. McMurry, *Acc. Chem. Res.*, 1974, **7**, 281; (*b*) J. E. McMurry, *Acc. Chem. Res.*, 1983, **16**, 405; (*c*) J. E. McMurry, *Chem. Rev.*, 1989, **89**, 1513; (*d*) D. Lenoir, *Synthesis*, 1989, 883; (*e*) A. Furstner and B. Bogdanovi, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2443; (*f*) D. Q. Shi, J. X. Chen, W. Y. Chai, W. X. Chen and T. Y. Kao, *Tetrahedron Lett.*, 1993, **34**, 2963.

14 L. H. Zhou, D. Q. Shi, Y. Gao, W. B. Shen, G. Y. Dai and W. X. Chen, *Tetrahedron Lett.*, 1997, **38**, 2729.
15 L. H. Zhou, S. J. Tu, D. Q. Shi, G. Y. Dai and W. X. Chen, *Synthesis*, 1998, 851.
16 G. L. Dou, C. L. Shi and D. Q. Shi, *J. Comb. Chem.*, 2008, **10**, 810–813.
17 D. Q. Shi, L. C. Rong, J. X. Wang, Q. Y. Zhuang, X. S. Wang and H. W. Hu, *Tetrahedron Lett.*, 2003, **44**, 319–3201.
18 D. Q. Shi, G. L. Dou, Z. Y. Li, S. N. Ni, S. N. Ni, X. Y. Li, X. S. Wang, H. Wu and S. J. Ji, *Tetrahedron*, 2007, **63**, 9764–9773.
19 D. Q. Shi, J. X. Wang, C. L. Shi, L. C. Rong, Q. Y. Zhuang, H. W. Hu and H. Wu, *Synlett*, 2004, 1098–1100.
20 G. L. Dou, M. M. Wang and D. Q. Shi, *J. Comb. Chem.*, 2009, **11**, 151–154.
21 G. L. Dou, D. Q. Shi and Y. H. Li, *J. Comb. Chem.*, 2010, **12**, 195–199.
22 Gaussian, Inc., Wallingford CT, 2009.

