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Facile synthesis of 4-substituted 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones by reductive cyclization of 2-chloro-*N*-(2-nitrobenzyl)acetamides

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ABSTRACT

A facile and efficient method was developed for the synthesis of 1,2,4,5-tetrahydro-1,4-benzodiazepine-3-ones from 2-chloro-*N*-(2-nitrobenzyl)acetamides through a reductive cyclization using iron-ammonium chloride in ethanol–water in good yields. This method provides a simple approach to these benzodiazepine-3-ones which are of high value in the field of medicinal chemistry research.

Introduction

1,4-Benzodiazepinone compounds (1,4-BDZ) are important heterocycles due to their biological activity and they have been extensively investigated. They are well known for their use as sedatives, myorelaxing agents, anticonvulsants and anxiolytics [1]. Diazepam and clonazepam are two examples that contain the 1,4-benzodiazepinone moiety (Fig. 1).

Although the pyrrolo-1,4-BDZ and 1,4-BDZ-2-ones were widely studied, the analogues 1,2,4,5-tetrahydro-1,4-benzodiazepine-3-ones were less investigated. They have recently attracted considerable attention due to their high AT2 receptor affinity and GPIIb/IIIa antagonistical activity [2]. Another known compound with this skeleton is the antithrombotic Lotrafiban (SB-214857) [3]. Also, these heterocycles, have been described as a protein kinase C modulator [4] and as γ-turn mimetics [5].

A number of synthetic approaches to 1,4-BDZ-3-ones have appeared during the last decade, the intramolecular cyclization of the heterocyclic ring is the key step. This particular reaction has been reported to take place by intramolecular nucleophilic aromatic substitution [2a,5,6] as well as the addition of Grignard reagents to 2-aminobenzonitriles [7] or intramolecular 1,3-dipolar cycloadditions [8]. Other methods include *retro*-Michael amidation [3b], palladium-catalyzed *N*-arylation [9], cascade coupling/condensation process of 2-bromobenzylamines with aminoacids [10] and Ullmann's aryl amination [11]. Also cyclization processes involving an Ugi reaction as a first step have been reported recently [12].

As part of our ongoing efforts in the synthesis of biologically active heterocycles [13], and due the interest that these substances have for us as potential antiepileptic agents, we designed and developed a simple method, that requires the use of inexpensive reagents and mild reaction conditions, to afford the corresponding *N*-substituted 1,4-benzodiazepinones in good yields. This method involves the synthesis of novel *N*-substituted 2-chloro-*N*-(2-nitrobencyl)acetamides **3** as cyclization reactants. In a second step, the chloroacetamides undertake intramolecular cyclization by the use of iron and ammonium chloride in ethanol–water to afford the desired 4-substituted 1,2,4,5-tetrahydro-1,4-benzodiazepine-3-ones **5**.

Results and discussion

The synthesis of these novel chloroacetamides is described in Scheme 1.

At first step, *N*-substituted *N*-(2-nitrobenzyl)amines **2** were prepared by reductive amination of *o*-nitrobenzaldehyde **1** using a standard method and $NaBH_4$ as a reduction agent [14]. 2-Nitrobenzylamines (**2**) were obtained in good yields and subsequently underwent amidation with chloroacetyl chloride in toluene at reflux to afford the chloroacetamides **3**. Due to the slow rotation

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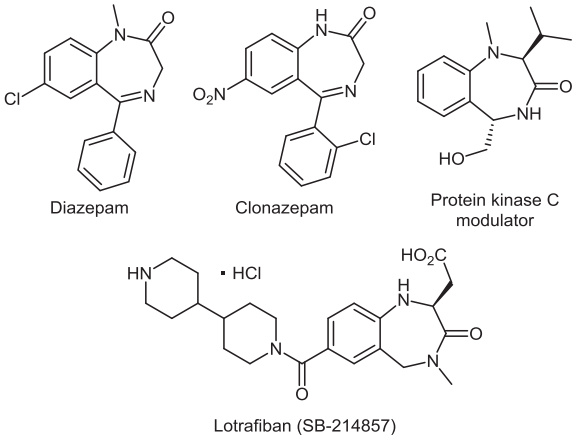
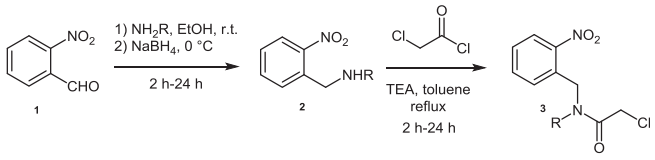
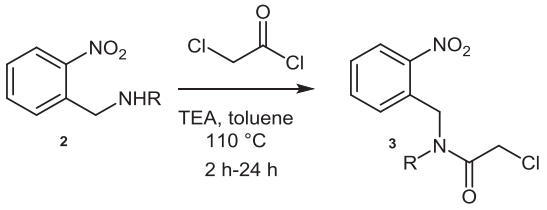


Fig. 1. Examples of bioactive 1,4-benzodiazepinones.



Scheme 1. *N*-substitutes 2-chloro-*N*-(2-nitrobenzyl)acetamides two step synthesis.

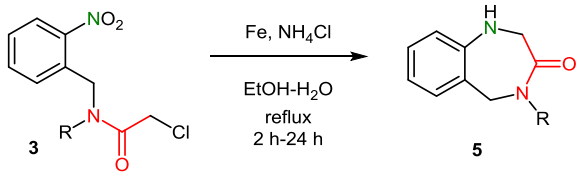
Table 1
Synthesis of 2-chloro-*N*-(2-nitrobenzyl)acetamides.



Entry	R	Product	Time (h)	mp (°C)	Yield (%)
1	Me	3a	2	78–79	65
2	Et	3b	2	oil	79
3	Pr	3c	2	81–83	72
4	*i*-Pr	3d	2	oil	82
5	*n*-Bu	3e	2	oil	83
6	Bn	3f	2	oil	77
7	4-fluorobenzyl	3g	2	oil	75
8	2-phenylethyl	3h	2	oil	85
9	phenyl	3i	24	78–80	88
10	4-bromophenyl	3j	24	101–102	82
11	4-methylphenyl	3k	24	oil	76
12	2-chlorophenyl	3l	24	93–95	75
13	2-fluorophenyl	3m	24	94–96	89

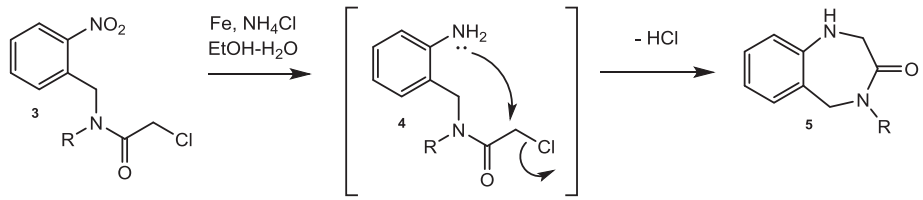
Reaction conditions: **2** (3.0 mmol), chloroacetyl chloride (3.0 mmol), TEA (3.0 mmol), toluene 10 ml, 110 °C.

Table 2
Synthesis of 4-substituted 1,2,4,5-tetrahydro-1,4-benzodiazepine-3-ones **5**.



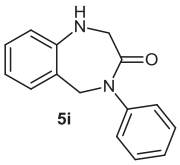
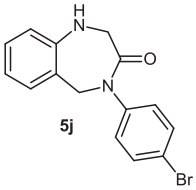
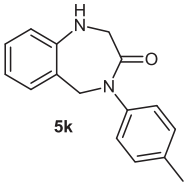
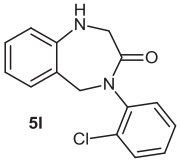
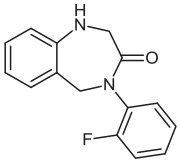
Entry	R	Product	Time (h)	mp (°C)	Yield (%)
1	Me	**5a**	6	138–139	68
2	Et	**5b**	2	184–185	65
3	Pr	**5c**	6	122–124	55
4	*i*-Pr	**5d**	2	90–91	77
5	*n*-Bu	**5e**	6	84–86	70
6	Bn	**5f**	6	165–166	67
7	4-fluorobenzyl	**5g**	2	135–136	67
8	2-phenylethyl	**5h**	6	147–148	69

(*continued on next page*)



Scheme 2. *One-pot* reductive cyclization process for the synthesis of 1,2,4,5-tetrahydro-1,4-benzodiazepine-3-ones **5.**

Table 2 (*continued*)

Entry	R	Product	Time (h)	mp (°C)	Yield (%)
9	phenyl	 **5i**	2	156–158	39
10	4-bromophenyl	 **5j**	2	178–180	30
11	4-methylphenyl	 **5k**	24	175–176	42
12	2-chlorophenyl	 **5l**	24	152–154	40
13	2-fluorophenyl		24	152–153	38

around the *N*-CO bond, these compounds exist in $CDCl_3$ solution as a mixture of *Z*/*E* rotamers that were detected by ^{1}H NMR and ^{13}C NMR.

As shown in Table 1 the desired products were obtained in good yields after 2 h when the *N*-substituent was alkyl or aralkyl. They required longer reaction times when R was aryl due to the less nucleophilic nitrogen of the aryl group.

Having obtained the corresponding chloroacetamides we proposed an annulation process to synthesize the novel 1,2,4,5-tetrahydro-1,4-benzodiazepine-3-ones heterocycles. A reductive cyclization reaction may take place, the $-NO_2$ group of **3** is first reduced by iron to obtain 2-chloro-*N*-(2-aminobenzyl)acetamides **4** that could undergo an intramolecular S_N2 reaction to afford **5** in a *one-pot* process of two steps (Scheme 2).

After evaluating different reductive agents and reactions conditions [15] the final target molecules (1,4-BDZ-3-ones **5**) were synthesized by reaction of **3** with iron dust and ammonium chloride in a mixture of ethanol and water at reflux [16].

The cyclization reactions afforded the desired products in good yields [17]. The best results were obtained when substrates with R = alkyl or aralkyl were used after refluxing the reaction mixture for 2–6 h (Table 2). When substrates with R = aryl were subjected to reaction it was possible to isolate and identified the intermediate **4** in some examples. This behavior must be due steric effects since annulation rate process is slower for these substrates. However, after longer reaction times the transformation of **4** into 1,4-BDZ-3-ones **5** was achieved. The novel 1,4-BDZ-3-ones were fully characterized by elemental analysis, ^{1}H NMR and ^{13}C NMR.

Conclusions

In conclusion, we have developed a facile and efficient synthesis of new 4-substituted 1,2,4,5-tetrahydro-1,4-benzodiazepine-3-ones in good yields by reductive cyclization of novel *N*-substituted 2-chloro-*N*-(2-nitrobencyl)acetamides under mild reaction conditions. Efforts to evaluate the affinity of 1,4-BDZ-3-ones to the BDZ-bs of $GABA_A$ by radioligand assays and the corresponding in vivo experiments are currently initiated with the invaluable aid of specialized partners [18].

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2018.12.029.

References

[1] (a) H. Mohler, T. Okada, Science 198 (1977) 849;
(b) C. Mombereau, K. Kaupmann, H. van der Putten, J.F. Cryan, Eur. J. Pharmacol. 497 (2004) 119;
(c) A.S. Basile, A.S. Lippa, P. Skolnick, Eur. J. Pharmacol. 500 (2004) 441;
(d) J.R. Davidson, J. Clin. Psychiatry 58 (1997) 26;
(e) K. Sorra, C.-S. Chen, C.-F. Chang, S. Pusuluri, K. Mukkanti, C.-R. Wu, T.-H. Chuang, Int. J. Mol. Sci. 15 (2014) 16500;
(f) R.M. Pinder, R.N. Brogden, T.M. Speight, G.S. Avery, Drugs 12 (1976) 321;
(g) R. Mandrioli, L. Mercolini, M.A. Raggi, Curr. Drug Metab. 9 (2008) 827;
(h) P. Czapiński, B. Blaszczyk, S.J. Czuczwar, Curr. Top. Med. Chem. 5 (2005) 3.
[2] (a) U. Rosenström, C. Sköld, G. Lindeberg, M. Botros, F. Nyberg, A. Karlén, A. Hallberg, J. Med. Chem. 47 (2004) 859;
(b) I.P. Andrews, R.J. Atkins, G.F. Breen, J.S. Carey, M.A. Forth, D.O. Morgan, A. Shamji, A.C. Share, S.A.C. Smith, T.C. Walsgrove, A.S. Wells, Org. Process Res. Dev. 7 (2003) 655.
[3] (a) J.M. Samanen, F.E. Ali, L.S. Barton, W.E. Bondinelli, J.L. Burgess, J.F. Callahan, R.R. Calvo, W. Chen, L. Chen, K. Erhard, G. Feuerstein, R. Heys, S.M. Hwang, D.R. Jakas, R.M. Keenan, T.W. Ku, C. Kwon, C.-P. Lee, W.H. Miller, K.A. Newlander, A. Nichols, M. Parker, C.E. Peishoff, G. Rhodes, S. Ross, A. Shu, R. Simpson, D. Takata, T.O. Yellin, I. Uzsinskas, J.W. Venslavsky, C.K. Yuan, W.F. Huffman, J. Med. Chem. 39 (1996) 4867;
(b) I.P. Andrews, R.J. Atkins, N.F. Badham, R.K. Bellingham, G.F. Breen, J.S. Carey, S.K. Etridge, J.F. Hayes, N. Hussain, D.O. Morgan, A.C. Share, A.C. Smith, T. C. Walsgrove, A.S. Wells, Tetrahedron Lett. 42 (2001) 4915;
(c) J.-B. Clement, J.F. Hayes, H.M. Sheldrake, P.W. Sheldrake, A.S. Wells, Synlett 9 (2001) 1423.
[4] D. Ma, G. Wang, S. Wang, A. Kozikowski, N.E. Lewin, P.M. Blumberg, Bioorg. Med. Chem. Lett. 9 (1999) 1371.
[5] U. Rosenström, C. Sköld, G. Lindeberg, M. Botros, F. Nyberg, A. Karlén, A. Hallberg, J. Med. Chem. 49 (2006) 6133.
[6] E.C. Clement, P.R. Carlier, Tetrahedron Lett. 46 (2005) 3633.
[7] B. Pettersson, A. Rydbeck, J. Bergman, Org. Biomol. Chem. 7 (2009) 1184.
[8] (a) I. Akritopoulou-Zanze, V. Gracias, S.W. Djuric, Tetrahedron Lett. 45 (2004) 8439;
(b) G. Molteni, P.D. Buttero, Tetrahedron: Asymmetry 12 (2001) 1201;
(c) L. Garanti, G. Molteni, G. Broggini, J. Chem. Soc., Perkin Trans. 1 (1816) 2001.
[9] M. Castellani, C. Catucci, G. Celentano, F. Ferraccioli, Synlett (2001) 803.
[10] H. Wang, Y. Jiang, G. Gao, D. Ma, Tetrahedron 65 (2009) 8956.
[11] (a) D. Ma, C. Xia, Org. Lett. 3 (2001) 2583;
(b) J.F. Hayes, Synlett (1999) 865.
[12] (a) Y. Zhong, H. Zhang, M.-W.J. Ding, Heterocyclic Chem. 52 (2015) 330;
(b) R.A. De Silva, S. Santra, P.R. Andreana, Org. Lett. 10 (2008) 4541.

[13] (a) L.D. Sasiambarrena, A.S. Cánepa, R.D. Bravo, Synth. Commun. 41 (2011) 205;
(b) L.D. Sasiambarrena, A.S. Cánepa, C.N. Luna, R.D. Bravo, Tetrahedron Lett. 56 (2015) 2054;
(c) L.D. Sasiambarrena, A.S. Cánepa, R.D. Bravo, Tetrahedron Lett. 56 (2015) 7184.
[14] A.D. Mills, M.Z. Nazer, M.J. Haddadin, M.J. Kurth, J. Org. Chem. 71 (2006) 2687.
[15] I. Pogorelić, M. Filipan-Litvić, S. Merkaš, G. Ljubić, I. Cepanec, M. Litvić, J. Mol. Catal. A: Chem. 274 (2007) 202.
[16] T. Jiang, Y. Zhou, Z. Chen, P. Sun, J. Zhu, Q. Zhang, Z. Wang, Q. Shao, X. Jiang, B. Li, K. Chen, H. Jiang, H. Wang, W. Zhu, J. Shen, ACS Med. Chem. Lett. 6 (2015) 602.
[17] Compounds 5, general procedure: compound 3 (1 mmol) was dissolved in ethanol (10 ml) and 560 mg (10 mmol) of iron dust was added at room temperature. The mixture was heated at 80 °C and 540 mg of ammonium chloride in 5 ml of water were added dropwise. The reaction was monitored by TLC (CH2Cl2) until it was complete, cooled, filtered through celite and concentrated under reduced pressure. The residue was dissolved in CH2Cl2 (20 ml) washed with water (10 ml), dried (Na2SO4) and the solvent evaporated to afford crude benzodiazepinone 5 as a white solid which was purified by recrystallization from ethanol or column chromatography (CH2Cl2). 4-Methyl-1,2,4,5-tetrahydro-1,4-benzodiazepine-3-one (5a) C10H12N2O; found C, 68.27; H, 6.80; N, 15.92%; requires C, 68.16; H, 6.86; N, 15.90; O, 9.08%. 1H NMR (600 MHz, Chloroform-d): δ 7.07 (t, J = 7.7 Hz, 1H), 6.91 (d, J = 7.5 Hz, 1H), 6.63 (t, J = 7.4 Hz, 1H), 6.54 (d, J = 8.0 Hz, 1H), 4.51 (s, 2H), 4.13 (s, 2H), 3.78 (s br, 1H), 3.07 (s, 3H). 13C NMR (151 MHz, CDCl3) δ 169.87, 145.75, 129.77, 129.38, 119.47, 117.84, 116.72, 53.93, 49.25, 34.50. 4-Ethyl-1,2,4,5-tetrahydro-1,4-benzodiazepine-3-one (5b) C11H14N2O; found C, 69.38; H, 7.44; N, 14.75%; requires C, 69.45; H, 7.42; N, 14.73; O, 8.41%. 1H NMR (600 MHz, Chloroform-d) δ 7.06 (t, J = 7.7 Hz, 1H), 6.91 (d, J = 7.5 Hz, 1H), 6.63 (t, J = 7.4 Hz, 1H), 6.53 (d, J = 8.1 Hz, 1H), 4.52 (s, 2H), 4.17 (s br, 1H), 4.12 (s, 2H), 3.53 (q, J = 7.2 Hz, 2H), 1.13 (t, J = 7.2 Hz, 3H). 13C NMR (151 MHz, CDCl3) δ 169.31, 145.78, 129.55, 129.25, 120.28, 117.99, 116.72, 51.74, 49.49, 42.16, 13.57. 4-Propyl-1,2,4,5-tetrahydro-1,4-benzodiazepine-3-one (5c) C12H16N2O; found C, 70.62; H, 8.00; N, 13.73%; requires C, 70.56; H, 7.90; N, 13.71; O, 7.83%. 1H NMR (600 MHz, Chloroform-d) δ 7.05 (t, J = 7.1 Hz, 1H), 6.90 (d, J = 7.4 Hz, 1H), 6.62 (t, J = 7.4 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 4.52 (s, 2H), 4.20 (s, 1H), 4.13 (d, J = 5.3 Hz, 2H), 3.47 – 3.41 (m, 2H), 1.55 (h, J = 7.4 Hz, 2H), 0.84 (t, J = 7.4 Hz, 3H). 13C NMR (151 MHz, CDCl3) δ 169.66, 145.76, 129.60, 129.23, 120.11, 117.91, 116.66, 52.23, 49.44, 49.05, 21.65, 11.35. 4-Isopropyl-1,2,4,5-tetrahydro-1,4-benzodiazepine-3-one (5d) C12H16N2O; found C, 70.58; H, 8.05; N, 13.60%; requires C, 70.56; H, 7.90; N, 13.71; O, 7.83%. 1H NMR (600 MHz, Chloroform-d) δ 7.07 – 7.00 (m, 1H), 6.91 (d, J = 7.3 Hz, 1H), 6.61 (t, J = 7.4 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 4.87 (hept, J = 6.8 Hz, 1H), 4.46 (s, 2H), 4.18 (s br, 1H), 4.13 (s, 2H), 1.12 (d, J = 6.8 Hz, 6H). 13C NMR (151 MHz, CDCl3) δ 169.36, 145.77, 129.39, 128.95, 120.64, 117.89, 116.51, 49.54, 45.16, 44.62, 20.48. 4-Butyl-1,2,4,5-tetrahydro-1,4-benzodiazepine-3-one (5e) C13H18N2O; found C, 69.38; H, 7.44; N, 14.75%; requires C, 71.53; H, 8.31; N, 12.83; O, 7.33%. 1H NMR (600 MHz, Chloroform-d) δ 7.08 – 7.03 (m, 1H), 6.90 (d, J = 7.4 Hz, 1H), 6.63 (t, J = 7.4 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 4.51 (s, 2H), 4.20 (s br, 1H), 4.12 (d, J = 4.7 Hz, 2H), 3.48 (t, J = 7.4 Hz, 2H), 1.54 – 1.47 (m, 2H), 1.26 (h, J = 7.4 Hz, 2H), 0.87 (t, J = 7.4 Hz, 3H). 13C NMR (151 MHz, CDCl3) δ 169.60, 145.78, 129.58, 129.23, 120.14, 117.92, 116.67, 52.15, 49.47, 47.11, 30.46, 20.09, 13.89. 4-Bencyl-1,2,4,5-tetrahydro-1,4-benzodiazepine-3-one (5f) C16H16N2O; found C, 76.10; H, 6.48; N, 11.25%; requires C, 76.16; H, 6.39; N, 11.10; O, 6.34%. 1H NMR (600 MHz, Chloroform-d) δ 7.36 – 7.31 (m, 2H), 7.31 – 7.25 (m, 3H), 7.08 (td, J = 7.7, 1.6 Hz, 1H), 6.75 (dd, J = 7.5, 1.5 Hz, 1H), 6.63 – 6.55 (m, 2H), 4.71 (s, 2H), 4.47 (s, 2H), 4.31 (s br, 1H), 4.24 (d, J = 5.3 Hz, 2H). 13C NMR (151 MHz, CDCl3) δ 170.00, 145.76, 137.07, 129.78, 129.24, 128.70, 128.17, 127.59, 119.61, 117.90, 116.64, 51.08, 49.85, 49.37. 4-(4-Fluorobencyl)-1,2,4,5-tetrahydro-1,4-benzodiazepine-3-one (5g) C16H15FN2O; found C, 71.13; H, 5.66; N, 10.20%; requires C, 71.10; H, 5.59; F, 7.03; N, 10.36; O, 5.92. 1H NMR (600 MHz, Chloroform-d) δ 7.21 (dd, J = 8.4, 5.5 Hz, 2H), 7.05 (td, J = 7.7, 1.6 Hz, 1H), 6.97 (t, J = 8.6 Hz, 2H), 6.70 (dd, J = 7.5, 1.5 Hz, 1H), 6.60 – 6.55 (m, 1H), 6.54 (d, J = 8.0 Hz, 1H), 4.65 (s, 2H), 4.44 (s, 2H), 4.20 (s, 2H), 4.18 (s br, 1H). 13C NMR (151 MHz, CDCl3) δ 170.00, 163.16, 161.53, 145.70, 132.94, 132.92, 129.89, 129.84, 129.74, 129.33, 119.67, 118.10, 116.72, 115.64, 115.50, 51.20, 49.45, 49.38. 4-(2-Phenylethyl)-1,2,4,5-tetrahydro-1,4-benzodiazepine-3-one (5h) C17H18N2O; found C, 76.60; H, 6.85; N, 10.40%; requires C, 76.66; H, 6.81; N, 10.52; O, 6.01%. 1H NMR (600 MHz, Chloroform-d) δ 7.28 (dd, J = 8.0, 6.7 Hz, 2H), 7.24 – 7.19 (m, 1H), 7.20 – 7.16 (m, 2H), 7.08 (td, J = 7.7, 1.6 Hz, 1H), 6.84 (dd, J = 7.6, 1.5 Hz, 1H), 6.64 (td, J = 7.4, 1.2 Hz, 1H), 6.54 (dd, J = 8.0, 1.1 Hz, 1H), 4.45 (s, 2H), 4.18 (s br, 1H), 4.12 (d, J = 3.6 Hz, 2H), 3.79 – 3.72 (m, 2H), 2.87 (dd, J = 8.3, 6.7 Hz, 2H). 13C NMR (151 MHz, CDCl3) δ 169.62, 145.74, 138.95, 129.61, 129.24, 128.89, 128.56, 126.47, 120.05, 118.01, 116.72, 53.01, 49.63, 49.41, 34.83. 4-Phenyl-1,2,4,5-tetrahydro-1,4-benzodiazepine-3-one (5i) C15H14N2O; found C, 75.50; H, 6.03; N, 11.76%; requires C, 75.61; H, 5.92; N, 11.76; O, 6.71%. 1H NMR (600 MHz, Chloroform-d) δ 7.38 (dd, J = 8.5, 7.2 Hz, 2H), 7.30 – 7.25 (m, 3H), 7.13 (td, J = 7.7, 1.6 Hz, 1H), 6.94 (dd, J = 7.5, 1.5 Hz, 1H), 6.69 (td, J = 7.4, 1.1 Hz, 1H), 6.61 (dd, J = 8.1, 1.1 Hz, 1H), 4.98 (s, 2H), 4.33 (s, 3H). 13C NMR (151 MHz, CDCl3) δ 169.19, 145.65, 143.02, 129.70, 129.49, 129.21, 126.89, 126.03, 119.98, 118.16, 116.79, 55.60, 49.81. 4-(4-Bromophenyl)-1,2,4,5-tetrahydro-1,4-benzodiazepine-3-one (5j) C15H13BrN2O; found C, 56.87; H, 4.02; N, 8.90%; requires C, 56.80; H, 4.13; Br, 25.19; N, 8.83; O, 6.24%. 1H NMR (600 MHz, Chloroform-d) δ 7.50 – 7.44 (m, 2H), 7.17 – 7.08 (m, 3H), 6.90 (dd, J = 7.5, 1.6 Hz, 1H), 6.67 (td, J = 7.4, 1.2 Hz, 1H), 6.58 (dd, J = 8.1, 1.2 Hz, 1H), 4.92 (s, 2H), 4.29 (s br, 3H). 13C NMR (151 MHz, CDCl3) δ 169.14, 145.56, 141.93, 132.29, 129.65, 129.63, 127.68, 120.29, 119.63, 118.30, 116.85, 55.47, 49.72. 4-(4-Methylphenyl)-1,2,4,5-tetrahydro-1,4-benzodiazepine-3-one (5k) C16H16N2O; found C, 76.01; H, 6.45; N, 11.29%; requires C, 76.16; H, 6.39; N, 11.10; O, 6.34%. 1H NMR (600 MHz, Chloroform-d) δ 7.20 – 7.07 (m, 5H), 6.89 (d, J = 7.4 Hz, 1H), 6.66 (t, J = 7.4 Hz, 1H), 6.58 (d, J = 8.0 Hz, 1H), 4.92 (s, 2H), 4.32 – 4.24 (m, 3H), 2.34 (s, 3H). 13C NMR (151 MHz, CDCl3) δ 169.17, 145.54, 140.36, 136.68, 130.21, 129.89, 129.75, 129.61, 129.35, 125.80, 119.99, 118.05, 116.69, 114.27, 55.59, 49.70, 21.06. 4-(2-Chlorophenyl)-1,2,4,5-tetrahydro-1,4-benzodiazepine-3-one (5l) C15H13ClN2O; found C, 66.21; H, 4.77; N, 10.41%; requires C, 66.06; H, 4.80; Cl, 13.00; N, 10.27; O, 5.87%. 1H NMR (500 MHz, Chloroform-d) δ 8.71 (s, 1H), 7.35 (dd, J = 7.9, 1.6 Hz, 1H), 7.32 – 7.22 (m, 3H), 7.16 (td, J = 7.7, 1.6 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 7.03 (d, J = 7.9 Hz, 1H), 6.97 (td, J = 7.6, 1.5 Hz, 1H), 4.44 (s, 2H), 4.08 (s, 2H). 13C NMR (126 MHz, CDCl3) δ 172.62, 147.47, 137.24, 130.91, 130.49, 129.09, 128.82, 128.57, 127.88, 125.26, 124.65, 122.63, 120.39, 57.49, 55.03. 4-(2-Fluorophenyl)-1,2,4,5-tetrahydro-1,4-benzodiazepine-3-one (5m) C15H13FN2O; found C, 70.53; H, 5.16; N, 10.99%; requires C, 70.30; H, 5.11; F, 7.41; N, 10.93; O, 6.24%. 1H NMR (600 MHz, Chloroform-d) δ 7.28 – 7.23 (m, 1H), 7.19 (t, J = 7.7 Hz, 1H), 7.14 – 7.06 (m, 3H), 6.84 (d, J = 7.5 Hz, 1H), 6.64 (t, J = 7.4 Hz, 1H), 6.59 (d, J = 8.1 Hz, 1H), 4.86 (s, 2H), 4.33 – 4.22 (m, 3H). 13C NMR (151 MHz, CDCl3) δ 169.41, 158.21, 156.55, 145.61, 129.85, 129.51, 129.11, 128.91, 124.70, 119.89, 118.26, 116.94, 116.73, 55.48, 49.44.
[18] (a) F.S. Duarte, M. Marder, A.A. Hoeller, M. Duzzioni, B.G. Mendes, M.G. Pizzolatti, T.C.M. De Lima, Psychopharmacology 197 (2008) 351;
(b) M.L. Villalba, A.V. Enrique, J. Higgs, R.A. Castaño, S. Goicoechea, F.D. Taborda, L. Gavernet, I.D. Lick, M. Marder, L.E. Bruno Blanch, Eur. J. Pharmacol. 774 (2016) 55;
(c) L.M. Loscalzo, C. Wasowski, A.C. Paladini, M. Marder, Eur. J. Pharmacol. 580 (2008) 306;
(d) A. Wasowski, L. Gavernet, I.A. Barrios, M.L. Villalba, V. Pastore, G. Samaja, A. Enrique, L.E. Bruno-Blanch, M. Marder, Biochem. Pharmacol. 83 (2012) 253.