Monatsh Chem
DOI 10.1007/s00706-013-1133-1

ORIGINAL PAPER

Synthesis of *N*-carboxyalkyl-1,4-benzothiazepine-3(2*H*)-one derivatives using esters of *N*-(2-chloro-5-nitrobenzyl)amino acids

Taras M. Tarasiuk · Tetiana A. Volovnenko · Yulian M. Volovenko · Volodymyr V. Medviediev · Oleg V. Shishkin

Received: 27 June 2013 / Accepted: 11 December 2013

Abstract Two alternative approaches for synthesis of esters of *N*-(2-chloro-5-nitrobenzyl) amino acids have been developed and compared. We have found synthesis of *N*-(2-chloro-5-nitrobenzyl) amino acids via alkylation of esters of amino acids in DMF in the presence of Et_3N and NaI to be more convenient and have higher yields in comparison with reduction of Schiff bases obtained from 2-chloro-5-nitrobenzaldehyde and corresponding esters of amino acids by $NaBH_4$. Treatment of the solutions of esters of *N*-(2-chloro-5-nitrobenzyl) amino acids in DMSO with methyl thioglycolate and following intramolecular acylation in xylene led to *N*-carboxyalkyl-1,4-benzothiazepine-3(2*H*)-one derivatives in 24–76 % yields.

Keywords Amino acids · Heterocycles · Cyclizations · Nucleophilic substitutions · X-ray structure determination · 1,4-Benzothiazepine-3(2*H*)-ones

Introduction

For the last decades, benzothiazepines have received noticeable attention from organic chemists due to various approaches for the synthesis of possible isomers, their biological activity and the usage in medicine. The benzothiazepine cycle is known to have ten isomers which can be divided into three groups: derivatives of 1,2-, 1,3-, and 1,4-thiazepines (Fig. 1) [1].

Our research group is interested in derivatives of 1,4-thiazepine **III** that include three isomers with an annulated phenyl ring: 1,4-, 4,1-, and 5,1-benzothiazepines. The 1,5-benzothiazepines [2–4] are more studied than 1,4- and 4,1-isomers [5–8].

Earlier, we have reported two alternative methods of synthesis of 1,4-benzothiazepine-3(2*H*)-ones [9, 10]. The objective of the present work was synthesis of novel 1,4-benzothiazepine-3(2*H*)-one derivatives, which contain fragments of amino acids in position 4. To our mind, the combination of a rigid nonplanar cycle and an amino acid residue can lead to the appearance of useful biological properties. There are a lot of pharmaceuticals based on peptides or containing amino acids in medicine. Saturated and partially saturated rigid seven-membered heterocycles are known to be a base of drugs. For example, CV5975 (**IV**) [11] is a synthetic inhibitor of angiotensin-converting enzyme (ACE), which plays an important role in regulating arterial blood pressure (Fig. 2).

Compounds of general formula **V** [12] were found to be potent agonists of bradykinin B_2 receptors. Bradykinin (BK) is a linear nonapeptide hormone (HArg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg-OH), which is involved in a wide variety of physiological and pathophysiological responses through activation of two types of receptors named B_1 and B_2. Bradykinin induces vascular and bronchial smooth muscle contraction and causes vasodilation and microvascular leakage [3].

T. M. Tarasiuk (✉) · T. A. Volovnenko · Y. M. Volovenko
Department of Organic Chemistry, Taras Shevchenko Kyiv National University, 64 Volodymyrska str., 01033 Kyiv, Ukraine
e-mail: taras88ximik@ukr.net

V. V. Medviediev · O. V. Shishkin
STC "Institute for Single Crystals", National Academy of Science of Ukraine, 60 Lenina ave., 61001 Kharkiv, Ukraine

O. V. Shishkin
Department of Inorganic Chemistry, V. N. Karazin Kharkiv National University, 4 Svobody sq., 61122 Kharkiv, Ukraine

Published online: 24 January 2014

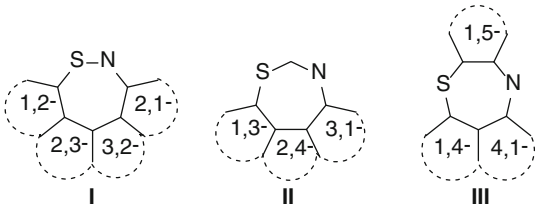


Fig. 1 Ten possible isomers of the benzothiazepine cycle

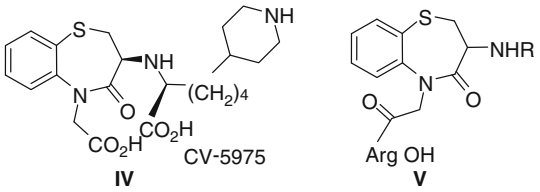


Fig. 2 Examples of biologically active compounds, which contain an amino acid fragment and a benzothiazepine moiety

Results and discussion

We have examined two alternative routes for synthesis of esters of *N*-(2-chloro-5-nitrobenzyl) amino acids **4a**–**4f** using esters of amino acids **2a**–**2f** and 2-chloro-5-nitrobenzaldehyde (**1**) as a source of the 2-chloro-5-nitrobenzyl moiety.

Initially, we have attempted to synthesize the desired amino acid derivatives **4a**–**4f** from aldehyde **1** and corresponding hydrochlorides of esters of amino acids **2a**–**2f** following a modified described technique [13] (method A). This method is based on the formation of Schiff base **3b**, **3c**, **3f** in CH_2Cl_2 in the presence of Et_3N and $MgSO_4$ and subsequent reduction by $NaBH_4$ in methanol (Scheme 1) in 48–58 % yields (Table 1). The structure of imines **3b**, **3c**, **3f** is confirmed by the presence of a characteristic singlet of methyne group in ^1H NMR spectra at 8.45–8.73 ppm and an intensive band of C=N at 1,634–1,644 cm^{-1} in IR spectra.

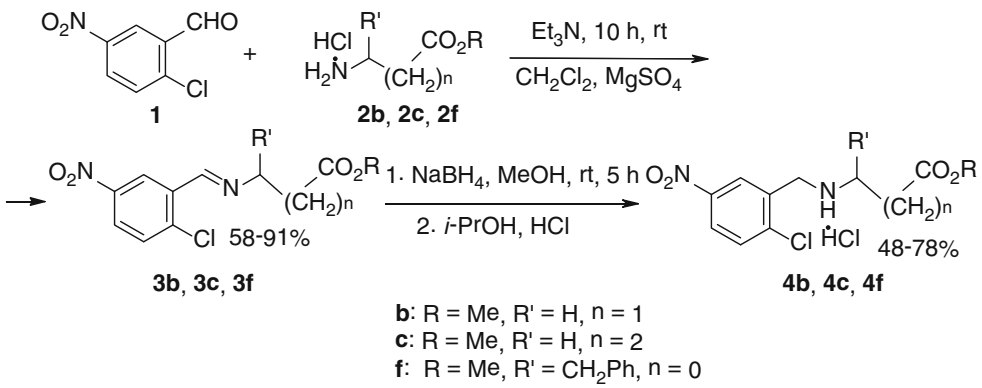
Method A is restricted because of side reactions and only some esters of *N*-(2-chloro-5-nitrobenzyl)amino acids (**4b**, **4c**, **4f**) can be obtained through following this technique. Method B is based on reduction of 2-chloro-5-nitrobenzaldehyde (**1**) by $NaBH_4$ in methanol with the following substitution of a hydroxyl group with chlorine with $SOCl_2$ similar to a described technique [14]. Treatment of solutions of esters **2a**–**2f** in DMF with 2-chloro-5-nitrobenzyl chloride (**6**) in the presence of Et_3N and KI (Scheme 2) afforded compounds **4a**–**4f** in 58–86 % yields (Table 1). The NMR spectra and other characteristics of obtained compounds **4b**, **4c**, **4f** using both methods are identical. According to experimental data shown in Table 1, method B is more convenient and allows obtaining *N*-(2-chloro-5-nitrobenzyl) amino acid derivatives **4a**–**4f**. At the same time, method A can be used only for **4b**, **4c**, **4f**.

Next step of the present work was aromatic nucleophilic substitution of chlorine with a residue of methyl thioglycolate and subsequent intramolecular acylation. The first reaction was carried out in DMSO using Et_3N as the base (Scheme 3). Products **7a**–**7f** were not isolated as individual compounds. These substances were immediately involved in cyclization in *o*-xylene.

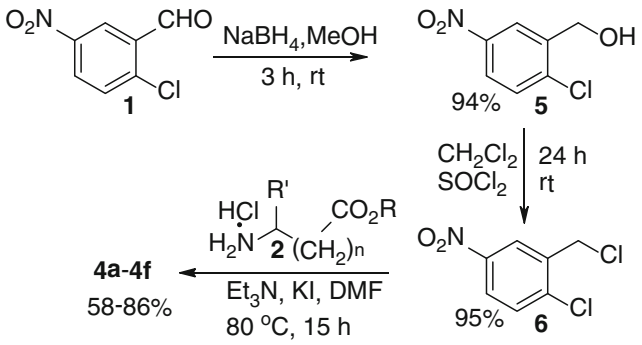
Table 1 Comparison of two alternative methods of synthesis of esters of *N*-(2-chloro-5-nitrobenzyl)amino acids **4a**–**4f**

Entry	AA residue	Yield/%	
		Method A	Method B
4a	Glycine	Side products	86
4b	β-Alanine	78	80
4c	GABA	74	76
4d	Alanine	Side products	79
4e	Leucine	No data	69
4f	Phenylalanine	48	58

Scheme 1

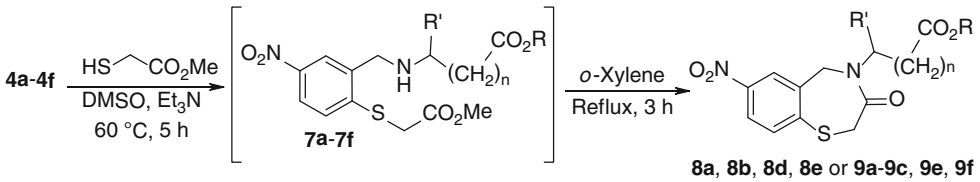


Scheme 2



a: R = Me, R' = H, n = 0
b: R = Me, R' = H, n = 1
c: R = Me, R' = H, n = 2
d: R = Me, R' = Me, n = 0
e: R = Et, R' = $CH_2CH(CH_3)_2$, n = 0
f: R = Me, R' = CH_2Ph, n = 0

Scheme 3



8a, **8b**, **8d**, **8e** or **9a-9c**, **9e**, **9f**
50-68% 24-76%

8a: R = Me, R' = H, n = 0; **8b**: R = Me, R' = H, n = 1;
8d: R = Me, R' = Me, n = 0; **8e**: R = Et, R' = $CH_2CH(CH_3)_2$, n = 0

9a: R = H, R' = H, n = 0; **9b**: R = H, R' = H, n = 1; **9c**: R = H, R' = H, n = 2;
9e: R = H, R' = $CH_2CH(CH_3)_2$, n = 0; **9f**: R = H, R' = CH_2Ph, n = 0

We observed partial hydrolysis of ester groups of amino acid residues in **4a**, **4b**, **4e** and full hydrolysis in the case of **4c** and **4f**. However, hydrolysis of compound **8d** has not been noticed. Esters **8** and acids **9** can be easily separated due to their different solubility in aqueous solution of $NaHCO_3$. Yields of esters **8** and acid **9** are shown in Table 2.

The characteristic signals in ^{1}H NMR spectra compounds **8a**, **8b**, and **9a**–**9c** are singlets of methylene groups in positions 2 and 5 of the benzothiazepine moiety at 4.05–4.13 and 4.81–4.85 ppm, correspondingly.

Table 2 Compounds **8** and **9**

Entry	*R*′	*n*	AA residue	Yield/%	
				Ester **8**[a]	Acid **9** (*R* = H)
a	H	0	Gly	68	25
b	H	1	β-Ala	65	24
c	H	2	GABA	Not obtained	76
d	Me	0	Ala	60	Not obtained
e	CH_2-*i*-Pr	0	Leu	50	40
f	CH_2Ph	0	Phe	Not obtained	57

[a] Compounds **8a**, **8b**, **8d** are methyl esters, **8e** is ethyl ester

Compounds **8d**, **8e** and **9e**, **9f** have spectra different from the spectra of **8a**, **8b**, and **9a**–**9c**. The presence of an asymmetric center in the side chain at nitrogen led to magnetic nonequivalence of protons of the CH_2 groups at positions 2 and 5. Methylene group 2-CH_2 appears as two doublets at 3.54–4.02 and 4.16–4.71 ppm. Two characteristic doublets of 5-CH_2 group are at 4.58–4.77 and 4.87–5.14 ppm. Carbonyl of the amide group in compounds **8** and **9** appears as an intensive band at 1,619–1,660 cm^{-1} in IR spectra. Structure of compounds **8a** and **8b** was confirmed by X-ray diffraction studies (Figs. 3, 4). A seven-membered ring in both molecules adopts a boat conformation with deviation of the N1 and C8 atoms from the mean plane of the remaining atoms of the ring by −1.18, −1.16 Å for **8a**, and 1.15, 1.15 Å for **8b**, respectively.

In summary, we have synthesized a number of novel 1,4-benzothiazepine derivatives with alkylcarboxy substituents (acids and esters) in position 4 of the cycle in 24–76 % yields. We have developed a convenient and efficient method for synthesis of esters of *N*-(2-chloro-5-nitrobenzyl) amino acids via alkylation of esters of corresponding amino acids by 2-chloro-5-nitrobenzylchloride.

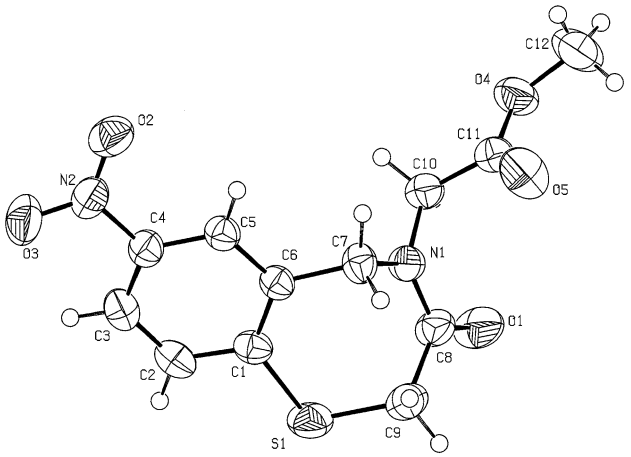


Fig. 3 Molecular structure of compound **8a** according to X-ray diffraction data. Thermal ellipsoids are drawn at 50 % probability level

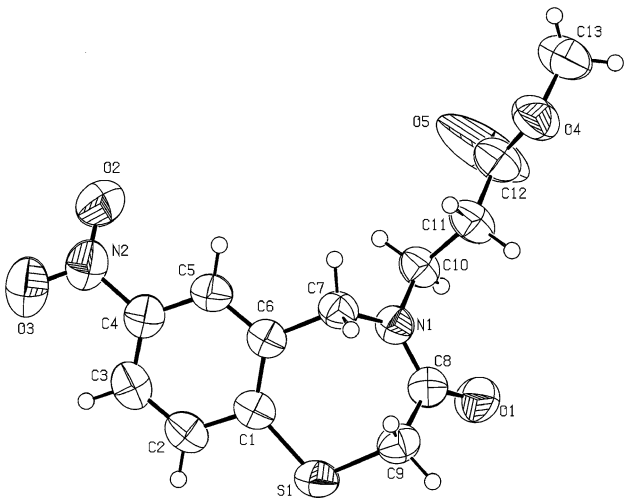


Fig. 4 Molecular structure of compound **8b** according to X-ray diffraction data. Thermal ellipsoids are drawn at 50 % probability level

Experimental

All commercially available chemicals were purchased from Aldrich (St. Louis, MO, USA) and Merck (Darmstadt, Germany). IR spectra were obtained on a Perkin Elmer BX II spectrometer in KBr tablets and are reported in cm^{-1}. The ^1H and ^{13}C NMR spectra of DMSO-d_6 solutions with TMS as an internal standard were recorded on a Varian Mercury 400 spectrometer at 400.45 and 100.61 MHz, respectively. Elemental analyses were determined on a Vario MICRO cube CHNOS elemental analyzer. Melting points were measured with a small Boetius apparatus equipped with a VEB Analytic RNMK apparatus. Purity of the compounds synthesized was monitored by TLC on Silufol UV-254 plates with 9:1 chloroform–methanol as eluent.

*Preparation of Schiff bases **3b**, **3c**, **3f***

To a stirred solution of 2-chloro-5-nitrobenzaldehyde (**1**, 0.05 mol) and Et_3N (0.06 mol) in 70 cm^3 CH_2Cl_2 were added hydrochloride of amino acid ester **2b**, **2c**, **2f** (0.06 mol) and 5 g $MgSO_4$. The reaction mixture was stirred for 10 h, filtered, washed with brine, dried, and evaporated in vacuo. The residue was quenched with *i*-PrOH and triturated. The precipitate was collected by filtration, dried, and crystallized to give compounds **3b**, **3c**, **3f** in 58–91 % yields.

Methyl N-(2-chloro-5-nitrobenzylidene)-β-alaninate (**3b**, $C_{11}H_{11}ClN_2O_4$)
Yield 91 %; m.p.: 66–67 °C (*i*-PrOH); ^1H NMR: $\delta = 2.73$ (t, $J = 6.4$ Hz, 2H, CH_2CO_2), 3.64 (s, 3H, CH_3), 3.93 (t, $J = 6.4$ Hz, 2H, C=NCH_2), 7.75 (d, $J = 8.4$ Hz, 1H, H-3), 8.26 (dd, $J = 8.4$, 2.8 Hz, 1H, H-4), 8.69 (d, $J = 2.8$ Hz, 1H, H-6), 8.73 (s, 1H, CH=N) ppm; ^{13}C NMR: $\delta = 36.1$, 52.1, 56.5, 123.1, 126.9, 132.3, 134.4, 140.8, 147.3, 157.3, 172.5 ppm; IR (KBr): $\bar{\nu} = 1{,}741$ (C=O), 1,635 (C=N), 1,525 (NO_2), 1,348 (NO_2) cm^{-1}.

Methyl 4-[[(1E)-(2-chloro-5-nitrophenyl) methylene]amino]butanoate (**3c**, $C_{12}H_{13}ClN_2O_4$)
Yield 88 %; m.p.: 61–62 °C (*i*-PrOH); ^1H NMR: $\delta = 1.98$ (quin, $J = 6.8$ Hz, 2H, CCH_2C), 2.41 (t, $J = 6.8$ Hz, 2H, CH_2CO_2), 3.62 (s, 3H, CH_3), 3.72 (t, $J = 6.8$ Hz, 2H, NCH_2), 7.75 (d, $J = 8.8$ Hz, 1H, H-3), 8.26 (dd, $J = 8.8$, 2.8 Hz, 1H, H-4), 8.69 (s, 1H, CH=N), 8.71 (d, $J = 2.8$ Hz, 1H, H-6) ppm; ^{13}C NMR: $\delta = 25.9$, 31.5, 51.6, 60.0, 122.8, 126.4, 132.0, 134.2, 140.4, 147.0, 156.2, 173.5 ppm; IR (KBr): $\bar{\nu} = 1{,}734$ (C=O), 1,634 (C=N), 1,522 (NO_2), 1,349 (NO_2) cm^{-1}.

Methyl N-(2-chloro-5-nitrobenzylidene)phenylalaninate (**3f**, $C_{17}H_{15}ClN_2O_4$)
Yield 58 %; m.p.: 103–105 °C (*n*-PrOH); ^1H NMR: $\delta = 3.07$ (m, 1H), 3.31 (m, 1H), 3.68 (s, 3H, CH_3), 4.60 (m, 1H), 7.21 (m, 5H, C_6H_5), 7.80 (d, $J = 8.8$ Hz, 1H, H-3), 8.29 (dd, $J = 2.8$, 8.8 Hz, 1H, H-4), 8.45 (s, 1H, CH=N), 8.62 (d, $J = 2.8$ Hz, 1H, H-6) ppm; ^{13}C NMR: $\delta = 39.2$, 52.4, 73.1, 122.8, 126.9, 127.0, 128.6, 129.9, 132.0, 133.7, 137.3, 140.6, 147.0, 158.9, 171.4 ppm; IR (KBr): $\bar{\nu} = 1{,}743$ (C=O), 1,644 (C=N), 1,522 (NO_2), 1,347 (NO_2) cm^{-1}.

*Preparation of esters of N-(2-chloro-5-nitrobenzyl)amino acids **4** (reduction)*

To a stirred at 0 °C solution of Schiff base **3b**, **3c**, **3f** (0.05 mol) in 90 $cm^{3,}$ MeOH was added to $NaBH_4$ (0.05 mol) by portions. The reaction mixture was stirred for 5 h, evaporated and quenched with water. The product

was extracted with CH_2Cl_2. After being dried over $MgSO_4$, removal of the solvent in vacuo gave oil. To the oil, 20 cm^3 *i*-PrOH and 6 cm^3 HCl were added. The precipitate was collected by filtration, washed with *i*-PrOH and dried to give the title compounds **4b**, **4c**, **4f** (yield 48–78 %).

*Preparation of esters of N-(2-chloro-5-nitrobenzyl)amino acids **4** (alkylation)*

To a stirred solution of 2-chloro-5-nitrobenzylchloride (**6**, 0.05 mol) and hydrochloride of amino acid ester **2a**–**2f** (0.06 mol) in DMF were added 0.15 mol Et_3N and 0.05 mol NaI. The reaction mixture was stirred at 80–90 °C for 15 h and evaporated in vacuo. The residue was quenched with water and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated at reduced pressure. To the residue, 20 cm^3 *i*-PrOH and 6 cm^3 HCl were added. The precipitate was collected by filtration, washed with *i*-PrOH, and dried to give the respective compounds **4a**–**4f** in 58–86 % yields. Yields of esters **4a**–**4f** for both methods are shown in Table 1.

Methyl N-(2-chloro-5-nitrobenzyl)glycinate hydrochloride (**4a**, $C_{10}H_{12}Cl_2N_2O_4$)
M.p.: 175–177 °C (*i*-PrOH); ^{1}H NMR: $\delta = 3.80$ (s, 3H, CH_3), 4.02 (s, 2H, CH_2), 4.45 (s, 2H, CH_2), 7.77 (d, $J = 8.8$ Hz, 1H, H-3), 8.25 (dd, $J = 8.8$, 2.8 Hz, 1H, H-4), 8.81 (d, $J = 2.8$ Hz, 1H, H-6), 10.45 (br s, 2H, NH_2) ppm; ^{13}C NMR: $\delta = 48.0$, 48.4, 52.9, 125.3, 126.6, 131.5, 135.4, 140.9, 147.0, 169.7 ppm; IR (KBr): $\bar{\nu} = 1{,}744$ (C=O), 1,526 (NO_2), 1,345 (NO_2) cm^{-1}.

Methyl N-(2-chloro-5-nitrobenzyl)-β-alaninate hydrochloride (**4b**, $C_{11}H_{14}Cl_2N_2O_4$)
M.p.: 201–203 °C (*i*-PrOH); ^{1}H NMR: $\delta = 2.93$ (t, $J = 7.6$ Hz, 2H, CH_2CO_2), 3.25 (t, $J = 7.6$ Hz, 2H, NCH_2CH_2), 3.68 (s, 3H, CH_3), 4.38 (s, 2H, CH_2N), 7.77 (d, $J = 8.4$ Hz, 1H, H-3), 8.25 (dd, $J = 8.4$, 2.4 Hz, 1H, H-4), 8.79 (d, $J = 2.4$ Hz, 1H, H-6), 10.15 (br s, 2H, NH_2) ppm; ^{13}C NMR: $\delta = 31.0$, 43.1, 47.3, 52.1, 125.4, 126.7, 131.3, 133.4, 140.8, 146.6, 171.0 ppm; IR (KBr): $\bar{\nu} = 1{,}747$ (C=O), 1,529 (NO_2), 1,347 (NO_2) cm^{-1}.

Methyl 4-[(2-chloro-5-nitrobenzyl)amino]butanoate hydrochloride (**4c**, $C_{11}H_{14}Cl_2N_2O_4$)
M.p.: 155–157 °C (*i*-PrOH); ^{1}H NMR: $\delta = 1.97$ (m, 2H, CH_2), 2.47 (t, $J = 6.8$ Hz, 2H, CH_2), 3.05 (t, $J = 7.2$ Hz, 2H, CH_2), 3.61 (s, 3H, CH_3), 4.37 (s, 2H, CH_2), 7.87 (d, $J = 8.8$ Hz, 1H, H-3), 8.28 (d, $J = 8.8$ Hz, 1H, H-4), 8.74 (s, 1H, H-6), 9.70 (br s, 2H, NH_2) ppm; ^{13}C NMR: $\delta = 21.6$, 30.9, 47.0, 47.2, 52.2, 126.0, 127.5, 131.7, 132.7, 141.3, 146.9, 173.3 ppm; IR (KBr): $\bar{\nu} = 1{,}738$ (C=O), 1,525 (NO_2), 1,347 (NO_2) cm^{-1}.

Methyl N-(2-chloro-5-nitrobenzyl)alaninate hydrochloride (**4d**, $C_{11}H_{14}Cl_2N_2O_4$)
M.p.: 157–159 °C (*i*-PrOH); ^{1}H NMR: $\delta = 1.65$ (d, $J = 7.2$ Hz, 3H, CH_3), 3.81 (s, 3H, OCH_3), 4.24 (q, $J = 7.2$ Hz, 1H, CH), 4.44 (s, 2H, CH_2), 7.77 (d, $J = 8.0$ Hz, 1H, H-3), 8.26 (d, $J = 8.0$ Hz, 1H, H-4), 8.87 (s, 1H, H-6), 10.63 (br s, 2H, NH_2) ppm; ^{13}C NMR: $\delta = 34.7$, 46.3, 53.5, 55.7, 125.8, 127.5, 131.6, 133.8, 141.3, 146.8, 171.3 ppm; IR (KBr): $\bar{\nu} = 1{,}752$ (C=O), 1,534 (NO_2), 1,349 (NO_2) cm^{-1}.

Ethyl N-(2-chloro-5-nitrobenzyl)leucinate (**4e**, $C_{15}H_{21}ClN_2O_4$)
M.p.: 53–55 °C (*i*-PrOH); ^{1}H NMR: $\delta = 0.91$ (dd, $J = 19.6$, 6.4 Hz, 6H, $CH(CH_3)_2$), 1.25 (t, $J = 6.8$ Hz, 3H, CH_2CH_3), 1.47 (m, 2H, $CHCH_2CH$), 1.85 (m, 1H, $CH_2CH(CH_3)_2$), 3.20 (t, $J = 6.8$ Hz, 1H, NCH), 3.71 (d, $J = 16$ Hz, 1H, C*H*HN), 3.93 (d, $J = 16$ Hz, 1H, CH*H*N), 4.01 (q, $J = 6.8$ Hz, 2H, CH_2CH_3), 7.63 (d, $J = 8.4$ Hz, 1H, H-3), 8.09 (dd, $J = 8.4$, 2.4 Hz, 1H, H-4), 8.43 (d, $J = 2.4$ Hz, 1H, H-6) ppm; ^{13}C NMR: $\delta = 14.8$, 22.5, 23.5, 25.1, 42.8, 48.5, 59.6, 60.5, 123.4, 124.6, 130.7, 140.0, 140.8, 147.0, 175.2 ppm; IR (KBr): $\bar{\nu} = 1{,}736$ (C=O), 1,521 (NO_2), 1,344 (NO_2) cm^{-1}.

Methyl N-(2-chloro-5-nitrobenzyl)phenylalaninate hydrochloride (**4f**, $C_{17}H_{18}Cl_2N_2O_4$)
M.p.: 199–201 °C (*n*-PrOH); ^{1}H NMR: $\delta = 3.14$ (m, 1H), 3.53 (m, 1H), 3.59 (s, 3H, CH_3), 4.30–4.40 (m, 3H), 7.27 (m, 5H, C_6H_5), 7.84 (d, $J = 8.8$ Hz, 1H, H-9), 8.27 (d, $J = 8.8$ Hz, 1H, H-8), 8.74 (s, 1H, H-6), 10.2 (br s, 2H, NH_2) ppm; ^{13}C NMR: $\delta = 46.5$, 46.8, 53.2, 61.5, 125.9, 127.8, 127.9, 129.2, 129.9, 131.6, 133.0, 135.9, 141.5, 148.8, 172.1 ppm; IR (KBr): $\bar{\nu} = 1{,}745$ (C=O), 1,527 (NO_2), 1,347 (NO_2) cm^{-1}.

*Preparation of (7-nitro-3-oxo-2,3-dihydro-1,4-benzothiazepin-4(5H)-yl)carboxylic acids **9** and esters **8***

To a stirred solution of *N*-(2-chloro-5-nitrobenzyl)amino acid hydrochloride **4a**–**4f** (0.05 mol) and 20.9 cm^3 Et_3N (0.15 mol) in 25 cm^3 DMSO was added 4.5 cm^3 methyl thioglycolate (0.05 mol). After being stirred at 60 °C for 5 h, the reaction mixture was evaporated, quenched with 250 cm^3 water, and extracted with CH_2Cl_2. The extract was washed with brine. After being dried over $MgSO_4$, removal of the solvent in vacuo gave the oil. This oil was taken up in 50 cm^3 of *o*-xylene, and the solution was refluxed for 3 h. The solvent was evaporated in vacuo. The residue was quenched with an aqueous solution of $NaHCO_3$. The precipitate was collected by filtration, washed with H_2O, and dried to give esters **8a**, **8b**, **8d**, **8e**. The filtrate was stirred with C act., filtered, and acidified

with HCl to pH 6. The precipitate was filtered, washed with H_2O, and dried to obtain acids **9a**–**9c**, **9e**, **9f**.

Methyl (7-nitro-3-oxo-2,3-dihydro-1,4-benzothiazepin-4(5H)-yl)acetate (**8a**, $C_{12}H_{12}N_2O_5S$)
Yield 68 %; m.p.: 171–173 °C (*i*-PrOH); ^{1}H NMR: $\delta = 3.62$ (s, 3H, CH_3), 4.14 (s, 2H, CH_2), 4.19 (s, 2H, 2-CH_2), 4.89 (s, 2H, 5-CH_2), 7.32 (d, $J = 8.4$ Hz, 1H, H-9), 7.97 (d, $J = 8.4$ Hz, 1H, H-8), 8.18 (s, 1H, H-6) ppm; ^{13}C NMR: $\delta = 32.1$, 48.5, 51.4, 52.5, 123.5, 125.8, 128.2, 133.3, 144.4, 146.0, 168.9, 170.0 ppm; IR (KBr): $\bar{\nu} = 1{,}748$ (C=O), 1,660 (C=O), 1,522 (NO_2), 1,344 (NO_2) cm^{-1}.

Methyl 3-(7-nitro-3-oxo-2,3-dihydro-1,4-benzothiazepin-4(5H)-yl)propanoate (**8b**, $C_{13}H_{14}N_2O_5S$)
Yield 65 %; m.p.: 141–143 °C (*i*-PrOH); ^{1}H NMR: 2.48 (t, $J = 7.2$ Hz, 2H, CH_2), 3.56 (s, 3H, CH_3), 3.62 (t, $J = 7.2$ Hz, 2H, CH_2), 4.05 (s, 2H, 2-CH_2), 4.82 (s, 2H, 5-CH_2), 7.31 (d, $J = 8.4$ Hz, 1H, H-9), 7.97 (dd, $J = 8.4$, 2.4 Hz, 1H, H-8), 8.22 (d, $J = 2.4$ Hz, 1H, H-6) ppm; ^{13}C NMR: $\delta = 32.5$, 33.0, 43.0, 50.7, 52.0, 123.6, 125.8, 128.3, 133.7, 144.5, 145.9, 168.4, 172.0 ppm; IR (KBr): $\bar{\nu} = 1{,}741$ (C=O), 1,656 (C=O), 1,516 (NO_2), 1,339 (NO_2) cm^{-1}.

Methyl 2-(7-nitro-3-oxo-2,3-dihydro-1,4-benzothiazepin-4(5H)-yl)propanoate (**8d**, $C_{13}H_{14}N_2O_5S$)
Yield 60 %; m.p.: 121–123 °C (*i*-PrOH); ^{1}H NMR: $\delta = 1.33$ (d, $J = 7.2$ Hz, 3H, CH_3), 3.52 (s, 3H, OCH_3), 3.85 (d, $J = 14.0$ Hz, 1H), 4.36 (d, $J = 14.0$ Hz, 1H), 4.77 (d, $J = 17.2$ Hz, 1H), 4.93 (m, 2H), 7.31 (d, $J = 8.4$ Hz, 1H, H-9), 7.96 (d, $J = 8.4$ Hz, 1H, H-8), 8.21 (s, 1H, H-6) ppm; ^{13}C NMR: $\delta = 15.7$, 32.2, 48.5, 52.5, 53.9, 123.4, 125.6, 128.3, 134.1, 144.5, 145.7, 169.0, 171.9 ppm; IR (KBr): $\bar{\nu} = 1{,}729$ (C=O), 1,656 (C=O), 1,510 (NO_2), 1,333 (NO_2) cm^{-1}.

Ethyl 4-methyl-2-(7-nitro-3-oxo-2,3-dihydro-1,4-benzothiazepin-4(5H)-yl)pentanoate (**8e**, $C_{17}H_{22}N_2O_5S$)
Yield 50 %; m.p.: 116–118 °C (*i*-PrOH); ^{1}H NMR: $\delta = 0.57$ (d, $J = 5.6$ Hz, 3H, CH_3), 0.78 (d, $J = 5.6$ Hz, 3H, CH_3), 1.04 (m, 4H), 1.58–1.88 (m, 2H, CH_2), 3.91 (m, 3H), 4.60 (d, $J = 12.4$ Hz, 1H), 4.73 (d, $J = 17.2$ Hz, 1H), 5.08 (m, 2H), 7.41 (d, $J = 8.4$ Hz, 1H, H-9), 7.99 (d, $J = 8.4$ Hz, 1H, H-8), 8.34 (s, 1H, H-6) ppm; ^{13}C NMR: $\delta = 14.1$, 21.4, 23.0, 24.3, 31.7, 37.7, 47.5, 55.3, 61.1, 122.9, 125.5, 128.0, 133.7, 144.2, 145.5, 169.7, 171.0 ppm; IR (KBr): $\bar{\nu} = 1{,}722$ (C=O), 1,649 (C=O), 1,519 (NO_2), 1,336 (NO_2) cm^{-1}.

(7-Nitro-3-oxo-2,3-dihydro-1,4-benzothiazepin-4(5H)-yl)acetic acid (**9a**, $C_{11}H_{10}N_2O_5S$)
Yield 25 %; m.p.: 223–225 °C (H_2O); ^{1}H NMR: $\delta = 4.08$ (s, 2H, CH_2), 4.13 (s, 2H, 2-CH_2), 4.85 (s, 2H, 5-CH_2), 7.31 (d, $J = 8.8$ Hz, 1H, H-9), 7.97 (d, $J = 8.8$ Hz, 1H, H-8), 8.21 (s, 1H, H-6), 12.53 (br s, 1H, CO_2H) ppm; ^{13}C NMR: $\delta = 32.5$, 48.3, 51.5, 123.1, 125.8, 127.9, 133.3, 144.5, 145.8, 168.3, 170.6 ppm; IR (KBr): $\bar{\nu} = 1{,}717$ (C=O), 1,653 (C=O), 1,518 (NO_2), 1,339 (NO_2) cm^{-1}.

3-(7-Nitro-3-oxo-2,3-dihydro-1,4-benzothiazepin-4(5H)-yl)propanoic acid (**9b**, $C_{12}H_{12}N_2O_5S$)
Yield 24 %; m.p.: 189–191 °C (H_2O); ^{1}H NMR: $\delta = 2.41$ (t, $J = 7.2$ Hz, 2H, CH_2), 3.58 (t, $J = 7.2$ Hz, 2H, CH_2), 4.05 (s, 2H, 2-CH_2), 4.82 (s, 2H, 5-CH_2), 7.31 (d, $J = 8.8$ Hz, 1H, H-9), 7.97 (dd, $J = 8.8$, 2.4 Hz, 1H, H-8), 8.21 (d, $J = 2.4$ Hz, 1H, H-6), 12.08 (br s, 1H, CO_2H) ppm; ^{13}C NMR: $\delta = 32.3$, 33.0, 42.7, 50.5, 123.3, 125.4, 128.0, 133.5, 144.2, 145.5, 167.9, 172.8 ppm; IR (KBr): $\bar{\nu} = 1{,}740$ (C=O), 1,645 (C=O), 1,517 (NO_2), 1,340 (NO_2) cm^{-1}.

4-(7-Nitro-3-oxo-2,3-dihydro-1,4-benzothiazepin-4(5H)-yl)butanoic acid (**9c**, $C_{13}H_{14}N_2O_5S$)
Yield 76 %; m.p.: 170–172 °C (H_2O); ^{1}H NMR: $\delta = 1.65$ (m, 2H, CH_2), 2.09 (t, $J = 6.4$ Hz, 2H, CH_2), 3.36 (t, $J = 6.4$ Hz, 2H, CH_2), 4.13 (s, 2H, 2-CH_2), 4.81 (s, 2H, 5-CH_2), 7.38 (d, $J = 8.0$ Hz, 1H, H-9), 7.98 (d, $J = 8.0$ Hz, 1H, H-8), 8.25 (s, 1H, H-6), 12.08 (br s, 1H, CO_2H) ppm; ^{13}C NMR: $\delta = 23.9$, 31.3, 32.6, 45.8, 50.4, 123.6, 125.7, 128.3, 133.9, 144.5, 145.9, 168.3, 174.6 ppm; IR (KBr): $\bar{\nu} = 1{,}741$ (C=O), 1,631 (C=O), 1,516 (NO_2), 1,340 (NO_2) cm^{-1}.

4-Methyl-2-(7-nitro-3-oxo-2,3-dihydro-1,4-benzothiazepin-4(5H)-yl)pentanoic acid (**9e**, $C_{15}H_{18}N_2O_5S$)
Yield 40 %; m.p.: 238–240 °C (H_2O); ^{1}H NMR: $\delta = 0.52$ (d, $J = 6.4$ Hz, 3H, CH_3), 0.80 (d, $J = 6.4$ Hz, 3H, CH_3), 0.99 (m, 1H, $CH(CH_3)_2$), 1.57–1.80 (m, 2H, CH_2), 3.54 (d, $J = 14.0$ Hz, 1H), 4.57 (d, $J = 17.6$ Hz, 1H), 4.71 (d, $J = 14.0$ Hz, 1H), 5.07 (dd, $J = 11.2$, 2.8 Hz, 1H), 5.14 (d, $J = 17.6$ Hz, 1H), 7.31 (d, $J = 8.8$ Hz, 1H), 7.95 (d, $J = 8.8$ Hz, 1H), 8.25 (s, 1H), 12.61 (br s, 1H, CO_2H) ppm; ^{13}C NMR: $\delta = 21.7$, 23.3, 24.7, 32.4, 38.7, 48.0, 55.3, 122.9, 125.6, 127.9, 134.1, 144.6, 145.5, 169.8, 173.0 ppm; IR (KBr): $\bar{\nu} = 1{,}728$ (C=O), 1,623 (C=O), 1,519 (NO_2), 1,339 (NO_2) cm^{-1}.

2-(7-Nitro-3-oxo-2,3-dihydro-1,4-benzothiazepin-4(5H)-yl)-3-phenylpropanoic acid (**9f**, $C_{18}H_{16}N_2O_5S$)
Yield 57 %; m.p.: 238–240 °C (H_2O); ^{1}H NMR: $\delta = 3.11$ (d, $J = 14.0$ Hz, 1H), 3.23 (dd, $J = 3.6$, 14.0 Hz, 1H), 4.02 (d, $J = 14.4$ Hz, 1H), 4.15 (d, $J = 14.4$ Hz, 1H), 4.69 (d, $J = 17.6$ Hz, 1H), 4.86 (d, $J = 17.6$ Hz, 1H), 4.97 (m, 1H), 6.92 (m, 5H, C_6H_5), 7.16 (d, $J = 8.8$ Hz, 1H, H-9), 7.83 (d, $J = 8.8$ Hz, 1H, H-8), 7.93 (s, 1H, H-6), 12.85 (br s, 1H, CO_2H) ppm; ^{13}C NMR: $\delta = 32.2$, 34.8, 50.5, 61.4, 122.9, 125.7, 126.4, 127.8, 128.4, 129.1, 133.4, 138.2,

144.4, 145.6, 169.5, 172.2 ppm; IR (KBr): $\bar{\nu} = 1{,}734$ (C=O), 1,619 (C=O), 1,519 (NO_2), 1,339 (NO_2) cm^{-1}.

X-ray diffraction study of compounds ***8a*** *and* ***8b***

Intensities of reflections were measured on an automatic «Xcalibur 3» diffractometer (graphite monochromated $Mo_{K\alpha}$ radiation, CCD-detector, ω scanning). All structures were solved by the direct method using SHELX97 package [15]. Positions of the hydrogen atoms were located from electron density difference maps and refined by "riding" model with $U_{iso} = nU_{eq}$ of a carrier non-hydrogen atom ($n = 1.5$ for methyl group and $n = 1.2$ for other hydrogen atoms). Full-matrix least-squares refinement against F^2 was performed for non-hydrogen atoms using anisotropic approximation. Final atomic coordinates, geometrical parameters, and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk). CCDC dep. numbers for structures **8a** and **8b** are 918768 and 918767, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/products/csd/request/.

Crystal data for **8a** at 293 K: $C_{12}H_{12}N_2O_5S$, $M = 296.30$, $a = 15.4768(5)$ Å, $b = 7.9854(3)$ Å, $c = 22.1580(7)$ Å, $\beta = 105.811(3)°$, $V = 2{,}634.86(15)$ $Å^3$, space group $C2/c$, $Z = 8$, $D_c = 1.494$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 0.267$ mm^{-1}, $F(000) = 1{,}232$. 14,990 reflections measured up to $2\theta_{max} = 60.0°$, 3,814 unique ($R_{int} = 0.0175$) which were used in all calculations. Refinement was converged at $wR_2 = 0.1190$ (all data), $R_1 = 0.0430$ (2,911 reflections with $I > 2\sigma(I)$), GoF = 1.06.

Crystal data for **8b** at 293 K: $C_{13}H_{14}N_2O_5S$, $M = 310.32$, $a = 9.5672(8)$ Å, $b = 15.2463(11)$ Å, $c = 9.9204(8)$ Å, $\beta = 102.024(8)°$, $V = 1{,}415.29(19)$ $Å^3$, space group $P2_1/c$, $Z = 4$, $D_c = 1.456$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 0.252$ mm^{-1}, $F(000) = 648$. 10,070 reflections measured up to $2\theta_{max} = 50.0°$, 2,483 unique ($R_{int} = 0.0535$), which were used in all calculations. Refinement was converged at $wR_2 = 0.1971$ (all data), $R_1 = 0.0666$ (1,748 reflections with $I > 2\sigma(I)$), GoF = 1.04.

References

1. Levai A (1986) Chem Heterocycl Compd 11:1161
2. Levai A (2000) J Heterocycl Chem 37:199
3. Bariwal JB, Upadhyay KD, Manvar AT, Trivedi JC, Singh JS, Jain KS, Shah AK (2000) Eur J Med Chem 43:2279
4. Levai A, Kiss-Szikszai A (2008) Arkivoc (i):65
5. Maruenda H, Johnson F (1995) J Med Chem 38:2145
6. Kataoka T, Nakamura Y, Matsumoto H, Iwama T, Shimizu H, Maruoka O, Tanabe G (1997) Chem Pharm Bull 45:265
7. Neo AG, Marcos CF, Marcaccini F, Pepino R (2005) Tetrahedron Lett 46:7977
8. Kamei K, Maeda N, Nomura K, Shibata M, Katsuragi-Ogino R, Koyama M, Nakajima M, Inoue T, Ohno T, Tatsuoka T (2006) Bioorg Med Chem 14:1978
9. Volovnenko TA, Tarasyuk TN, Volovenko YuM (2011) Zh Org Farm Khim 9:60
10. Volovnenko TA, Tarasiuk TN, Volovenko YuM, Tkachuk TM (2011) Chem Heterocycl Compd 47:1043
11. Inada Y, Itoh K, Kamiya K, Sugihara H, Nishikawa K (1988) Jpn J Pharmacol 47:135
12. Amblard M, Daffix I, Bedos P, Berge G, Pruneau D, Paquet J-L, Luccarini J-M, Belichard P, Dodey P, Martinez J (1999) J Med Chem 42:4185
13. Park K-H, Olmstead MM, Kurth MJ (1998) J Org Chem 63:113
14. Alajarín M, Lopez-Leonardo C, Berna J (2006) Tetrahedron 62:6190
15. Sheldrick G (2008) Acta Crystallogr Sect A 64:112