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Boron complexes of *S*-trityl-L-cysteine and *S*-tritylglutathione

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Abstract

S-Trityl-L-cysteine and *S*-tritylglutathione have been converted to 1,3,2-oxazaborolidine-5-ones by reaction with *B*-methoxydialkylborane derivatives. The synthesis of dicyclohexyl[*S*-trityl-(*R*)-cysteinato-*O*,*N*]boron (**2**), diisopinocampheyl[*S*-trityl-(*R*)-cysteinato-*O*,*N*]boron (**3**) and 9-borabicyclo[3.3.1]non-9-yl[*S*-tritylglutathionato-*O*,*N*]boron (**5**), dicyclohexyl[*S*-tritylglutathionato-*O*,*N*]boron (**6**) and diisopinocampheyl[*S*-tritylglutathionato-*O*,*N*]boron (**7**) from *S*-trityl-L-cysteine and *S*-tritylglutathione, respectively, with potential application in boron neutron capture therapy is reported. The structure of 9-borabicyclo[3.3.1]non-9-yl[*S*-trityl-(*R*)-cysteinato-*O*,*N*]boron **1** has been determined by X-ray diffraction. © 2000 Published by Elsevier Science S.A. All rights reserved.

Keywords: Boron neutron capture therapy; Cancer; Glutathione

1. Introduction

Inorganic and organic boron compounds possess interesting pharmacological properties, such as hypolipidemic, anti-inflammatory, anti-osteoporosis, and antineoplastic activities [1]. There is much current interest in the synthesis of boron compounds with potential use in boron neutron capture therapy for the treatment of certain malignant cancers, such as melanoma and glioblastoma multiforme brain tumors [2]. The synthesis of boron derivatives of biomolecules such as amino acids, peptides, nucleosides, porphyrins and sugars is a major area of research [2, 3]. Boron neutron capture therapy is based on the selective delivery of a substance labeled with ^{10}B to a tumor before the area is irradiated by epithermal neutrons. Important necessary requirements of the designed compounds are that they possess the capability of penetrating the blood–brain barrier [4], have low toxicity, and achieve appropriate tumor concentration and differential concentration over normal tissues during the entire neutron irradiation period [2].

Two different strategies have been used with some success: either the synthesis of compounds containing a single boron atom or containing several boron atoms in the same molecule. Two boron compounds are currently being used clinically, 4-dihydroxyborylphenylalanine [5] (BPA) and sodium mercaptoundecahydrododecaborate [6] (BSH).

As early as 1964, *S*-(2-boronoethyl)-L-cysteine was synthesized, unfortunately with little success in boron neutron capture therapy because of extremely low boron levels in tissues [7]. To the best of our knowledge, no further studies on L-cysteine boron derivatives have been carried out. We first focused our attention on the use of boron complexes of (*R*)-thiazolidine-4-carboxylic acid derivatives [8]. Recent studies have shown that *S*-trityl-L-cysteine can act as a mitotic inhibitor even though it does not seem to interact directly with tubulin [9]. Although the precise mechanism of action of *S*-trityl-L-cysteine is not known, the fact that the amino acid portion of compound **1** may act as an active carrier for the transport of the trityl radical or used in protein synthesis, coupled with the complexation of a boron moiety makes this compound labeled with ^{10}B particularly attractive for biological studies offering a potential twofold action mechanism against tumors.

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2. Results

9-Borabicyclo[3.3.1]non-9-yl[*S*-trityl-(*R*)-cysteinato-*O*,*N*]boron **1** is readily available from *S*-trityl-L-cysteine by stirring with 9-methoxy-9-borabicyclo-[3.3.1]nonane in dichloromethane at room temperature (r.t.) for 24 h [8]. These conditions for the protection of the amino acid function are very mild and were profitably employed in the synthesis of dicyclohexyl[*S*-trityl-(*R*)-cysteinato-*O*,*N*]boron **2** and diisopinocampheyl[*S*-trityl-(*R*)-cysteinato-*O*,*N*]boron **3** by treatment of *S*-trityl-L-cysteine with dicyclohexylmethoxyborane and (−)-*B*-methoxydiisopinocampheylborane, respectively (Fig. 1).

In this context, as a part of our synthetic investigation of L-cysteine boron complexes, we initiated the study of small peptides incorporating this amino acid. The aim of our work was to synthesize boron-containing derivatives of *S*-tritylglutathione [10]. This molecule was chosen because of higher lipophilicity than glutathione so it might permeate the blood brain barrier and act as a carrier for the transport of the trityl group. This approach has also been exploited with L-cysteine and glutathione to carry organometallic side chains [11]. Glutathione (γ-Glu-L-Cys-Gly) is widely distributed in human tissues, serves as storage and transport of L-cysteine, participates in the synthesis of proteins and protects cells from the toxic effects of free radicals. There is currently much interest in modulation of glutathione levels during chemotherapy and radiotherapy [12].

Although the synthesis of *S*-tritylglutathione **4** has been described [10], we did not have experimental details at hand. Our initial attempts to use trityl alcohol in trifluoroacetic acid, followed by aqueous work-up met with little success [13]. We soon found, that addition of ether to the crude reaction mixture precipitates the desired *S*-tritylglutathione **4** in good yield. This compound was subsequently converted into the FMOC derivative **8** in good yield using standard conditions.

Addition of 9-methoxy-9-borabicyclo[3.3.1]nonane in acetonitrile to *S*-tritylglutathione **4** and heating the mixture at 70°C for 19 h in a closed reactor gives adduct **5** in which the boron moiety is coordinated to both amino and carboxylic groups. This chelation enhances the solubility of the peptide in organic solvents.

We then examined the reaction of *S*-tritylglutathione **4** with dicyclohexylmethoxyborane [14]. The reaction was run by adding the peptide to the freshly prepared borane at −20°C and heating the mixture in acetonitrile at 70°C for 19 h in a closed reactor. Removal of solvent followed by column chromatography on silylated silica gel [15] allowed the isolation of the boron complex **6**. Subsequently, reaction of *S*-tritylglutathione **4** with (−)-*B*-methoxydiisopinocampheylborane in acetonitrile at 75°C for 24 h in a closed reactor afforded the boron complex **7** in a moderate yield. Boron complexes **5**, **6** and **7** were isolated in reasonable yields after column chromatography and showed good stability in D_2O although their solubility is rather low, as shown in their ^{1}H-NMR spectra (Fig. 2).

An X-ray crystallography analysis of 9-borabicyclo[3.3.1]non-9-yl[*S*-trityl-(*R*)-cysteinato-*O*,*N*]boron (**1**) was performed after it was recrystallized from ethyl acetate. An ORTEP drawing of the structure of **1** is shown below (Fig. 3). The five membered 1,3,2-oxazaborolidine-5-one ring is not planar as demonstrated by the dihedral angles: B(1)–N(1)–C(2)–C(3) = −29.4(3); N(1)–C(2)–C(3)–O(1) = 6.1(3); B(1)–O(1)–C(3)–C(2) = 12.4(3) and C(3)–O(1)–B(1)–N(1) = −23.3(3). The boron atom is tetrahedrally coordinated with the bond angles ranging from 97.3 (2) to 114.4° (2) (Table 1).

3. Conclusions

Efficient syntheses of 1,3,2-oxazaborolidine-5-one derivatives from *S*-trityl-L-cysteine and *S*-tritylglutathione using 9-methoxy-9-borabicyclo[3.3.1]nonane, dicyclohexylmethoxyborane and (−)-*B*-methoxydiisopinocampheylborane are reported. The complexation reaction of the α-amino acid group is based on previous literature reports [16]. The remarkable feature of this method is that a large amount of optically pure intermediates are easily obtainable.

The synthesis of dicyclohexyl[*S*-trityl-(*R*)-cysteinato-*O*,*N*]boron (**2**), diisopinocampheyl[*S*-trityl-(*R*)-cysteinato-*O*,*N*]boron (**3**) and 9-Borabicyclo[3.3.1]non-9-yl[*S*-tritylglutathionato-*O*,*N*]boron (**5**), Dicyclohexyl[*S*-tritylglutathionato-*O*,*N*]boron (**6**) and diisopinocampheyl[*S*-tritylglutathionato-*O*,*N*]boron (**7**) from *S*-trityl-

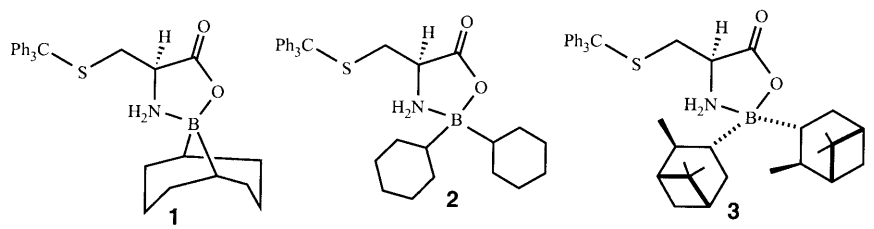

Fig. 1. Structures for the *S*-trityl-L-cysteine derivatives.

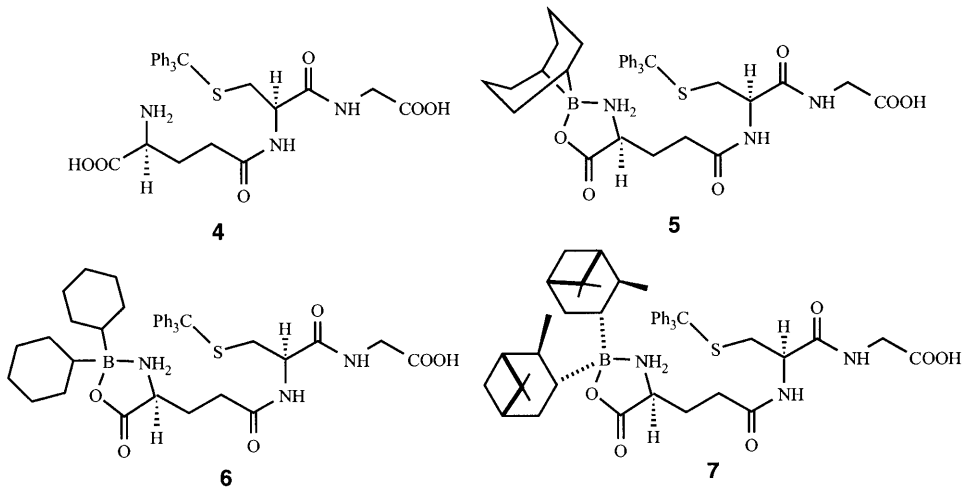

Fig. 2. Structures for the *S*-tritylglutathione derivatives.

L-cysteine and *S*-tritylglutathione **4** respectively, with potential application in boron neutron capture therapy is reported.

4. Experimental

4.1. Instruments and reagents

All solvents were dried by standard methods. All reagents were of commercial quality from freshly opened containers. M.p.s were obtained on a Gallenkamp melting point apparatus and are uncorrected. Unless otherwise noted, ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini 200 instrument at 200 and 50 MHz respectively, chemical shifts are reported in ppm downfield (δ) of tetramethylsilane internal standard. The assignments of ^{13}C-NMR signals were made with the aid of DEPT sequence. IR spectra were recorded on a Nicolet 205 FT infrared spectrophotometer, and noteworthy absorptions are listed (cm^{-1}). Chromatography refers to flash chromatography and was carried out on silylated [15] SiO_2 (silica gel 60, SDS, 230–400 mesh ASTM). Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona. Mass spectra were determined on a Hewlett–Packard 5930A mass spectrometer; ions are recorded as m/z with percentage abundances given in parentheses. MALDI–TOF mass spectra were used to confirm the purity and identity of the peptides (matrix: α-cyano-4-hydroxycinnamic acid), and were determined on a Bruker BIFLEX at the Faculty of Chemistry.

4.2. Preparation of 9-borabicyclo[3.3.1]non-9-yl[S-trityl-(R)-cysteinato-O,N]boron (1)

A mixture of 9-methoxy-9-borabicyclo[3.3.1]nonane (4 ml, 4 mmol, 1 M in hexane), and *S*-trityl-(*R*)-cysteine (1.45 g, 4 mmol) in 60 ml of CH_2Cl_2 under a nitrogen atmosphere was stirred at r.t. for 24 h. After evaporation of solvent, the orange solid was purified by recrystallization (ethyl acetate), the product was isolated by filtration, as white needles with m.p. 196–7°C in 87% yield (1.68 g).

4.3. Preparation of dicyclohexyl[S-trityl-(R)-cysteinato-O,N]boron (2)

A mixture of dicyclohexylmethoxyborane [14] (1.25 mmol), prepared from 0.25 ml (2.5 mmol) of cyclohexene and 1.25 ml (1.25 mmol) of borane in THF (1 M) and 0.5 ml of methanol, *S*-trityl-(*R*)-cysteine (0.363 g, 1 mmol) in 15 ml of CH_2Cl_2 was stirred at r.t. for 12 h under argon atmosphere. After evaporation of solvent,

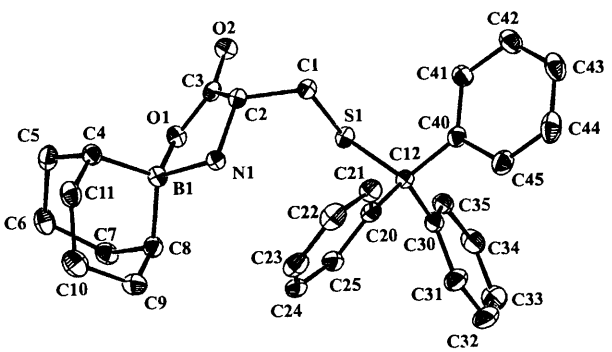

Fig. 3. ORTEP drawing of compound **1**.

Table 1
Selected bond lengths (Å) and angles (°) for **1**

O(1)–C(3)	1.293(4)
O(1)–B(1)	1.542(4)
O(2)–C(3)	1.212(3)
N(1)–C(2)	1.480(4)
N(1)–B(1)	1.632(4)
B(1)–C(8)	1.580(5)
B(1)–C(4)	1.599(4)
C(1)–C(2)	1.525(4)
C(2)–C(3)	1.529(4)
S(1)–C(1)	1.821(3)
S(1)–C(12)	1.856(3)
C(1)–S(1)–C(12)	104.68(13)
C(3)–O(1)–B(1)	113.5(2)
C(2)–N(1)–B(1)	106.4(2)
O(1)–B(1)–C(8)	112.3(2)
O(1)–B(1)–C(4)	109.4(2)
C(8)–B(1)–C(4)	108.7(2)
O(1)–B(1)–N(1)	97.3(2)
C(8)–B(1)–N(1)	114.4(2)
C(4)–B(1)–N(1)	114.4(2)
C(2)–C(1)–S(1)	111.61(19)
N(1)–C(2)–C(3)	104.0(2)
N(1)–C(2)–C(1)	114.9(2)
C(3)–C(2)–C(1)	111.2(2)
O(2)–C(3)–O(1)	125.5(3)
O(2)–C(3)–C(2)	122.7(3)
O(1)–C(3)–C(2)	111.8(2)

the white solid was triturated with (2:1) hexane–ether and isolated by filtration, m.p. 153–55°C in 79% yield (0.43 g).

4.4. Preparation of diisopinocampheyl[S-trityl-(R)-cysteinato-O,N]boron (3)

A mixture of (−)-*B*-methoxydiisopinocampheylborane (0.395 g, 1.25 mmol), and *S*-trityl-(*R*)-cysteine (0.363 g, 1 mmol) in 15 ml of CH_2Cl_2 was stirred at r.t. for 12 h under argon atmosphere. After evaporation of solvent, the white solid was triturated with (2:1) hexane–ether and isolated by filtration, m.p. 147–8°C in 79% yield (0.51 g).

4.5. Preparation of S-tritylglutathione trifluoroacetate (4)

To a mixture of glutathione (0.5 g, 1.63 mmol) and triphenylmethanol (0.43 g, 1.63 mmol), trifluoroacetic acid (3 ml) was added under stirring. The resulting red mixture was stirred at r.t. for 1 h and then ether (25 ml) was added. The resulting white solid was filtered and washed with ether (2 × 5 ml) and dried under vacuum to yield 0.8 g (74%).

4.6. Preparation of 9-borabicyclo[3.3.1]non-9-yl[S-tritylglutathionato-O,N]boron (5)

A mixture of 9-methoxy-9-borabicyclo[3.3.1]nonane (1.2 ml, 1.2 mmol,1 M in hexanes), and *S*-tritylglutathione trifluoroacetate (**4**) (0.6 g, 0.9 mmol) in 30 ml of acetonitrile was heated at 70°C for 19 h under argon atmosphere in a closed reactor. After evaporation of solvent, the residue was column chromatographed on silylated silica gel (ether) to give compound **5** (0.4 g, 66%) as white foam after solvent evaporation.

4.7. Preparation of dicyclohexyl[S-tritylglutathionato-O,N]boron (6)

A mixture of dicyclohexylmethoxyborane [14] (1 mmol), prepared from 0.2 ml (2 mmol) of cyclohexene and 1 ml (1 mmol) of borane in THF (1 M), and *S*-tritylglutathione trifluoroacetate (**4**) (0.44 g, 0.66 mmol) in 25 ml of acetonitrile under argon atmosphere was heated at 70°C for 19 h. After evaporation of solvent, the residue was column chromatographed on silylated silica gel (ether–hexane 1:1) to give compound **6** (0.33 g, 69%) as white flakes after solvent evaporation.

4.8. Preparation of diisopinocampheyl[S-tritylglutathionato-O,N]boron (7)

A mixture of (−)-*B*-methoxydiisopinocampheylborane (0.2 g, 0.63 mmol), and *S*-tritylglutathione trifluoroacetate (**4**) (0.33 g, 0.49 mmol) in 15 ml of acetonitrile was heated at 75°C for 24 h under argon atmosphere in a closed reactor. After evaporation of solvent, the residue was column chromatographed on silylated silica gel (ether–hexane 1:1) to give compound **7** (0.3 g, 73%) as white flakes after solvent evaporation.

4.9. Preparation of N-(fluoren-9-ylmethoxycarbonyl)-S-tritylglutathione (8)

S-tritylglutathione trifluoroacetate (**4**) (0.35 g, 0.53 mmol) was dissolved in 10% aqueous sodium carbonate (4 ml) and dioxane (4 ml) with stirring at 0°C, followed by fluoren-9-ylmethyl chloroformate [17] (0.14 g, 0.54 mmol) in three portions during 30 min. The reaction mixture was stirred for 1 h at 0°C and at r.t. overnight, then poured into ice-water (40 ml) and extracted with ether. The aqueous solution is cooled and acidified carefully with 6 M HCl. The mixture is stored in the refrigerator overnight, decanted and the oily residue dried under vacuum. The product was isolated as white foam (0.33 g, 81%) after solvent evaporation which could not be crystallized.

4.10. X-ray crystal structure determination of **1**

Intensity data for **1** were collected on a Nonius-Mach3 diffractometer equipped with a graphite monochromated Mo–K_α radiation ($\lambda = 0.71073$ Å) using an $\omega/2\theta$ scan technique to a maximum value of 58°. Crystals are orthorhombic of space group $P2_12_12_1$ with one molecule ($C_{30}H_{34}BNO_2S$; formula weight, 483.44) per unit cell. Unit-cell parameters were obtained from a least-squares fit to automatically centered settings for 25 reflections: $a = 9.952(5)$, $b = 14.4933(7)$, $c = 18.633(9)$ Å; $V = 2687.6(14)$ Å^3, $Z = 4$, $D_{calc} = 1.190$ g cm^{-3}.

Data were corrected for Lorentz-polarization effects and for linear decay of the two periodically measured reference reflections. No absorption correction was necessary ($\mu = 1.47$ cm^{-1}). The structure was solved by a combination of direct methods and Fourier synthesis and then refined by full-matrix least-squares (SHELXL-97, G.M. Sheldrick, Program for the refinement of Crystal Structures from Diffraction data, University of Göttingen, Germany, 1997). All non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were included in their calculated positions except H1 and H2 which were located in the difference-Fourier map and refined isotropically. Weights were optimized in the final refinement cycles. Refinement of 324 parameters against 6448 intensity data converged at $wR_2 = 0.1333$ and $R_1 = 0.0572$; $S = 1.068$. Maximum and minimum residual electron densities are 0.202 and -0.163 e A^{-3}.

4.11. Characterization data

1: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ (ppm): C_6H_5, 7.5–7.2 (m, 15H); NH, 3.6 (broad s, 1H); NH, 3.4 (broad s, 1H); CH (L–Cys), 3.14 (quint, 1H); CH_2–S, 3.00 (d, $J = 6.2$ Hz, 2H); CH_2, 2.0–1.2 (m, 12H); CH–B, 0.35 (broad s,2H). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ (ppm): 172.0 (C=O), 144.3 (C), 129.4 (CH), 128.4 (CH), 127.1 (CH), 66.7 (C), 53.9 (CH)(L–Cys), 31.9 (CH_2)(L–Cys), 31.5 (CH_2), 31.4 (CH_2), 30.8 (CH_2), 30.7 (CH_2), 24.5 (CH_2), 24.1 (CH_2), 23.2 (CH), 21.9 (CH).

2: IR (KBr): 3218, 3060, 2923, 1646, 1489, 1444, 1388, 742, 699 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 200 MHz): δ (ppm): C_6H_5, 7.4–7.2 (m, 15H); NH, 3.4 (m, 2H); CH (L–Cys), 2.9 (dd, $J = 4.0$ Hz, 8.4, 1H); CH_2–S, 2.6–2.3 (m, 2H); CH_2, 1.8–1.0 (m, 20H); CH–B, 0.3 (broad s,2H). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ (ppm): 168.7 (C=O), 144.4 (C), 129.3 (CH), 128.3 (CH), 126.9 (CH), 66.3 (C), 53.4 (CH)(L–Cys), 35.6 (CH_2), 33.5 (CH_2)(L–Cys), 28.2 (CH), 25.5 (CH_2), 23.9 (CH_2). MS: 243 (100), 228 (12), 215 (8), 165 (83), 115 (5), 77 (3). Elem. Anal.: $C_{34}H_{42}BNO_2S$ (539.21) requires: C, 75.67; H, 7.85; N, 2.59; Found: C, 75.45; H, 7.59; N, 2.78%. MALDI–TOF MS calculated: 562.2 $(M + Na)^+$; found: 561.9.

3: IR (KBr): 3200, 2900, 1650, 1490, 1444, 1200, 740, 700 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 200 MHz): δ (ppm): C_6H_5, 7.4–7.2 (m, 15H); NH, 3.8 (m, 2H); CH (L–Cys), 2.9 (dd, $J = 4.4$, 8.4 Hz, 1H); CH_2–S, 2.5–2.2 (m, 2H); CH_2/CH, 1.9–1.5 (m, 14 H); CH_3, 1.3–0.8 (m, 18H); CH–B, 0.8 (broad s, 2H). ^{13}C-NMR (DMSO-d_6, 50 MHz): δ (ppm): 169.2 (C=O), 144.1, 129.1, 128.1, 126.8, 66.1 (C), 53.1 (CH)(L–Cys), 47.4 (CH), 47.1 (CH), 41.3 (CH), 40.3 (CH_2), 37.9 (CH_2), 33.7 (CH_2)(L–Cys), 27.6 (CH_3), 23.6 (CH_3), 23.4 (CH),20.7 (CH_3). MS: 243 (100), 228 (13), 215 (9),165 (89), 119 (6), 77 (3). Elem. Anal.: $C_{42}H_{54}BNO_2S$ (647.30) requires: C, 77.86; H, 8.41; N, 2.16; found: C, 77.45; H, 8.29; N, 2.38%.

4: IR (KBr): 3380, 3058, 1731, 1660, 1546, 1202, 1144, 740, 701 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 200 MHz): δ (ppm): NH, 8.3 (2H); NH, 8.2 (2H); C_6H_5, 7.3–7.2 (15 H); CH, 4.4 (1H); CH, 3.8 (1H); CH_2 (Gly), 3.7 (2H); CH_2 (L–Cys)/CH_2, 2.5–2.3 (4H); CH_2, 2.0 (2H). ^{13}C-NMR (DMSO-d_6, 50 MHz): δ (ppm): 170.8 (C=O), 170.7 (C=O), 170.0 (C=O), 144.2 (C), 129.0 (CH), 128.0 (CH), 126.7 (CH), 65.8 (C), 51.8 (CH), 51.4 (CH), 40.8 (CH_2), 33.9 (CH_2), 30.6 (CH_2), 26.1 (CH_2). MALDI–TOF MS calculated: 550.3 $(M + H)^+$; found: 550.6.

5: IR (KBr): 3270, 2930, 2844, 1709, 1533, 1256, 1217, 740, 701 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ (ppm): NH, 8.3 (3H); C_6H_5, 7.4–7.2 (15H); NH, 6.4 (1H); NH, 6.1 (1H); CH, 4.4 (1H); CH, 3.7 (1H); CH_2 (Gly), 3.5 (2H); CH_2 (L–Cys)/CH_2, 2.4 (4H); CH_2, 2.0 (2H); CH_2 boron, 1.9–1.3 (12H); CH–B, 0.5 (1H); CH–B, 0.4 (1H). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ (ppm): 173.6 (C=O), 171.9 (C=O), 171.1 (C=O), 170.3 (C=O), 144.5 (C), 129.3 (CH), 128.2 (CH), 127.0 (CH), 66.0 (C), 54.2 (CH), 51.5 (CH), 40.9 (CH_2), 34.2 (CH_2), 31.9 (CH_2), 31.4 (CH_2), 31.0 (CH_2), 26.6 (CH_2), 24.5 (CH_2), 24.1 (CH_2), 23.7 (CH), 22.5 (CH). MALDI–TOF MS calculated: 692.2 $(M + Na)^+$; found: 692.3.

6: IR (KBr): 3400, 2921, 2847, 1706, 1530, 1445, 1211, 743, 701 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ (ppm): NH, 8.3 (3H); C_6H_5, 7.3–7.2 (15H); NH, 6.2 (1H); NH, 5.4 (1H); CH, 4.4 (1H); CH, 3.7 (1H); CH_2 (Gly), 3.3 (2H); CH_2 (L–Cys)/CH_2, 2.4 (4H); CH_2, 2.0 (2H); CH_2 boron, 1.8–0.8 (20H); CH–B, 0.3 (2H). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ (ppm): 173.8 (C=O), 172.1 (C=O), 171.0 (C=O), 170.2 (C=O), 144.4 (C), 129.2 (CH),128.2 (CH),126.9 (CH), 66.0 (C), 54.8 (CH), 51.5 (CH), 40.9 (CH_2), 34.1 (CH_2), 32.0 (CH_2), 29.2/28.6 (CH_2), 28.2/27.8 (CH_2), 27.5/27.1 (CH_2), 26.8 (CH_2), 23.2 (CH). MALDI–TOF MS calculated: 749.3 $(M + H + Na)^+$; found: 750.9.

7: IR (KBr): 3425, 3217, 2933, 1641, 1498, 1450, 1204, 743, 700 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ (ppm): NH, 8.4 (1H); NH, 8.2 (2H); C_6H_5, 7.4–7.2 (15H); NH, 6.2 (1H); NH, 5.2 (1H); CH, 4.4 (1H); CH_2 (Gly)/CH, 3.7 (3H); CH_2 (L–Cys)/CH_2, 2.4 (4H); CH_2, 2.1 (2H); CH_2/CH boron, 1.9–1.2 (14H); CH_3, 1.1 (6H); CH_3, 1.06 (3H); CH_3, 1.0 (3H); CH_3, 0.9 (d,

$J = 6.6$ Hz, 3H); CH_3, 0.90 (d, $J = 6.9$ Hz, 3H); CH–B, 0.5 (2H). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ (ppm): 173.4 (C=O), 172.7 (C=O), 171.0 (C=O), 170.2 (C=O), 144.5 (C), 129.3 (CH), 128.2 (CH), 127.0 (CH), 66.1 (C), 55.4 (CH), 51.9 (CH), 48.9 (CH), 41.6/41.4 (CH), 39.0/38.9 (CH), 38.6/37.7 (CH), 34.2 (CH_2), 32.4 (CH_2), 31.7/31.2 (CH_2), 29.5 (CH_2), 28.8/28.3 (CH_3), 25.9 (CH_2), 24.1/23.8 (CH_3), 23.0 (CH_3). MALDI–TOF MS calculated: 857.4 $(M + H + Na)^+$; found: 857.2.

8: IR (KBr): 3300, 3060, 2940, 1717, 1650, 1509, 1446, 1254, 1216, 741, 701 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ (ppm): NH, 8.2 (2H); C_6H_4, 7.9 (2H); C_6H_4, 7.7 (2H); C_6H_5, 7.4–7.2 (19H); CH, 4.4 (1H); CH_2/CH, 4.2 (3H); CH, 4.0 (1H); CH_2 (Gly), 3.7 (2H); CH_2, 2.4 (2H); CH_2, 2.3 (2H); 2.0 (1H), 1.8 (1H). ^{13}C-NMR (DMSO-d_6, 50 MHz): δ (ppm): 173.6 (C=O), 171.3 (C=O), 170.7 (C=O), 170.1 (C=O), 156.0 (O–CO–NH), 144.2 (C), 143.7 (C),140.6 (C), 129.0 (CH), 128.0 (CH), 127.6 (CH), 127.0 (CH), 126.7 (CH), 125.3 (CH), 120.1 (CH), 66.4 (CH_2), 65.8 (C), 53.5 (CH), 51.3 (CH), 46.7 (CH), 40.8 (CH_2), 33.9 (CH_2), 31.7 (CH_2), 26.8 (CH_2). MALDI–TOF MS calculated: 794.4 $(M + Na)^+$; found: 794.3.

5. Supplementary material

Crystallographic data (which include atomic coordinates, thermal parameters and complete set of bond lengths and angles) for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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