

## Short communication

# Synthesis of 4-(4-guanidinobenzoyloxy)benzamides and 1-(4-guanidinobenzoyloxy)benzoyloxy acetamides as trypsin inhibitors

P Zlatoidský, T Maliar

Drug Research Institute, SK-90001 Modra, Slovakia

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**Summary** — Seventeen new compounds of 4-(4-guanidinobenzoyloxy)benzamides and 4-(4-guanidinobenzoyloxy)benzoyloxyacetamides were prepared and their inhibitory activities on trypsin, thrombin and porcine pancreatic elastase were measured. These compounds were found to be selective trypsin inhibitors with inhibiting activities from 0.44 to 43  $\mu\text{M}$ .

serine protease / serine protease inhibitor / trypsin / 4-guanidinobenzoic acid derivatives

## Introduction

Sturzelbecker et al [1–7] published some derivatives of benzamidine and benzylamine as inhibitors of trypsin and thrombin along with quantitative structure–activity relationships (QSAR) analyses for this set of such compounds [8]. Derivatives of 6-amidino-2-naphthol [9], *N*-arylsulfonyl-4-amidinophenylalanine [10] and *N*-arylsulfonyl-4-amidinophenylglycine [11, 12] have also been described as strong thrombin and trypsin inhibitors. Esters and amides of *N*-arylsulfonyl arginines have been reported to be strong thrombin inhibitors [13] and a QSAR study of some sets of similar compounds has been published [14]. Phenol-esters of 4-guanidinobenzoic acid show strong inhibiting activity against trypsin [15]. Three compounds, Camostate mesylate (Foypan) [16], Gabexate mesylate [17] and Nafamostate mesylate (Futhan) [18], are used clinically against pancreatitis. This paper reports our results for the synthesis and inhibiting activities on trypsin of 4-(4-guanidinobenzoyloxy)benzamides and 1-(4-guanidinobenzoyloxy)benzoyloxyacetamides.

## Chemistry

Most of the synthetic methods for preparation of 4-hydroxybenzamides and 4-hydroxybenzoyloxyacetamides were described in our previous contribution [19]. Many intermediates were also described therein.

To avoid handling the irritating compound 4-acetoxybenzoyl chloride, we generated it in situ using oxalyl chloride and triethylamine [20]. The acylation of amides followed immediately in ‘one pot’ without

isolation of acetoxy derivatives. Deprotection of the phenol group was performed immediately and hydroxy derivatives **4a–m** were isolated (scheme 1). Final compounds **1a–m** were prepared by esterification of these hydroxy derivatives by 4-guanidinobenzoic acid via dicyclohexylcarbodiimide (DCC) coupling [9, 21]. The 4-hydroxybenzoyloxyacetamides **2** were prepared by a different method which is described in scheme 2. Intermediates **5a–d** and **6a–d** were prepared according to ref [19]. The structure of all intermediates and final compounds was confirmed by elemental analysis (see tables II–IV below).  $^1\text{H-NMR}$  spectral data are reported in table V (see below) [20].

## Conclusion

Inhibitory activities of prepared compounds **1a–m** and **2a–d** are presented in table I.

In the group **1a–m**, only two compounds, **1a** and **1h**, show micromolar inhibiting activity on trypsin. Among the second group **2a–d**, two compounds, **2a** and **2b**, show submicromolar inhibiting activity. Activities of **2c** and **2d** are about tenfold lower.

## Experimental protocols

### Chemistry

Melting points were measured on a Boetius apparatus and are uncorrected. Elemental analyses were carried out on a Carlo Erba 1106. NMR spectra were measured on a Varian 200 MHz. All chemicals were supplied by Merck and Lachema, and

**Table I.** Inhibiting activities of compounds **1a–m** and **2a–d** on trypsin in comparison with two clinically used standards.

Compound	$IC_{50}$ ( $\mu$ M)
<b>1a</b> <sup>a</sup>	6.92
<b>1b</b>	41.04
<b>1c</b>	22.15
<b>1d</b>	29.83
<b>1e</b>	25.53
<b>1f</b>	36.97
<b>1g</b>	43.36
<b>1h</b> <sup>b</sup>	6.76
<b>1i</b>	18.23
<b>1j</b>	13.00
<b>1k</b>	43.22
<b>1l</b>	13.36
<b>1m</b>	24.36
<b>2a</b> <sup>b</sup>	0.24
<b>2b</b>	2.14
<b>2c</b>	9.76
<b>2d</b>	5.78
Gabexate mesylate	3.18
Camostate mesylate	30.12

<sup>a</sup>Inhibiting activity on thrombin: 74.1  $\mu$ M; <sup>b</sup>inhibiting activity on porcine pancreatic elastase: **1h**: 94.1  $\mu$ M; **2a**: 70.01  $\mu$ M.

enzymes and their substrates by Sigma. The purity of final compounds was monitored by HPLC (Tessek column  $0.5 \times 25$  cm, C-18 Separon; acetonitrile/0.1 N ammonium acetate, 4:1 v/v, pH = 6.05 as mobile phase; flow rate 1 mL/min).


#### 4-Guanidinobenzoic acid mesylate [9]

4-Aminobenzoic acid (54 g, 0.49 mol) was dissolved in a mixture of 500 mL water and 70 mL conc HCl, and cyanamide (38.4 g, 0.91 mol) was added. The reaction mixture was stirred at 90–95 °C for 1 h and was then allowed to stand overnight at room temperature. The precipitated hydrochloride of 4-guanidinobenzoic acid was filtered and without purification added to a stirred solution of  $K_2CO_3$  (70 g) in water (500 mL). After the mixture had been stirred for 1 h, the precipitate was filtered, washed thoroughly with distilled water and dried in vacuo over  $P_2O_5$ . Guanidinobenzoic acid (81.2 g, 92%, mp > 260 °C) was added to dry methanol (500 mL), and then 99% methanesulfonic acid (0.33 mol, 31.1 mL) was added. The mixture was stirred for 1 h, filtered to remove the insoluble impurities, and the product was precipitated by addition of excess diethyl ether and recrystallized from ethanol: 94 g, 78.9%. Mp 211–213 °C;  $C_9H_{13}N_3O_5S$  ( $M_r$  = 275.22), C, N, H, S. <sup>1</sup>H-NMR (DMSO,  $\delta$ , [ppm]): 2.22 s (3H), 7.44 d ( $J$  = 5.55 Hz, 2H), 7.91 d ( $J$  = 5.56 Hz, 2H), 8.91 (2H), 9.64 (bs, 2H), 10.11s (1H).

#### Compounds **3b–m**

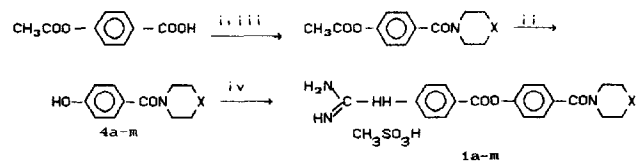
Compounds **3b–m** were prepared according to a previously described procedure [19]; data for **3c,d,h–j** are also reported therein. Data for **3e,f,g,k–m** are reported in table II.

**Table II.** Characteristic data for compounds **3e–g,k–m**.

			
Compound	Formula $M_w$	$B_p$ (°C)/ Pascals	Yield (%)
<b>3e</b>	$C_8H_{18}N_2$ 142.01	121–124/27.6	53
<b>3f</b>	$C_9H_{20}N_2$ 184.1	139–142/26.7	64
<b>3g</b>	$C_{10}H_{22}N_3$ 184.0	87–88/13.4	73
<b>3k</b> <sup>a</sup>	$C_{14}H_{22}N_2O_2$ 342.1	(Mp 66–67 °C)/74	74
<b>3l</b>	$C_9H_{18}N_2O_2$ 186.1	120–122/53.4	56
<b>3m</b>	$C_{10}H_{20}N_2O_2$ 199.9	88–89/13.4	55

<sup>a</sup>Recrystallized from hexane/ethylacetate.

**Scheme 1.** i:  $(COCl)_2/Et_3N$ ; ii:  $K_2CO_3$ ; iii: **3a–m**; iv: 4-guanidinobenzoic acid mesylate, DCC/pyridine.



1,3,4	X
<b>a</b>	O
<b>b</b>	$NCH_3$
<b>c</b>	$NCH_2CH_2CH_3$
<b>d</b>	$NCH(CH_3)_2$
<b>e</b>	$NCH(CH_3)CH_2CH_3$
<b>f</b>	$NCH(CH_3)CH_2CH_2CH_3$
<b>g</b>	$N(CH_2)_5CH_3$
<b>h</b>	$NCH_2CH_2NEt_2$
<b>i</b>	$NCH_2CONEt_2$
<b>j</b>	$NCH_2C_6H_5$
<b>k</b>	$NCH_2C_6H_2-3,4,5-(OMe)_3$
<b>l</b>	$NCH_2CH_2COOEt$
<b>m</b>	$NCH_2CH_2CH_2COOEt$

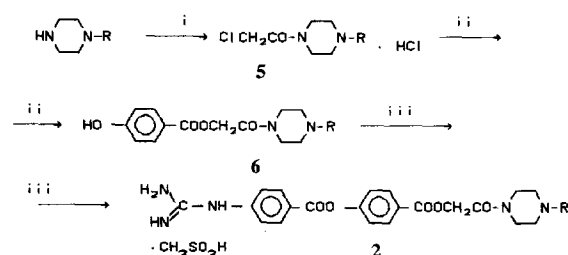
**Table III.** Characteristic data for compounds **4a,b,e-g,k-m**, **5c,d** and **6c,d**.

Compound	Formula Mw	Mp (°C) Recryst solvent	Yield (%)
<b>4a</b>	C <sub>11</sub> H <sub>13</sub> NO <sub>3</sub> 207.01	144–145 EtOAc/hexane	68
<b>4b</b>	C <sub>12</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> 205.98	175–178 EtOAc/hexane	64
<b>4e</b>	C <sub>15</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub> 248.1	119–120 EtOAc/hexane	62
<b>4f</b>	C <sub>16</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub> 276.1	92–95 EtOAc/hexane	56
<b>4g</b>	C <sub>17</sub> H <sub>26</sub> N <sub>2</sub> O <sub>2</sub> 267.0	88–90 Toluene/hexane	
<b>4k</b>	C <sub>21</sub> H <sub>26</sub> N <sub>2</sub> O <sub>5</sub> 372.0	Oil <sup>a</sup>	66
<b>4l</b>	C <sub>16</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub> 306.1	188–190 EtOAc/hexane	68
<b>4m</b>	C <sub>17</sub> H <sub>24</sub> N <sub>2</sub> O <sub>4</sub> 320.0	164–166 EtOAc/hexane	66
<b>5c</b>	C <sub>10</sub> H <sub>19</sub> N <sub>3</sub> Cl <sub>2</sub> O <sub>2</sub> 282.0	172–173 EtOAc/EtOH	98 <sup>b</sup>
<b>5d</b>	C <sub>12</sub> H <sub>23</sub> N <sub>3</sub> Cl <sub>2</sub> O <sub>2</sub> 312.2	192–193 EtOAc/EtOH	95 <sup>b</sup>
<b>6c</b>	C <sub>17</sub> H <sub>23</sub> N <sub>3</sub> O <sub>5</sub>	89–90 <i>i</i> -PrOH/ <i>i</i> Pr <sub>2</sub> O	62
<b>6d</b>	C <sub>19</sub> H <sub>27</sub> N <sub>3</sub> O <sub>5</sub>	121–122 <i>i</i> -PrOH/ <i>i</i> Pr <sub>2</sub> O	62

<sup>a</sup>Flash chromatography: EtOAc/EtOH/Et<sub>3</sub>N, 10:2:1 (v/v/v);  
<sup>b</sup>crude product.

**Compounds 5a–d and 6a–d**

Compounds **5a–d** were prepared according to ref [19]; data for **5a,b** are reported therein. For data for **5c,d**, see table III. Compounds **6a–d** were prepared according to ref [19]; data for **6a,b** are reported therein. For data for **6c,d**, see table III.

**Scheme 2.** i: ClCH<sub>2</sub>COCl; ii: 4-hydroxybenzoic acid/Et<sub>3</sub>N; iii: 4-guanidinobenzoic acid mesylate/pyridine/DCC.

2,5,6	R
<b>a</b>	-CH(CH <sub>3</sub> ) <sub>2</sub>
<b>b</b>	-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>
<b>c</b>	-CH <sub>2</sub> CONMe <sub>2</sub>
<b>d</b>	-CH <sub>2</sub> CONEt <sub>2</sub>

**Table IV.** Characteristic data for compounds **1a–m** and **2a–d**.

Compound	Formula Mw	Mp (°C)	Yield (%)
<b>1a</b>	C <sub>20</sub> H <sub>24</sub> N <sub>4</sub> O <sub>7</sub> S 464.9	170 dec	48
<b>1b</b>	C <sub>21</sub> H <sub>25</sub> N <sub>5</sub> O <sub>6</sub> S 475.02	Amorphous	46
<b>1c</b>	C <sub>23</sub> H <sub>31</sub> N <sub>5</sub> O <sub>6</sub> S 505.0	105–109	55
<b>1d</b>	C <sub>23</sub> H <sub>31</sub> N <sub>5</sub> O <sub>6</sub> S 505.0	Amorphous	49
<b>1e</b>	C <sub>24</sub> H <sub>33</sub> N <sub>5</sub> O <sub>6</sub> S 519.0	Amorphous	34
<b>1f</b>	C <sub>25</sub> H <sub>35</sub> N <sub>5</sub> O <sub>6</sub> S 533.6	Amorphous	36
<b>1g</b>	C <sub>26</sub> H <sub>37</sub> N <sub>5</sub> O <sub>6</sub> S 547.1	Amorphous	33
<b>1h</b>	C <sub>28</sub> H <sub>38</sub> N <sub>6</sub> O <sub>6</sub> S 526.1	56–58	32
<b>1i</b>	C <sub>26</sub> H <sub>36</sub> N <sub>6</sub> O <sub>7</sub> S 576.1	150–153	36
<b>1j</b>	C <sub>27</sub> H <sub>31</sub> N <sub>5</sub> O <sub>6</sub> S 539.0	205–207	44
<b>1k</b>	C <sub>30</sub> H <sub>33</sub> N <sub>5</sub> O <sub>9</sub> S 643.1	150 dec	42
<b>1l</b>	C <sub>25</sub> H <sub>33</sub> N <sub>5</sub> O <sub>8</sub> S 563.1	Amorphous	39
<b>1m</b>	C <sub>26</sub> H <sub>35</sub> N <sub>5</sub> O <sub>8</sub> S 577.1	Amorphous	39
<b>2a</b>	C <sub>25</sub> H <sub>33</sub> N <sub>5</sub> O <sub>8</sub> S 536.0	136–139	34
<b>2b</b>	C <sub>29</sub> H <sub>33</sub> N <sub>5</sub> O <sub>8</sub> S 611.1	180	32
<b>2c</b>	C <sub>26</sub> H <sub>34</sub> N <sub>6</sub> O <sub>9</sub> S 606.0	Amorphous	38
<b>2d</b>	C <sub>28</sub> H <sub>38</sub> N <sub>6</sub> O <sub>9</sub> S 634.1	Amorphous	33

**Table V.**  $^1\text{H}$  NMR spectra of compounds **1a–m** and **2a–d** (in  $d_6$ -DMSO).

Compound	$\delta$ (ppm)
<b>1a</b>	2.36 s (3H), 3.11–3.71 m, 8H), 6.73 d ( $J$ = 6.5 Hz, 2H), 6.96–7.30 m (4H), 8.22 d ( $J$ = 5.6 Hz, 2H)
<b>1b</b>	2.38 s (3H), 2.70–2.95 bs (4H), 3.65s (3H), 3.70–3.95 bs (4H), 6.75–6.85 d ( $J$ = 5.8 Hz, 2H), 7.00–7.67 m (4H), 8.11 ( $J$ = 75 Hz, 2H)
<b>1c</b>	1.1 d ( $J$ = 9.3 Hz, 6H), 2.36 s (3H), 2.75–3.00 bs (4H), 3.70–3.95 m (7H), 6.66 d ( $J$ = 5.6 Hz, 2H), 6.80–7.80 m (4H), 8.05 d ( $J$ = 5.5 Hz, 2H)
<b>1d</b>	0.9 t ( $J$ = 6.5 Hz, 3H), 1.61–1.85 m (2H), 2.22 s (3H), 2.81–3.00 m (2H), 3.11–3.21 m (4H), 3.84–3.95 m (4H), 6.72 d ( $J$ = 5.2 Hz, 2H), 7.11–7.59 m (4H), 8.15–8.24 d ( $J$ = 5.2 Hz, 2H)
<b>1e</b>	0.85 t ( $J$ = 3.7 Hz, 3H), 1.6 m (2H), 1.73 m (2H), 2.29 s (3H), 2.35 m (1H), 2.41 m (4H), 3.66 m (4H), 7.1 d ( $J$ = 5.73 Hz, 2H), 7.25–7.91 m (4H), 8.10 d ( $J$ = 5.74 Hz, 2H)
<b>1f</b>	0.91 t ( $J$ = 3.4 Hz, 3H), 0.98 d ( $J$ = 3.0 Hz, 3H), 1.23 m (2H), 1.45 m (4H), 2.33 s (3H), 3.55 m (1H), 3.61–3.68 bs (4H), 3.93 bs (4H), 7.00 d ( $J$ = 5.6 Hz, 2H), 7.31–7.85 m (4H), 7.91 d ( $J$ = 5.6 Hz)
<b>1g</b>	0.91 t ( $J$ = 3.7 Hz, 3H), 1.05–1.55 m (8H), 2.41 s (3H), 3.00 bs (4H), 3.23 m (2H), 3.9 bs (4H), 6.95 d ( $J$ = 5.58 Hz, 2H), 7.11–7.76 m (4H), 7.83 d ( $J$ = 5.57 Hz, 2H), 8.6 bs (2H), 10.1 bs (2H)
<b>1h</b>	1.11–1.21 2 x t, (6H), 2.33 s (3H), 3.05–3.33 m (8H), 3.55 bs (4H), 4.04 q ( $J$ = 6.55 Hz, 2H), 4.10 q ( $J$ = 6.56 Hz, 2H), 6.80 d ( $J$ = 5.93 Hz, 2H), 7.11–7.77 m (4H), 7.91 d ( $J$ = 5.93 Hz, 2H), 8.55 bs (2H), 9.91 bs (2H)
<b>1i</b>	2.51 s (3H), 2.93 bs (3H), 2.90 s (3H), 3.10 s (3H), 3.55 bs (4H), 6.91 d ( $J$ = 5.7 Hz, 2H), 7.21–7.63 m (4H), 7.90 d ( $J$ = 5.7 Hz, 2H), 8.55 bs (2H), 10.1 bs (1H)
<b>1j</b>	2.45 s (3H), 3.32 bs (4H), 3.94 bs (4H), 4.11 s (2H), 7.01 d ( $J$ = 8.94 Hz, 2H), 7.24–7.48 m (4H), 7.61 d ( $J$ = 8.93 Hz, 2H), 11.1 bs (2H)
<b>1k</b>	2.61 s (3H), 3.33 bs (4H), 3.61 s (3H), 3.78 s (6H), 4.00 s (2H), 6.64 s (2H), 7.04 d ( $J$ = 8.52 Hz, 2H), 7.21–7.46 m (4H), 7.87 d ( $J$ = 8.52 Hz), 8.84 bs (2H), 9.91 bs (2H)
<b>1l</b>	1.1 t ( $J$ = 5.76 Hz, 3H), 2.55 s (3H), 2.72 dd (2H), 2.91–3.25 m (6H), 3.65 bs (4H), 4.05 q ( $J$ = 5.75 Hz, 2H), 6.75 d ( $J$ = 8.62 Hz, 2H), 7.11–7.43 m (4H), 7.89 d ( $J$ = 8.6 Hz, 2H), 8.8 bs (2H), 10.1 bs (1H)
<b>1m</b>	1.12–1.36 2 x t (5H), 2.45 s (3H), 3.00 bs (4H), 3.53 m (2H), 3.72 bs (4H), 4.11 q ( $J$ = 4.98, 2H), 6.84 d ( $J$ = 8.8 Hz, 2H), 7.29–7.55 m (4H), 8.11 d ( $J$ = 8.8 Hz, 2H), 8.89 bs (2H), 10.00 bs (2H), 10.50 s (1H)
<b>2a</b>	1.01 d (6H), 2.56 s (3H), 3.36 m (4H), 3.95 bs (4H), 4.01 m (1H), 5.11 s (2H), 7.01–8.13 m (8H), 8.55 bs (1H), 10.10 bs (1H)
<b>2b</b>	2.25 s (3H), 2.72 bs (4H), 3.29 s (2H), 3.49 bs (4H), 5.01 s (2H), 7.10–8.21 m (8H), 10.11 bs (2H)
<b>2c</b>	2.45 m (3H), 2.90 s (3H), 2.97 s (3H), 3.07 s (2H), 3.19 bs (4H), 3.89 bs (4H), 5.05 s (2H), 7.09–8.11 m (8H), 10.20 bs (1H), 10.55 bs (2H)
<b>2d</b>	0.71–1.03 2 x t (6H), 2.71 s (3H), 2.92 bs (4H), 3.01 s (2H), 3.56–3.72 m (8H), 4.01–4.44 2 x q (4H), 4.92 s (2H), 7.01–8.00 m (8H), 10.11 bs (2H)

*General procedure for preparation of 4a–m*

4-Acetoxybenzoic acid (3.64 g, 0.02 mol) was suspended in dry dichloromethane and triethylamine (2.7 mL, 0.021 mol) was added. The mixture was cooled to  $-10^\circ\text{C}$  under stirring and oxalyl chloride (1.7 mL, 0.02 mol) was added in three portions through a septum. The mixture was warmed to room temperature over 1 h. The reaction mixture was cooled to  $-10^\circ\text{C}$  and *N*-alkylpiperazine (0.02 mol) or morpholine

(0.04 mol) was added dropwise to 10 mL dry dichloromethane. After the mixture had been stirred for 1 h ( $-10$  to  $0^\circ\text{C}$ ), the volatile compounds were evaporated in vacuo, sat  $\text{K}_2\text{CO}_3$  (30 mL) and methanol (30 mL) were added, and the mixture was stirred for 1 h. Then, 100 mL water was added and the mixture was extracted four times with ethyl acetate, dried ( $\text{Na}_2\text{SO}_4$ ), evaporated in vacuo, and recrystallized. Data for **4c,d,h–j** are reported in ref [19], and for the others in table III.

### General procedure for 1a–m and 2a–d

The mesylate of 4-guanidinobenzoic acid (1.3 g, 0.005 mol) and its corresponding hydroxyderivative **4a–m**, **7a–d** (0.005 mol) were dissolved in dry pyridine (20 mL) and cooled to 0 °C under stirring. Then, DCC (1.03 g, 0.005 mol) was added in one portion and the mixture was stirred at room temperature overnight under a calcium chloride tube. Dicyclohexylurea was removed by filtration, washed with two small portions of pyridine and the filtrate was poured into 100 mL ethyl acetate. The precipitated compound was decanted, dissolved in methanol (20 mL) and filtered through a neutral Al<sub>2</sub>O<sub>3</sub> column (1 × 5 cm) which was washed once with 20 mL methanol. The volume of the filtrate was reduced in vacuo to ca 15 mL and the product was precipitated by ethyl acetate. The purification was repeated, if required, according to HPLC analysis results.

### Inhibiting activities

Inhibiting activities were screened according to ref [22]. Tosyl arginine methylester hydrochloride (TAME) was used as substrate for trypsin and thrombin [22], and methoxysuccinyl-Ala-Ala-Pro-Val-*p*-nitroanilide as a substrate for porcine pancreatic elastase [23]. The reaction mixture consisted of Tris-HCl pH = 8.1 in 50% MeOH (v/v) without Ca or other activators, and 0.3 mL 0.01 M substrate solution 50% MeOH (v/v), and the reaction was started by addition of 0.1 mL of the enzyme solution (0.05 mg/mL 0.001 N HCl). The change of the absorbance at 247 nm (and 405 nm for leaving *para*-nitroaniline) was monitored over 4 min and the results were analysed by least-squares methods. Reaction conditions for measuring inhibition activities of compounds on porcine pancreatic elastase were according to Nakajima et al [23].

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