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Synthesis and Antimicrobial Evaluation of Novel Platensimycin Analogues

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Since the isolation of the natural products platensimycin and platencin as new antibiotic lead structures, several total syntheses as well as syntheses of derivatives have been developed. Most of these approaches are very laborious and the target molecules are often produced in only poor overall yields. The following approach describes the synthesis of rather simple platensimycin analogues focussing on some structure elements that have previously been identified as being essential for binding to the Fab F enzyme in fatty acid biosynthesis. Two of the new analogues show significant antimicrobial activities.

Keywords: Antimicrobial activity / Corey–Seebach reaction / Dithiane / Platensimycin

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Introduction

The natural products platensimycin (**1**) and platencin (Fig. 1), isolated from *Streptomyces platensis* in 2006 by researchers at Merck [1–4], are interesting leads for the development of new antibiotic drugs. These compounds exhibit potent activity against Gram-positive bacteria by a new mechanism of action, namely by inhibiting the Fab F enzyme in bacterial fatty acid synthesis. Prior to this, only two antimicrobial drugs targeted this biosynthesis pathway, triclosan and isoniazid (INH). But triclosan is only used in topical formulations, and INH is used only against mycobacteria (antituberculosis drug) [5].

Since 2006 several total syntheses of platensimycin and platencin have been described, but all these syntheses are laborious and expensive [6–12]. Moreover, a number of derivatives of platensimycin and platencin have been synthesised [13–17].

In continuation of our efforts on the development of novel simple platensimycin analogues [17] we focused on compounds containing the anilide group and the ketone, both identified as being essential for binding of the active components to the Fab F complex (Fig. 2). The complete docking protocol and the docking experiments as well as a comparison of binding to the Fab F complex of platensimycin, platencin and adamantaplatensimycin were described in Ref. [18].

The complex enone partial structure of the side chain was to be replaced by a simple open-chain enone or a phenyl ketone moiety, moreover, the effect of a deletion of the carboxylate group was investigated.

Results and discussion

Chemistry

Both benzaldehyde (**2a**) and *trans*-crotonaldehyde (**2b**) were reacted with propane-1,3-dithiol to give the corresponding 1,3-dithianes **3a**/**3b**. These dithianes have been used as building blocks in organic synthesis previously [19, 20]. Using the Corey–Seebach method [21], dithianes **3a**/**3b** were lithiated with *n*-butyllithium and alkylated with trimethyl 4-bromoorthobutyrate to give, after aqueous workup, the methyl esters **4a**/**4b**. The orthoester group avoids undesired reaction of the lithiated dithiane with the ester moiety [22]. After alkaline hydrolysis of the esters **4a**/**4b** with Na_2CO_3 the resulting carboxylic acids **5a**/**5b** were converted to the anilides **6a–6d** with aniline or methyl 3-aminobenzoate using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and *N*-hydroxybenzotriazole (HOBt) [23]. Subsequent cleavage of the dithiane groups with BF_3-etherate and mercuric oxide [24] gave the target ketones **7a–d**. Exemplarily the ester **7c** was hydrolysed to the corresponding carboxylic acid **8c** (Scheme 1).

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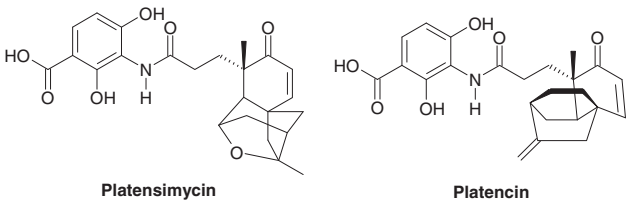


Figure 1. Structures of the antibiotics platensimycin (**1**) and platencin.

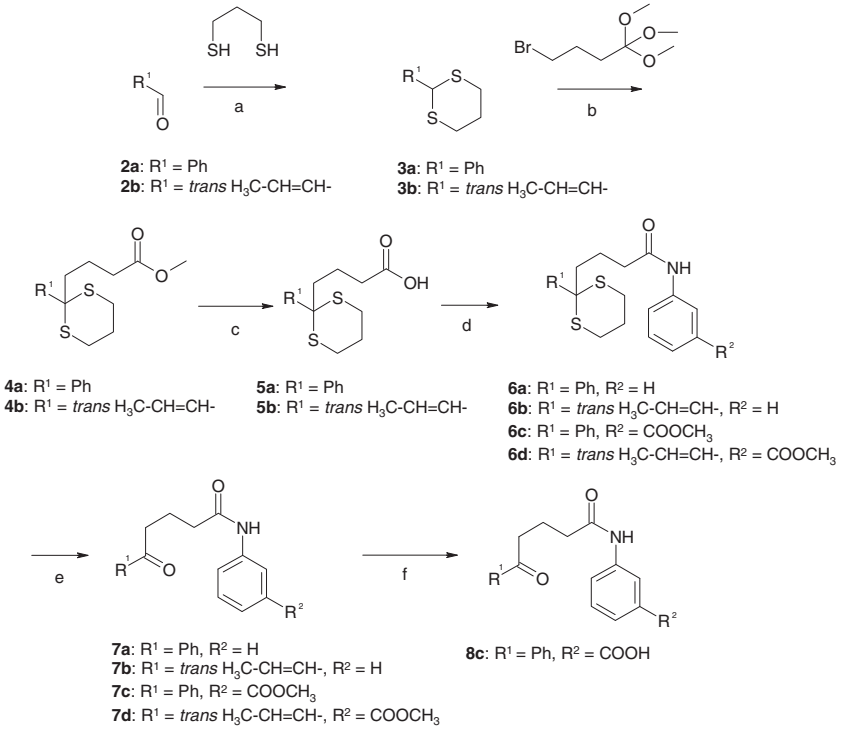
Antimicrobial activity

The target compounds **7a–d** and **8c** and the precursors **6a–d** were tested in a standardised (DIN) agar diffusion assay [25] against several Gram-negative bacteria (*Escherichia coli* and *Pseudomonas antimicrobia*), Gram-positive bacteria (*Staphylococcus equorum* and *Streptococcus entericus*) and some fungi (Table 1). The ketones **7a** and **7b** showed a broad spectrum of antibacterial activity comparable to the antibiotic tetracycline.

Exemplarily the cytotoxicity of the compounds **6b** and **7a–7d** was evaluated in an MTT assay [26] against a HL 60 cell line. The compounds showed only poor to moderate cytotoxicities with IC_{50} values between 32 and 41 μM.

Conclusion

Highly simplified analogues of the antibiotic platensimycin were synthesised starting from appropriate 1,3-dithianes following the Corey–Seebach method. Both phenyl ketone **7a** and propenyl ketone **7b** showed high activity against Gram-negative, Gram-positive bacteria and a few yeasts and fungi (*Candida glabrata* and *Hyphopichia burtonii*). Surprisingly, the analogues **7c** and **7d** containing additional



Scheme 1. (a) Methanol, BF_3-etherate; (b) THF, *n*-BuLi, then trimethyl 4-bromoorthobutyrate; (c) K_2CO_3, methanol; (d) DCC, HOBt, dichloromethane; (e) BF_3-etherate, HgO, THF, H_2O; (f) K_2CO_3, methanol.

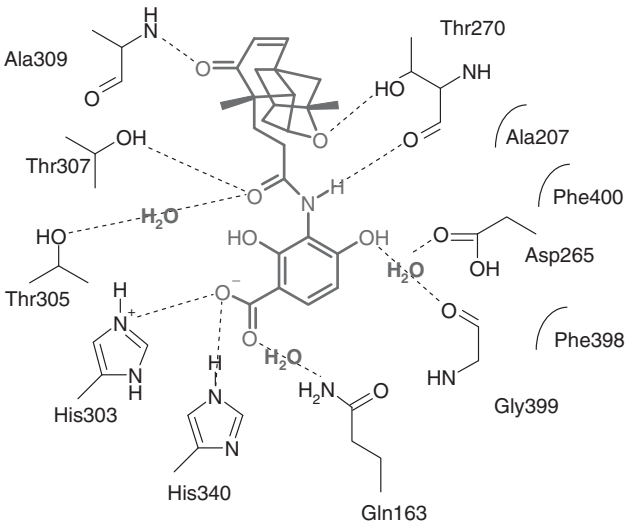


Figure 2. Schematic diagram showing the key interactions between platensimycin (red) and Fab F [18]. Most prominent interactions take place with the carboxylate, amide and side chain enone moieties.

Table 1. Agar diffussion assay (te: tetracycline, cl: clotrimazol, 50 μg/disc)

	6a	6b	6c	6d	7a	7b	7c	7d	8c	te	cl
Escherichia coli	0	0	0	0	11	10	0	0	0	25	0
Pseudomonas antimicrobia	0	0	0	8	14	10	0	7	0	23	0
Staphylococcus equorum	0	6	0	0	0	11	0	6	0	23	9
Streptococcus entericus	0	0	0	10	16	14	0	9	0	12	11
Candida glabrata	0	0	0	0	20	17	8	0	8	nt	15
Aspergillus niger	0	0	0	7	0	6	0	8	0	nt	15
Yarrowia lipolytica	0	0	0	0	0	7	0	0	0	nt	20
Hyphopichia burtonii	0	0	0	0	10	15	6	6	0	nt	17

Zones of inhibition (in mm). nt, not tested, 0, no measurable zone of inhibition.

ester groups at the anilide moiety, and compound **8c** containing a carboxylic acid group in analogy to the arene substitution pattern of platensimycin, did not show significant activities. This is in contrast to the proposed central role of the carboxylate group in the binding of platensimycin to the target Fab F complex. In contrast to the natural product platensimycin with highest activities against Gram-positive bacteria our compounds **7a** and **7b** showed a broad spectrum of antimicrobial activities. Unspecific cytotoxic effects of the active compounds can, however, be excluded due to the poor cytotoxicity against a HL cell line.

Experimental

M.p. (uncorr.) Büchi B-540; IR-Spectra: Perkin-Elmer FT-IR Paragon 1000; MS: Hewlett Packard MS-Engine, electron ionisation (EI) 70 eV, chemical ionisation (CI) with CH_4 (300 eV); NMR: Jeol GSX 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz); GLC-MS: Shimadzu GC 17 A; flash column chromatography: silica gel 60 (230–400 mesh, E. Merck, Darmstadt).

Agar diffusion assay

The bacteria and fungi were cultivated on an AC agar (Sigma). The substances were placed on 6 mm paper discs on the agar, each impregnated with 50 μg of the test compound or 50 μg of the reference drugs. The bacteria media were incubated for 24 h at 32°C, the fungi media for 48 h at 28°C, and the diameters of the zones of inhibition (mm) were registrated.

General procedure 1

About 10 mmol of aldehyde and 1.05 equivalents of propane-1,3-dithiol were dissolved in 20 mL $CHCl_3$ and 0.2 mmol of $BF_3 \times Et_2O$ was added. The solution was stirred for 3 h at 0°C, then 10% aqueous KOH (20 mL) was added and the organic layer was separated. After drying over Na_2SO_4 the solvent was evaporated and the residue was purified by flash column chromatography (isohexane/ethyl acetate 5:1).

General procedure 2

Dithiane **3a**/**3b** was dissolved in dry THF (7 mL/mmol dithiane) and under N_2 atmosphere at −40°C 1.5 equivalents of 1.6 M *n*-butyllithium solution in *n*-hexane were added dropwise. The solution was stirred for 30 min at −40°C and then allowed to warm up to 0°C. After 12 h the mixture was cooled to −40°C again, and 1.2 equivalents of trimethyl 4-bromoorthobutyrate were added dropwise. After stirring for 1 h at −40°C the mixture was allowed to warm up to 0°C and stirred at this temperature for 36 h. The mixture was quenched with water, 2 M HCl were added to reach pH 5 and the solution was extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by flash column chromatography (isohexane/ethyl acetate 10:1).

General procedure 3

Methyl ester **4a**/**4b** was dissolved in 50 mL 5% methanolic K_2CO_3 solution (50 mL/mmol) and the mixture refluxed for 24 h. The solvent was evaporated, the residue was dissolved in 30 mL H_2O and 10 mL aqueous 10% HCl. The mixture was extracted with diethyl ether (3 × 30 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated and the residue purified by flash column chromatography (isohexane/ethyl acetate 1:1).

General procedure 4

Carboxylic acid **5a**/**5b** was dissolved in CH_2Cl_2 (30 mL/mmol). At 0°C equimolar amounts of DCC and HOBt were added. The solution was stirred at 0°C for 30 min under N_2 atmosphere, then 1.5 equivalents of the aniline (dissolved in 5 mL CH_2Cl_2 per mmol) were added and the solution was stirred for 30 min at 0°C and 12 h at room temperature. The resulting suspension was filtered and the filtrate was extracted with 6 M aqueous HCl and 6 M aqueous NaOH. The organic layer was dried over Na_2SO_4, the solvent was evaporated and the residue was purified by FSC (isohexane/ethyl acetate 1:1).

General procedure 5

Dithiane **6a**/**6b**/**6c**/**6d** was dissolved in THF/H_2O (7:3; 50 mL/mmol) and 3 equivalents of red HgO and 3 equivalents of $BF_3 \times Et_2O$ were added. After stirring for 30 min at room temperature 50 mL of CH_2Cl_2 was added and the mixture was extracted with 100 mL ethyl acetate. The organic layer was dried over Na_2SO_4, the solvent was evaporated and the residue was purified by flash column chromatography (isohexane/ethyl acetate 5:1).

*2-Phenyl-1,3-dithiane **3a***

The compound was prepared according to General procedure 1 from 1.107 g (0.01043 mol) benzaldehyde, 1.19 g (0.0110 mol)

propane-1,3-dithiol and 0.305 g (2.15 mmol) $BF_3 \times Et_2O$ to give 1.95 g (95%) of **3a** as colourless crystals. M.p.: 72.2°C. IR (KBr): ν (cm^{-1}) = 3067, 3031, 2948, 2929, 2890, 2810, 1581, 1494, 1480, 1450, 1422, 1411, 1274, 1170, 1071, 1024, 908, 881, 725, 695, 673. HRMS: $C_{10}H_{12}S_2$. Calcd.: 196.0381. Found: 196.0392. MS (CI) m/z (%) = 197 ($[M+1]^+$, 100). MS (EI) m/z (%) = 196 ($[M]^+$, 74), 177 (80), 149 (40), 121 (96), 83 (56), 69 (66), 57 (100), 55 (84). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 2.18 (m, 2 H, CH_2), 2.91 (m, 4 H, 2 CH_2), 5.17 (s, 1 H, CH), 7.38 (m, 5 H, CH, aromat.). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 25.11 (CH_2), 32.11 (2 CH_2), 51.48 (CH), 127.75 (2 aromat. CH), 128.43 (aromat. CH), 128.73 (2 aromat. CH), 139.07 (quart. C). This compound has been described in several publications [20, 21], but not with a complete dataset.

((E)-Prop-2-en-1-yl)-1,3-dithiane ***3b***

The compound was prepared according to General procedure 1 from 0.972 g (0.0139 mol) *trans*-crotonaldehyde, 1.57 g (0.0145 mol) propane-1,3-dithiol and 0.422 g (2.97 mmol) $BF_3 \times Et_2O$ to give 2.16 g (97%) of **3b** as a colourless oil. IR (NaCl, film): ν (cm^{-1}) = 3022, 2931, 2912, 1677, 1447, 1422, 1275, 1041, 961. HRMS: $C_7H_{12}S_2$. Calcd.: 160.0381. Found: 160.0421. MS (CI) m/z (%) = 161 ($[M+1]^+$, 100). MS (EI) m/z (%) = 160 ($[M]^+$, 22), 119 (50), 113 (80), 108 (100), 85 (98). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 1.72 (d, J = 6.5 Hz, 3 H, CH_3), 2.09 (m, 2 H, CH_2), 2.87 (m, 4 H, 2 CH_2), 4.62 (d, J = 7.9 Hz, 1 H, CH), 5.53 (m, 1 H, CH), 5.87 (m, 1 H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 17.83 (CH_3), 25.19 (CH_2), 30.47 (2 CH_2), 47.72 (CH), 127.70 (=CH–), 130.13 (=CH–). The compound has been described in several publications [19], but not with a complete dataset.

Methyl 4-(2-phenyl-1,3-dithian-2-yl)-butanoate ***4a***

The compound was prepared according to General procedure 2 from 0.503 g (2.57 mmol) 2-phenyl-1,3-dithiane (**3a**), 2.4 mL 1.6 M *n*-butyllithium solution in THF (3.84 mmol) and 0.706 g (3.11 mmol) trimethyl 4-bromoorthobutyrate to give 0.42 g (55%) of **4a** as a colourless oil. IR (NaCl, film): ν (cm^{-1}) = 3056, 2949, 2906, 2360, 2342, 1736, 1442, 1256, 1173, 701. HRMS: $C_{15}H_{20}O_2S_2$. Calcd.: 296.0905. Found: 296.0901. MS (CI) m/z (%) = 297 ($[M+1]^+$, 100), 195 (25). MS (EI) m/z (%) = 296 ($[M]^+$, 29), 195 (100), 129 (56), 121 (66), 115 (34), 106 (40), 91 (20), 77 (34), 55 (26). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 1.57 (m, 2 H, CH_2), 1.93 (m, 2 H, CH_2), 2.03 (m, 2 H, CH_2), 2.18 (t, J = 7.5 Hz, 2 H, CH_2), 2.69 (m, 4 H, 2 CH_2), 3.60 (s, 3 H, CH_3), 7.25 (m, 1 H, CH, aromat.), 7.37 (t, J = 7.9 Hz, 2 H, 2 aromat. CH), 7.89 (d, J = 7.5 Hz, 2 H, 2 aromat. CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 19.55 (CH_2), 25.14 (CH_2), 27.66 (2 CH_2), 33.76 (CH_2), 44.16 (CH_2), 51.50 (CH_3), 58.55 (quart. C), 126.98 (aromat. CH), 128.52 (2 aromat. CH), 128.70 (2 aromat. CH), 141.41 (quart. C) 173.43 (quart. C).

Methyl 4-[2-((E)-prop-2-en-1-yl)-1,3-dithian-2-yl]-butanoate ***4b***

The compound was prepared according to General procedure 2 from 0.533 g (3.33 mmol) **3b**, 3.2 mL 1.6 M *n*-butyllithium solution in THF (5.12 mmol) and 0.899 g (3.96 mmol) trimethyl 4-bromoorthobutyrate to give 0.417 g (1.60 mmol) (48%) of **4b** as a pale yellow oil. IR (NaCl, film): ν (cm^{-1}) = 3019, 2950, 2913, 2855, 1738, 1435, 1423, 1253, 1169, 970. HRMS: $C_{12}H_{20}O_2S_2$. Calcd.: 260.0905. Found: 260.0913. MS (CI) m/z (%) = 261 ($[M+1]^+$, 100), 159 (18). MS (EI) m/z (%) = 260 ($[M]^+$, 48), 159 (100), 147 (66), 119 (58), 85 (90). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 1.35 (m, 2 H, CH_2), 1.77 (dd, J = 1.3 Hz, J = 6.6 Hz, 3 H, CH_3), 1.83 (m, 4 H, 2 CH_2), 2.29 (t, J = 7.4 Hz, 2 H, 2-H), 2.68 (m, 2 H, CH_2), 2.83 (m, 2 H, CH_2), 3.65 (s, 3 H, OCH_3), 5.42 (dd, J = 1.3 Hz, J = 15.2 Hz, 1′-H), 5.88 (dq, J = 6.6 Hz, J = 15.2 Hz, 1 H, 2′-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 17.57 (CH_3), 19.69 (CH_2), 25.41 (CH_2), 26.98 (2 CH_2), 33.88 (CH_2), 40.95 (CH_2), 51.54 (CH_3), 54.11 (quart. C), 129.38 (CH), 133.22 (CH), 173.64 (quart. C).

4-(2-Phenyl-1,3-dithian-2-yl)-butanoic acid ***5a***

The compound was prepared according to General procedure 3 from 0.169 g (0.571 mmol) **4a** to give 0.152 g (94%) of **5a** as white crystals. M.p.: 116°C. IR (NaCl, film): ν (cm^{-1}) = 3053, 3029, 2953, 2902, 2756, 2697, 2607, 2540, 1693, 1441, 1432, 1411, 1281, 1272, 946, 762, 698. HRMS: $C_{14}H_{18}O_2S_2$. Calcd.: 282.0748. Found: 282.0743. MS (CI) m/z (%) = 283 ($[M+1]^+$, 30), 197 (28), 195 (100), 175 (28) MS (EI) m/z (%) = 282 ($[M]^+$, 28), 195 (100), 129 (34), 121 (74), 85 (34), 77 (40). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 1.59 (m, 2 H, CH_2), 1.94 (m, 2 H, CH_2), 2.05 (m, 2 H, CH_2), 2.22 (t, J = 7.7 Hz, 2 H, CH_2), 2.69 (m, 4 H, 2 CH_2), 7.27 (m, 1 H, aromat. CH), 7.38 (t, J = 7.6 Hz, 2 H, 2 aromat. CH), 7.89 (d, J = 7.6 Hz, 2 H, 2 aromat. CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 19.30 (CH_2), 25.15 (CH_2), 27.56 (2 CH_2), 33.36 (CH_2), 44.05 (CH_2), 58.52 (quart. C), 127.05 (aromat. CH), 128.57 (2 aromat. CH), 128.71 (2 aromat. CH), 141.36 (quart. C), 178.35 (quart. C).

4-[2-((E)-Prop-2-en-1-yl)-1,3-dithian-2-yl]-butyric acid ***5b***

The compound was prepared according to General procedure 3 from 0.307 g (1.18 mmol) **4b** to give 0.245 g (84%) of **5b** as a pale yellow oil. IR (NaCl, film): ν (cm^{-1}) = 3021, 2934, 2912, 2670, 1707, 1422, 1413, 1276, 969, 907. HRMS: $C_{11}H_{18}O_2S_2$. Calcd.: 246.0748. Found: 246.0747. MS (CI) m/z (%) = 247 ($[M+1]^+$, 100), 159 (12), 139 (22). MS (EI) m/z (%) = 246 ($[M]^+$, 52), 159 (52). 139 (28), 100 (27), 85 (100). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 1.20 (t, J = 7.2 Hz, 2 H, CH_2), 1.79 (d, J = 7.2 Hz, 3 H, CH_3), 1.88 (m, 4 H, 2 CH_2), 2.35 (t, J = 7.2 Hz, 2 H, CH_2), 2.69 (m, 2 H, CH_2), 2.84 (ddd, J_1 = 12.4 Hz, J_2 = 10.4 Hz, J_3 = 3.4 Hz, 2 H, CH_2), 5.43 (dd, J_1 = 15.2 Hz, J_2 = 1.5 Hz, 1 H, CH), 5.89 (m, 1 H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 17.57 (CH_3), 19.40 (CH_2), 25.39 (CH_2), 26.98 (2 CH_2), 33.84 (CH_2), 40.80 (CH_2), 54.07 (quart. C), 129.47 (=CH–), 133.17 (=CH–), 179.59 (quart. C).

N-Phenyl-4-(2-phenyl-1,3-dithian-2-yl)-butyramide ***6a***

The compound was prepared according to General procedure 4 from 0.139 g (0.493 mmol) **5a**, 0.1086 g (0.526 mmol) DCC, 0.0695 g (0.514 mmol) HOBt and 0.083 g (0.89 mmol) aniline to give 0.1595 g (91%) of **6a** as a pale yellow oil IR (NaCl, film): ν (cm^{-1}) = 3302, 3057, 2932, 2906, 1662, 1599, 1544, 1498, 1442, 1310, 755, 700. HRMS: $C_{20}H_{23}NOS_2$. Calcd. 357.1221. Found: 357.1229. MS (CI) m/z (%) = 358 ($[M+1]^+$, 100), 265 (32), 195 (34). MS (EI) m/z (%) = 357 ($[M]^+$, 4), 251 (100), 195 (34), 121 (32), 93 (94), 77 (28), 55 (48). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 1.69 (m, 2 H, CH_2), 1.94 (m, 2 H, CH_2), 2.09 (m, 2 H, CH_2), 2.21 (t, J = 7.6 Hz, 2 H, CH_2), 2.70 (m, 4 H, 2 CH_2), 6.99 (s, 1 H, NH), 7.08 (t, J = 7.5 Hz, 1 H, aromat. CH), 7.28 (m, 3 H, 3 aromat. CH), 7.38 (t, J = 7.8 Hz, 2 H, 2 aromat. CH), 7.45 (d, J = 7.8 Hz, 2 H, 2 aromat. CH), 7.91 (d, J = 7.8 Hz, 2 H, 2 aromat. CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 19.42 (CH_2), 24.31 (CH_2), 26.76 (2 CH_2), 36.59 (CH_2), 43.34 (CH_2), 57.76 (quart. C), 118.86 (2 aromat. CH), 123.34 (aromat. CH), 126.23 (aromat. CH),

127.77 (2 aromat. CH), 127.91 (2 aromat. CH), 128.10 (2 aromat. CH), 136.89 (quart. C), 140.56 (quart. C), 169.47 (quart. C).

N-Phenyl-4-[2-((E)-prop-2-en-1-yl)-1,3-dithian-2-yl]-butyramide ***6b***

The compound was prepared according to General procedure 4 from 0.165 g (0.671 mmol) **5b**, 0.141 g (0.683 mmol) DCC, 0.093 g (0.69 mmol) HOBt and 0.105 g (1.13 mmol) aniline to give 0.1738 g (80%) of **6b** pale yellow oil. IR (NaCl, film): ν (cm^{-1}) = 3300, 3196, 3136, 3019, 2933, 2912, 1661, 1600, 1544, 1499, 1442, 1310, 1256, 969, 755, 692. HRMS: $C_{17}H_{23}NOS_2$. Calcd.: 321.1221. Found: 321.1215. MS (CI): m/z (%) = 322 ($[M+1]^+$, 100), 229 (28). MS (EI): m/z (%) = 321 ($[M]^+$, 26), 246 (30), 215 (56), 93 (100), 55 (48). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 1.25 (m, 2 H, CH_2), 1.78 (d, J = 7.0 Hz, 3 H, CH_3), 1.88 (m, 4 H, 2 CH_2), 2.35 (t, J = 7.0 Hz, 2 H, CH_2), 2.69 (d, J = 14.0 Hz, 2 H, CH_2), 2.84 (ddd, J_1 = 14.0 Hz, J_2 = 10.4 Hz, J_3 = 2.8 Hz, 2 H, CH_2), 5.44 (d, J = 14.0 Hz, 1 H, CH), 5.90 (m, 1 H, CH), 7.09 (t, J = 8.0 Hz, 1 H, aromat. CH), 7.22 (s, 1 H, NH), 7.31 (t, J = 8.0 Hz, 2 H, 2 aromat. CH), 7.50 (d, J = 8.0 Hz, 2 H, 2 aromat. CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 17.57 (CH_3), 20.38 (CH_2), 25.44 (CH_2), 27.05 (2 CH_2), 37.53 (CH_2), 41.10 (CH_2), 54.24 (quart. C), 119.78 (=CH–), 124.20 (=CH–), 128.97 (2 aromat. CH), 129.48 (aromat. CH), 133.28 (2 aromat. CH), 137.84 (quart. C), 170.57 (quart. C).

Methyl 3-[4-(2-phenyl-1,3-dithian-2-yl)-butanoylamino]-benzoate ***6c***

The compound was prepared according to General procedure 4 from 327 mg (1.16 mmol) **5a**, 263 mg (1.74 mmol) methyl 3-aminobenzoate, 239 mg (1.16 mmol) DCC and 157 mg (1.16 mmol) HOBt to give 478 mg (99%) of **6c** as colourless crystals. M.p. 125°C. IR (NaCl, film): ν (cm^{-1}) = 3415, 3305, 3213, 3089, 3030, 2950, 2931, 2901, 2362, 2345, 1719, 1670, 1596, 1550, 1427, 1300, 1273, 1230, 756. HRMS: $C_{22}H_{25}NO_3S_2$. Calcd.: 415.1276. Found: 415.1305. MS (CI) m/z (%) = 416 ($[M+1]^+$, 100), 265 (34), 225 (28). MS (EI) m/z (%) = 415 ($[M]^{+\cdot}$, 6), 309 (100). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 1.68 (m, 2 H, CH_2), 1.92 (m, 2 H, CH_2), 2.07 (m, 2 H, CH_2), 2.23 (t, J = 7.2 Hz, 2 H, CH_2), 2.67 (m, 4 H, 2 CH_2), 3.87 (s, 3 H, O–CH_3), 7.25 (m, 1 H, CH), 7.35 (m, 2 H, 2 CH), 7.52 (s, 1 H, CH), 7.73 (d, J = 7.2 Hz, 1 H, CH), 7.83 (d, J = 7.2 Hz, 1 H, CH), 7.89 (d, J = 7.2 Hz, 2 H, 2 CH), 7.97 (s, 1 H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 20.12 (CH_2), 25.13 (CH_2), 27.57 (2 CH_2), 37.19 (CH_2), 44.17 (CH_2), 52.25 (OCH_3), 58.06 (quart. C), 120.57 (aromat. CH), 124.33 (aromat. CH), 125.15 (aromat. CH), 127.07 (aromat. CH), 128.60 (2 aromat. CH), 128.73 (2 aromat. CH), 129.08 (aromat. CH), 130.69 (quart. C), 138.10 (quart. C), 141.39 (quart. C), 166.77 (CO), 170.80 (CO).

Methyl 3-{4-[2-((E)-prop-2-en-1-yl)-1,3-dithian-2-yl]-butanoylamino}-benzoate ***6d***

The compound was prepared according to General procedure 4 from 241 mg (0.98 mmol) **5b**, 224 mg (1.48 mmol) methyl 3-aminobenzoate, 201 mg (0.97 mmol) DCC and 139 mg (1.0 mmol) HOBt to give 140 mg (38%) of **6d** as pale yellow oil. IR (NaCl, film): ν (cm^{-1}) = 3300, 3017, 2933, 2855, 1723, 1551, 1488, 1442, 1299, 1107, 755. HRMS: $C_{19}H_{25}NO_3S_2$. Calcd.: 379.1276. Found: 379.1238. MS (CI) m/z (%) = 380 ($[M+1]^+$, 100), 229 (30), 120 (38). MS (EI) m/z (%) = 379 ($[M]^{+\cdot}$, 62), 309 (60), 273 (78), 151 (76), 55 (100). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 1.79 (dd, J_1 = 6.6 Hz, J_2 = 1.6 Hz, 3 H, CH_3), 1.88 (m, 2 H, CH_2), 1.91 (m, 2 H, CH_2), 2.38 (t, J = 7.0 Hz, 2 H, CH_2), 2.69 (m, 2 H, CH_2), 2.85 (m, 4 H, 2 CH_2), 3.90 (s, 3 H, OCH_3), 5.45 (d, J = 15.4 Hz, 1 H, CH), 5.91 (m, 1 H, CH), 7.33 (s, 1 H, NH), 7.39 (dd, J_1 = 7.9 Hz, J_2 = 7.9 Hz, 1 H, CH), 7.77 (d, J = 7.9 Hz, 1 H, CH), 7.90 (d, J = 7.9 Hz, 1 H, CH), 8.01 (s, 1 H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 17.62 (CH_3), 20.28 (CH_2), 25.44 (CH_2), 27.05 (2 CH_2), 37.46 (CH_2), 41.10 (CH_2), 52.27 (OCH_3), 54.25 (quart. C), 120.55 (CH), 124.31 (CH), 125.26 (CH), 129.19 (CH), 129.60 (CH), 130.82 (quart. C), 133.22 (CH), 138.06 (quart. C), 166.72 (CO), 170.83 (CO).

5-Oxo-5-phenylpentanoic acid phenylamide ***7a***

The compound was prepared according to General procedure 5 from 0.123 g (0.344 mmol) of **6a**, 0.281 g (1.30 mmol) HgO and 0.175 g (1.23 mmol) $BF_3 \times Et_2O$ to give 0.0.079 g (86%) of **7a** as pale yellow oil. IR (NaCl, film): ν (cm^{-1}) = 3302, 3057, 2932, 2906, 1662, 1599, 1544, 1498, 1442, 1310, 755, 700. HRMS: $C_{20}H_{23}NOS_2$. Calcd.: 357.1221. Found: 357.1229. MS (CI) m/z (%) = 358 ($[M + 1]^+$, 100), 265 (32), 195 (34). MS (EI) m/z (%) = 357 ($[M]^+$, 4), 251 (100), 195 (34), 121 (32), 93 (94), 77 (28), 55 (48). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 1.69 (m, 2 H, CH_2), 1.94 (m, 2 H, CH_2), 2.09 (m, 2 H, CH_2), 2.21 (t, J = 7.6 Hz, 2 H, CH_2), 2.70 (m, 4 H, 2 CH_2), 6.99 (s, 1 H, NH), 7.08 (t, J = 7.5 Hz, 1 H, aromat. CH), 7.28 (m, 3 H, 3 aromat. CH), 7.38 (t, J = 7.8 Hz, 2 H, 2 aromat. CH), 7.45 (d, J = 7.8 Hz, 2 H, 2 aromat. CH), 7.91 (d, J = 7.8 Hz, 2 H, 2 aromat. CH) ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 19.42 (CH_2), 24.31 (CH_2), 26.76 (2 CH_2), 36.59 (CH_2), 43.34 (CH_2), 57.76 (quart. C), 118.86 (2 aromat. CH), 123.34 (aromat. CH), 126.23 (aromat. CH), 127.77 (2 aromat. CH), 127.91 (2 aromat. CH), 128.10 (2 aromat. CH), 136.89 (quart. C), 140.56 (quart. C), 169.47 (quart. C).

(E)-5-Oxo-oct-6-enoic acid phenylamide ***7b***

The compound was prepared according to General procedure 5 from 0.133 g (0.414 mmol) **6b**, 0.279 g (1.29 mmol) HgO and 0.181 g (1.28 mmol) $BF_3 \times Et_2O$ to give 0.047 g (49%) of **7b** as a pale yellow solid. M.p.: 83.4°C. IR (KBr): ν (cm^{-1}) = 3341, 3053, 3010, 2964, 2941, 2896, 1670, 1596, 1524, 1443, 1380, 1316, 1175, 968, 754, 691, 500. HRMS: $C_{14}H_{17}NO_2$. Calcd.: 231.1259. Found: 231.1270. MS (CI) m/z (%) = 232 ($[M+1]^+$, 100), 139 (64). MS (EI) m/z (%) = 231 ($[M]^+$, 6), 139 (32), 111 (38), 93 (100), 69 (48), 55 (22). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 1.87 (d, J = 7.0 Hz, 3 H, CH_3), 2.01 (tt, J_1 = 7.0 Hz, J_2 = 7.0 Hz, 2 H, CH_2), 2.38 (t, J = 7.0 Hz, 2 H, CH_2), 2.66 (t, J = 7.0 Hz, 2 H, CH_2), 6.10 (d, J = 15.7 Hz, 1 H, CH), 6.87 (m, 1 H, CH), 7.07 (t, J = 7.2 Hz, 1 H, aromat. CH), 7.29 (t, J = 7.2 Hz, 2 H, 2 aromat. CH), 7.52 (t, J = 7.2 Hz, 2 H, 2 aromat. CH), 7.94 (s, 1 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 18.35 (CH_3), 20.06 (CH_2), 36.51 (CH_2), 38.50 (CH_2), 119.91 (=CH–), 124.23 (=CH–), 129.05 (2 aromat. CH), 131.89 (2 aromat. CH), 138.05 (quart. C), 143.77 (aromat. CH), 171.09 (quart. C), 200.49 (quart. C).

Methyl 3-(5-oxo-5-phenyl-pentanoylamino)-benzoate ***7c***

The compound was prepared according to General procedure 5 from 470 mg (1.13 mmol) **6c**, 733 mg (3.39 mmol) HgO and 480 mg (3.40 mmol) $BF_3 \times Et_2O$ to give 320 mg (87%) of **7c** as colourless crystals. IR (NaCl, film): ν (cm^{-1}) = 3347, 2926, 2850, 1715, 1680, 1588, 1529, 1428, 1229, 754, 687. HRMS: $C_{19}H_{19}NO_4$. Calcd.: 325.1314. Found: 325.1289. MS (CI) m/z (%) = 326 ($[M+1]^+$, 44), 225 (100), 175 (52). MS (EI) m/z (%) = 325 ($[M]^{+\cdot}$, 4), 175 (52), 151 (54), 105 (62), 56 (100). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 2.18 (quint., J = 7.3 Hz, 2 H, CH_2), 2.51 (t, J = 7.3 Hz, 2 H, CH_2), 3.14 (t, J = 7.3 Hz, 2 H, CH_2), 3.90 (s, 3 H, OCH_3), 7.40

(t, $J = 8.0$ Hz, 1 H, CH), 7.46 (t, $J = 7.4$ Hz, 2 H, 2 CH), 7.57 (t, $J = 8.0$ Hz, 1 H, CH), 7.77 (d, $J = 7.4$ Hz, 1 H, CH), 7.90 (d, $J = 8.0$ Hz, 1 H, CH), 7.97 (d, $J = 8.0$ Hz, 2 H, 2 CH), 8.08 (s, 1 H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 20.01 (CH_2), 36.39 (CH_2), 37.24 (CH_2), 52.28 (CH_3), 120.61 (CH), 124.01 (CH), 125.20 (CH), 128.12 (CH), 128.70 (CH), 129.15 (CH), 130.81 (quart. C), 133.36 (CH), 136.59 (quart. C), 138.26 (quart. C), 166.79 (CO), 171.18 (COO), 200.23 (CO).

Methyl 3-((E)-5-oxooct-6-enoylamino)-benzoate ***7d***

The compound was prepared according to General procedure 5 from 139 mg (0.343 mmol) **6d**, 273 mg (1.26 mmol) HgO and 192 mg (1.35 mmol) $BF_3 \times Et_2O$ to give 22 mg (22%) of **7d** as a yellow oil. IR (NaCl, film): ν (cm^{-1}) = 3323, 3144, 3035, 2932, 2855, 1723, 1667, 1594, 1549, 1488, 1442, 1299, 1222, 1107, 970, 756. HRMS $C_{16}H_{19}NO_4$. Calcd.: 289.1314. Found: 289.1284. MS (CI) m/z (%) = 290 ($[M+1]^+$, 86), 139 (100). MS (EI) m/z (%) = 289 ($[M]^{+\cdot}$, 8), 151 (100), 139 (84), 111 (100), 69 (100), 55 (54). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 1.89 (dd, $J_1 = 6.9$ Hz, $J_2 = 1.6$ Hz, 3 H, CH_3), 2.03 (quint., $J = 7.0$ Hz, 2 H, CH_2), 2.42 (t, $J = 7.0$ Hz, 2 H, CH_2), 2.68 (t, $J = 7.0$ Hz, 2 H, CH_2), 3.89 (s, 3 H, OCH_3), 1.11 (dd, $J_1 = 15.8$ Hz, $J_2 = 1.6$ Hz, 1 H, CH), 6.88 (m, 1 H, CH), 7.37 (dd, $J_1 = 8.0$ Hz, $J_2 = 8.0$ Hz, 1 H, CH), 7.75 (d, $J = 8.0$ Hz, 1 H, CH), 7.90 (d, $J = 8.0$ Hz, 1 H, CH), 8.06 (s, 1 H, CH), 8.09 (s, 1 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 18.37 (CH_3), 19.95 (CH_2), 36.37 (CH_2), 38.32 (CH_2), 52.26 (OCH_3), 120.56 (aromat. CH), 124.26 (aromat. CH), 125.14 (aromat. CH), 129.12 (aromat. CH), 130.78 (quart. C), 131.78 (CH), 138.30 (quart. C), 143.74 (CH), 166.81 (CO), 171.22 (CO), 200.47 (CO).

3-(5-Oxo-5-phenylpentanoylamino)-benzoic acid ***8c***

Of **7c**, 258 mg (0.79 mmol) was dissolved in 50 mL methanol, 45.1 mg (0.33 mmol) K_2CO_3 was added and the suspension was refluxed for 24 h. Then 20 mL 10% aqueous HCl was added and the solution was extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated and the residue was purified by flash column chromatography to give 239 mg (97%) of **8c** as colourless crystals. M.p.: 191°C. IR (NaCl, film): ν (cm^{-1}) = 3293, 3062, 2927, 2850, 2359, 2341, 1973, 1908, 1689, 1653, 1591, 1537, 1455, 1415, 1307, 1270, 1179, 963, 756, 688, 679. MS (ESI) m/z (%) = 312.1 ($[M+1]^+$), 225.2. MS (CI) m/z (%) = 225 (100). MS (EI) m/z (%) = 224 (12), 143 (14), 99 (24), 62 (34), 56 (100). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 1.94 (quint., $J = 7.2$ Hz, 2 H, CH_2), 2.44 (t, $J = 7.2$ Hz, 2 H, CH_2), 3.10 (t, $J = 7.2$ Hz, 2 H, CH_2), 7.40 (t, $J = 8.1$ Hz, 1 H, CH), 7.52 (t, $J = 8.1$ Hz, 2 H, 2 CH), 7.59 (d, $J = 8.0$ Hz, 1 H, CH), 7.63 (t, $J = 7.4$ Hz, 1 H, CH), 7.85 (d, $J = 8.0$ Hz, 1 H, CH), 7.96 (s, 1 H, NH), 7.97 (d, $J = 8.0$ Hz, 2 H, 2 CH), 8.27 (s, 1 H, CH), 10.31 (s, 1 H, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 19.56 (CH_2), 35.29 (CH_2), 37.18 (CH_2), 117.72 (CH), 123.08 (CH), 123.65 (CH), 127.78 (2 CH), 128.64 (2 CH), 128.76 (CH), 131.08 (quart. C), 133.04 (CH), 136.50 (quart. C), 139.47 (quart. C), 167.10 (COOH), 171.15 (CO), 199.59 (CO).

The authors have declared no conflict of interest.

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