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Solid Phase Synthesis and Biological Evaluation of a Pepticinnamin E-Library

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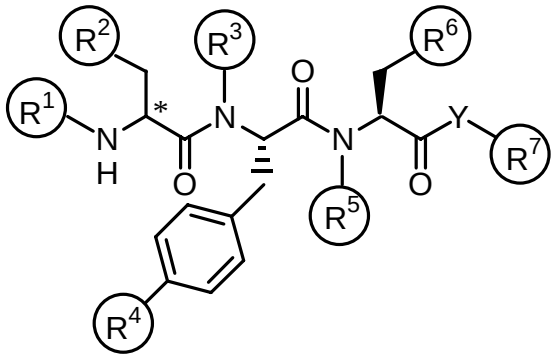


Entry	compd.	R^1	R^2	*	R^3	R^4	R^5	R^6	YR^7	yield (yield/ step) [%]	purity
1	**14/1**	g	o	D	Me	OMe	Me	n	u	14 (80)	>95
2	**14/2**	g	o	D	Me	OMe	Me	n	v	10 (77)	>95
3	**14/3**	c	o	D	Me	OMe	Me	n	OAll	31 (85)	>95
4	**14/4**	c	o	D	Me	OMe	Me	n	p	40 (90)	>95
5	**14/5**	c	o	D	Me	OMe	Me	n	q	28 (87)	>95
6	**14/6**	c	o	D	Me	OMe	Me	n	r	8 (76)	91
7	**14/7**	*p*NO_2Cbz	o	D	Me	OMe	Me	n	s	10 (77)	>95
8	**14/8**	*p*NO_2Cbz	o	D	Me	OMe	Me	n	t	5 (72)	>95
9	**14/9**	*p*NO_2Cbz	o	D	Me	OMe	Me	n	w	13 (78)	60
10	**13/1**	a	o	D	Me	OMe	Me	n	OH	14 (78)	>95
11	**11/1**	i	o	D	Me	OMe	Me	n	OH	10 (75)	>95
12	**11/2**	Cbz	o	D	Me	OMe	Me	n	OH	13 (77)	>95
13	**11/3**	b	m	D	Me	H	H	o	OH	21 (82)	>95
14	**11/4**	i	m	L	H	H	H	o	OH	13 (77)	89
15	**11/5**	Cbz	m	D	Me	H	H	o	OH	24 (84)	>95
16	**11/6**	g	o	D	Me	OMe	Me	n	OH	12 (76)	>95
17	**11/7**	f	o	D	Me	OMe	Me	n	OH	13 (77)	>95
18	**11/8**	d	o	D	Me	OMe	Me	n	OH	13 (77)	95
19	**11/9**	b	o	D	Me	OMe	Me	n	OH	18 (81)	>95
20	**11/10**	h	o	D	Me	OMe	Me	n	OH	13 (77)	>95
21	**11/11**	Fmoc	o	D	Me	OMe	Me	n	OH	11 (76)	>95

22	**11/12**	c	o	D	Me	OMe	Me	n	OH	36 (88)	95
23	**11/13**	*p*-NO_2Cbz	o	D	Me	OMe	Me	n	OH	5 (69)	>95

Table S1: Continues on the next page.

Entry	compd.	R^1	R^2	*	R^3	R^4	R^5	R^6	YR^7	yield (yield/ step) [%]	purity
24	**11/14**	Cbz	o	D	Me	H	H	o	OH	14 (78)	78
25	**11/15**	Cbz	o	D	H	H	H	o	OH	18 (81)	>95
26	**11/16**	Cbz	o	D	H	OH	H	o	OH	21 (82)	>95
27	**11/17**	Cbz	o	L	H	OH	H	o	OH	31 (86)	>95
28	**11/18**	Cbz	m	L	H	H	H	o	OH	24 (84)	95
29	**11/19**	Cbz	m	L	Me	H	H	o	OH	24 (84)	85
30	**11/20**	Cbz	n	D	H	H	H	o	OH	18 (81)	>95
31	**11/21**	*p*-NO_2Cbz	m	D	H	H	H	o	OH	58 (81)	>95
32	**11/22**	d	o	D	H	H	H	o	OH	31 (86)	>95
33	**11/23**	d	m	D	H	H	H	o	OH	15 (79)	95
34	**11/24**	b	m	D	H	H	H	o	OH	24 (84)	>95
35	**11/25**	b	m	L	H	H	H	o	OH	19 (81)	93
36	**11/26**	b	m	L	Me	H	H	o	OH	30 (86)	>95
37	**11/27**	e	m	D	H	H	H	o	OH	3 (65)	E/Z-mixt. 1:1
38	**11/28**	f	m	D	H	H	H	o	OH	13 (77)	>95
39	**11/29**	g	m	D	H	H	H	o	OH	38 (89)	90
40	**11/30**	a	m	D	H	H	H	o	OH	30 (86)	95
41	**11/31**	i	m	D	H	H	H	o	OH	10 (75)	E/Z-Mixt. 1:2.5
42	**11/32**	j	m	L	H	H	H	o	OH	21 (82)	91
43	**11/33**	j	m	D	H	H	H	o	OH	28 (85)	E/Z-mixt. 1.7:1
44	**11/34**	k	m	L	H	H	H	o	OH	11 (76)	E/Z-mixt. 1.6:1
45	**11/35**	k	m	D	H	H	H	o	OH	10 (75)	>95
46	**13/2**	l	m	D	H	H	H	o	OH	34 (87)	>95
47	**14/10**	Fmoc	o	D	Me	OMe	H	n	OAll	26 (76)	>95
48	**14/11**	Fmoc	o	D	Me	OMe	Me	n	OAll	19 (71)	>95
49	**14/12**	Fmoc	n	L	H	H	H	o	OAll	44 (85)	>95
50	**14/13**	Fmoc	m	L	H	H	H	o	OAll	63 (91)	>95

Table S1: Compound library of the synthesized Pepticinnamin E derivatives. For definition of substituents see figure S1.

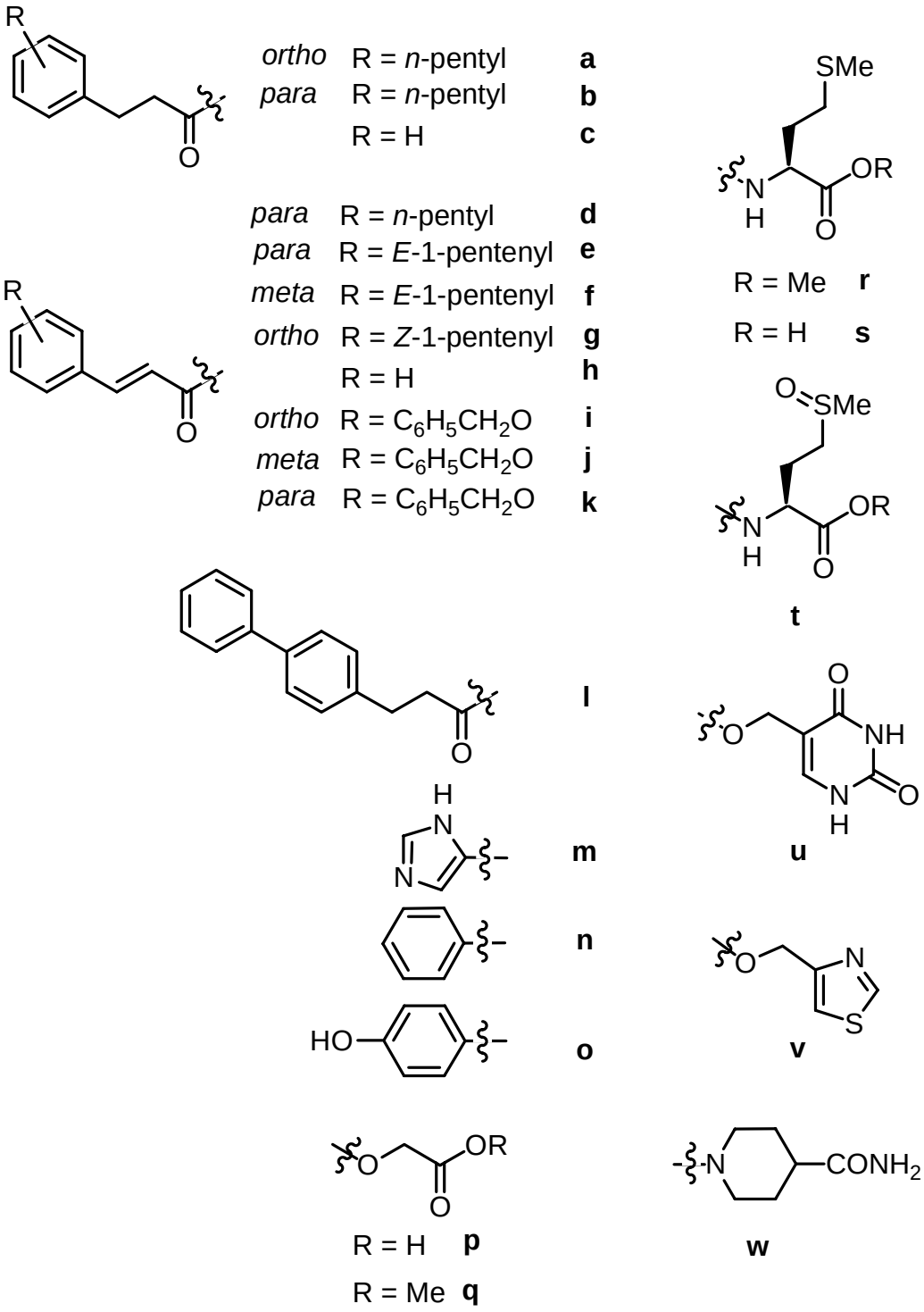
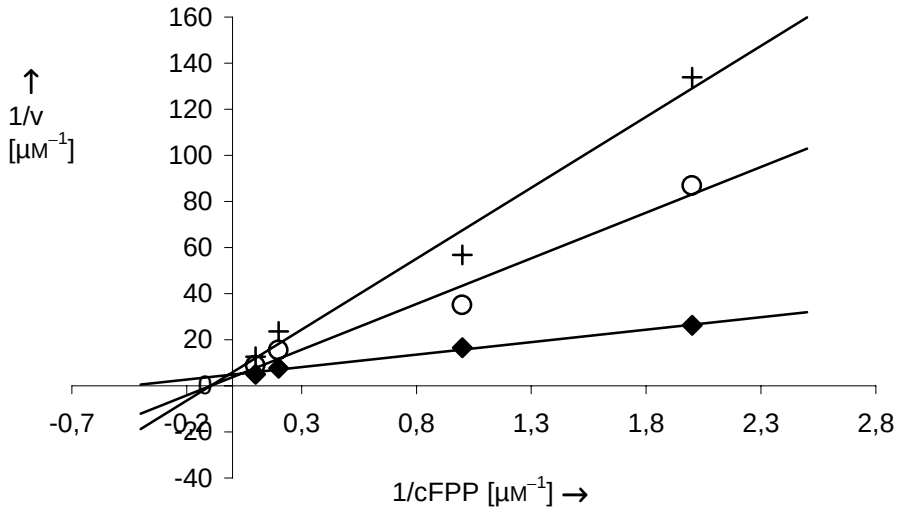


Figure S1: Definition of substituents in table S1

a)



b)

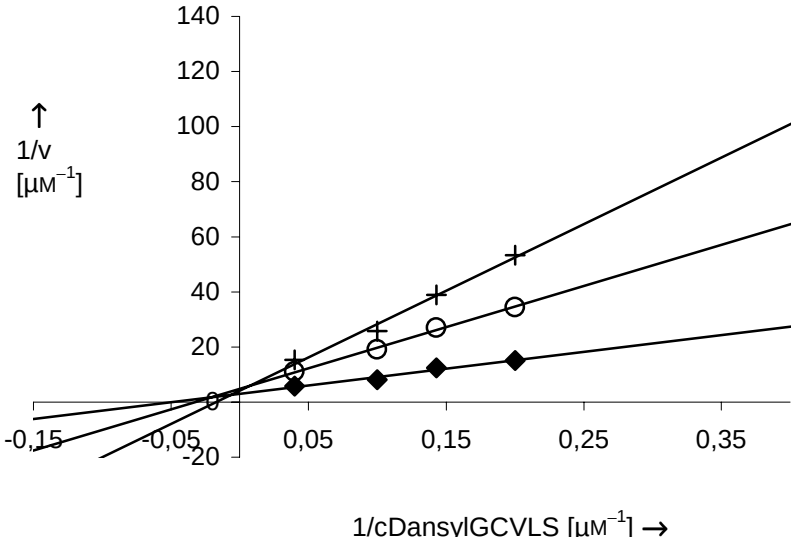


Figure S2: Inhibition of the Rat-PFT by **11/4**. (a) Lineweaver-Burk plot with FPP as varied substrate with constant concentration of DansGCVLS with 10 µM. Concentration of **11/4** with 0 (♦), 10 (O) und 20 (+) µM. (b) Lineweaver-Burk plot with DansGCVLS as varied substrate with constant

concentration of FPP with 10 µM. Concentration of **11/4** with 0 (♦), 10 (O) und 20 (+) µM.

Molecular Modelling

The coordinates of rat PFT were taken from the PDB (1JCR[1]). Protonation, assignment of atom types and preparation of input files for the CHARMM minimizations were carried out using WitnotP[2]. For minimization of the protein, all backbone atoms were fixed and all other atoms minimized using the steepest-descent method as implemented in CHARMM (200 cycles). The structures of the inhibitors were created with WitnotP and minimized with CHARMM[3]. The inhibitors were docked into the active site manually and the protein/inhibitor complexes minimized. All Atoms positioned more than 8 Å from any inhibitor atom were fixed, the other protein atoms were free to move. Figures 3a-c were created from the resulting structures with WitnotP. The solvent accessible surface of PFT was created with the radius of the probe being set to 1.4 Å.

[1] S. B.Long, P. J. Hancock, A. M. Kral, H.W. Hellinga, L. S. Beese, *Proc. Natl. Acad. Sci.* **2001**, *98*, 12948-12953.

[2] WitnotP is a molecular modeling software developed by A. Widmer at Novartis AG, Basel. For further information concerning WitnotP and the tools available therein please consult: armin.widmer@pharma.novartis.com

[3] B. R. Brooks, R. E. Bruccoleri, B. D. Olafson, D. J. States, S. Swaminathan, M. Karplus, *J. Comp. Chem* **1983**, *4*, 187-217.