CH_2-Gruppe [^{1}H: 2 m_c: 1,22 u. 1,65 ppm; ^{13}C: 22,60 ppm)] eine gute Übereinstimmung mit **3a**.
$C_{20}H_{26}ClNO$ (331,9): **3c**-HCl

2.4. 1-(2-Dimethylaminoethyl)-1-(4-fluorphenyl)-isochroman (**3d**)

Ausbeute: 62%; Schmp.: 206–208 °C (**3d**-HCl). ^{1}H-NMR ($CDCl_3$, 200 MHz): δ (ppm) = 2,5–2,9 (m, 3 H); 2,72 (s, 6 H); 3,10 (m_c, 2 H); 3,48 (m_c, 2 H); 3,86 (m_c, 1 H); 7,02 (m_c, 2 $H_{ar.}$); 7,1–7,5 (m, 6 $H_{ar.}$). ^{13}C-NMR ($CDCl_3$, 50,3 MHz): δ(ppm) = 28,62 (C-4); 36,90 (CH_3); 43,14 (CH_2); 54,52 (CH_2); 59,82 (C-3); 79,26 (C-1); 114,93; 115,35; 126,52; 127,02; 127,69; 128,99; 129,15; 129,89; 134,69; 135,40; 139,85; 139,91; 159,87; 164,79 [$C_{ar.}$]. MS: m/z (%) = 299 (21, M^+), 271 (12), 227 (12), 212 (10), 103 (7), 95 (7), 77 (4), 72 (10), 59 (11), 58 (100), 57 (36).
$C_{19}H_{23}ClNOF$ (335,9): **3d**-HCl

2.5. 1-(4-Fluorphenyl)-1-morpholinoethyl-isochroman (**3e**)

Ausbeute: 58%; Schmp.: 230–233 °C (**3e**-HCl). ^{1}H-NMR ($CDCl_3$, 200 MHz): δ (ppm) = 1,98 (m_c, 1 H); 2,2–2,7 (m_c, 7 H); 2,98 (m_c, 1 H); 3,4–3,7 (m, 6 H); 3,78 (m_c, 1 H); 6,88 (m_c, 2 $H_{ar.}$); 7,0–7,3 (m, 6 $H_{ar.}$).
$C_{21}H_{25}ClFNO_2$ (377,9); (**3e**-HCl)

2.6. 1-(3-Dimethylaminopropyl)-1-(4-fluorphenyl)-isochroman (**3f**)

Ausbeute: 48%; Schmp.: 188–190 °C (**3f**-HCl). Die NMR-Daten zeigen bis auf die zusätzliche CH_2-Gruppe [^{1}H: 2m_c: 1,60 u. 1,85 ppm; ^{13}C: 19,52 ppm)] eine gute Übereinstimmung mit **3d**.
$C_{20}H_{25}ClNOF$ (349,9): (**3f**-HCl)

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Enalapril maleate polymorphs: instability of form II in a tablet formulation

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Like most angiotensin converting enzyme inhibitors enalapril maleate is inherently prone to degradation in solid dosage forms, the main degradate being a diketopiperazine derivative (DKP) arising from an intramolecular nucleophilic attack of the secondary amino nitrogen in the aliphatic chain on the carboxylic carbon resulting in expulsion of water, formation of a N−C-bond and cyclization. This reaction may be arrested or minimized for example by including basic reagents, e.g. sodium hydrogen carbonate, in the formulation that transform the carboxylic moiety into a carboxylate anion [1].
Enalapril maleate is polymorphic and two polymorphic forms, form I and form II, have been described and characterized by spectroscopic methods [2, 3]. The X-ray powder diffraction spectra are rather similar but form II exhibits a distinctive peak of medium intensity at 13.0° 2θ whereas form I displays no peak at this position. Although these two polymorphs have been stated to be very similar in energy, differing only by 0.6 kcal/mol [2], evidence presented in the sequel indicates that form II is much less stable in a tablet formulation.
The two polymorphic forms of enalapril maleate used in this study were produced by the same manufacturer and were very similar in assay, purity and particle size distributions. Two tablet batches (1 and 2) were prepared from each polymorph using identical conditions: batch size 5.2 kg, strength 10 mg, tablet mass 130 mg, wet granulation, drying of granulate to less than 2.0% loss on drying (IR-balance, 105 °C), main excipient lactose monohydrate, stabilizing agent sodium hydrogen carbonate in a practically stoichiometric amount [4], compaction in a rotary tablet press. The tablets obtained were packaged into aluminium/aluminium (Al/Al) blisters and put on stability trial at 40 °C/75% RH for one month. The results of DKP analyses performed by HPLC [5] on the tablets at the zero and one month points are enumerated in the Table.

Table: Results of the DKP analyses

	DKP-content (%)	
Polymorph	0 point	1 month
Form I, batch 1	< 0.15	< 0.15
Form I, batch 2	< 0.15	< 0.15
Form II, batch 1	0.34	7.94
Form II, batch 2	0.23	6.77

These results clearly show that enalapril maleate Form II is unsuitable for tablet production at least in the formulation employed.

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Cytotoxic activity of physalins and related compounds against HeLa cells

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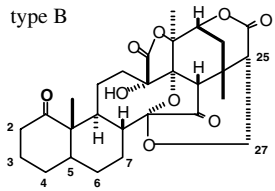
Physalins are 16,24-cyclo-13,14-secoergostane steroids which are classified to types B or A according to the presence or absence of a C(14)−O−C(27) acetalic linkage [1]. Some of the physalins including physalins B and H are known to demonstrate cytotoxic activity against tumor cells *in vitro* and *in vivo* [2, 3]. However, extensive study on the structure-cytotoxic activity relationship has not been reported. In this communication we will describe an extensive study on the cytotoxic activity against HeLa cells of naturally isolated physalins and their derivatives prepared by various chemical conversions.

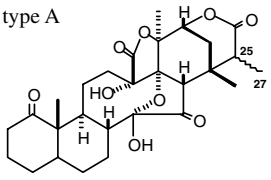
Cytotoxic activity of various physalins and their derivatives are summarized in the Table. Physalins B [4], C [5] and F [6] belong to most active physalins (entries 3, 58, 15) and some of halogen-containing derivatives are also potent (entries 30, 33, 42, 72). Conjugated 2-en-1-one moiety at A ring was shown to be essential for high activity by the lower activity of the 2,3-saturated derivatives (e.g., entries 47 vs. 3, 52 vs. 15) and the isomeric 3-en-1-one compounds (e.g., entries 11 vs. 3, 65 vs. 63). Type A physalins possessing a C(25)=C(27) double bond exhibited comparable activity to those of the corresponding type B physalins (entries 58 vs. 3, 62 vs. 8), which is not surprising considering the tautomerism under certain conditions [1], while the corresponding physalins possessing a C(27)-secondary methyl group exhibited lower cytotoxicity (entries 59 vs. 3, 63 vs. 8). In general introduction of a hydroxy group at C(25) [7] decreased the activity significantly (e.g., entries 3 vs. 4, 8 vs. 9) although in the cases of some inactive compounds their 25-hydroxy analogs were found to show activity (entries 2 and 18). Presence of a 7-hydroxy function also decreased the activity (e.g., entries 8 vs. 3, 62 vs. 58). As exemplified by physalins F and J [6] (entries 13 vs. 15) the 5,6-epoxy derivatives with β-configuration were more potent than the cor-

Table: Cytotoxic activity of physalins of types B and A and thier derivatives against HeLa cells

type B



type A



Entry	Type	AB ring (other than 1-oxo function)	C(25)−C(27)	IC_{50} (μg/ml)	References
1	B	Δ^2, Δ^4, Δ^6	CH−CH_2−O	>100	[4]
2	B	Δ^2, Δ^4, Δ^6	C(OH)−CH_2−O	10	
3	B	Δ^2, Δ^5	CH−CH_2−O	0.32	[4] (physalin B)
4	B	Δ^2, Δ^5	C(OH)−CH_2−O	13	[7]
5	B	Δ^2, Δ^4, 6α-OH	CH−CH_2−O	62	[9]
6	B	Δ^2, Δ^4, 6β-OH	CH−CH_2−O	37	[9]
7	B	Δ^2, Δ^4, 2-Cl, 6β-OH	CH−CH_2−O	30	
8	B	Δ^2, Δ^5, 7α-OH	CH−CH_2−O	1.2	[11] (physalin N)