

Neue Antimykotika 2014/15

Romuald Bellmann

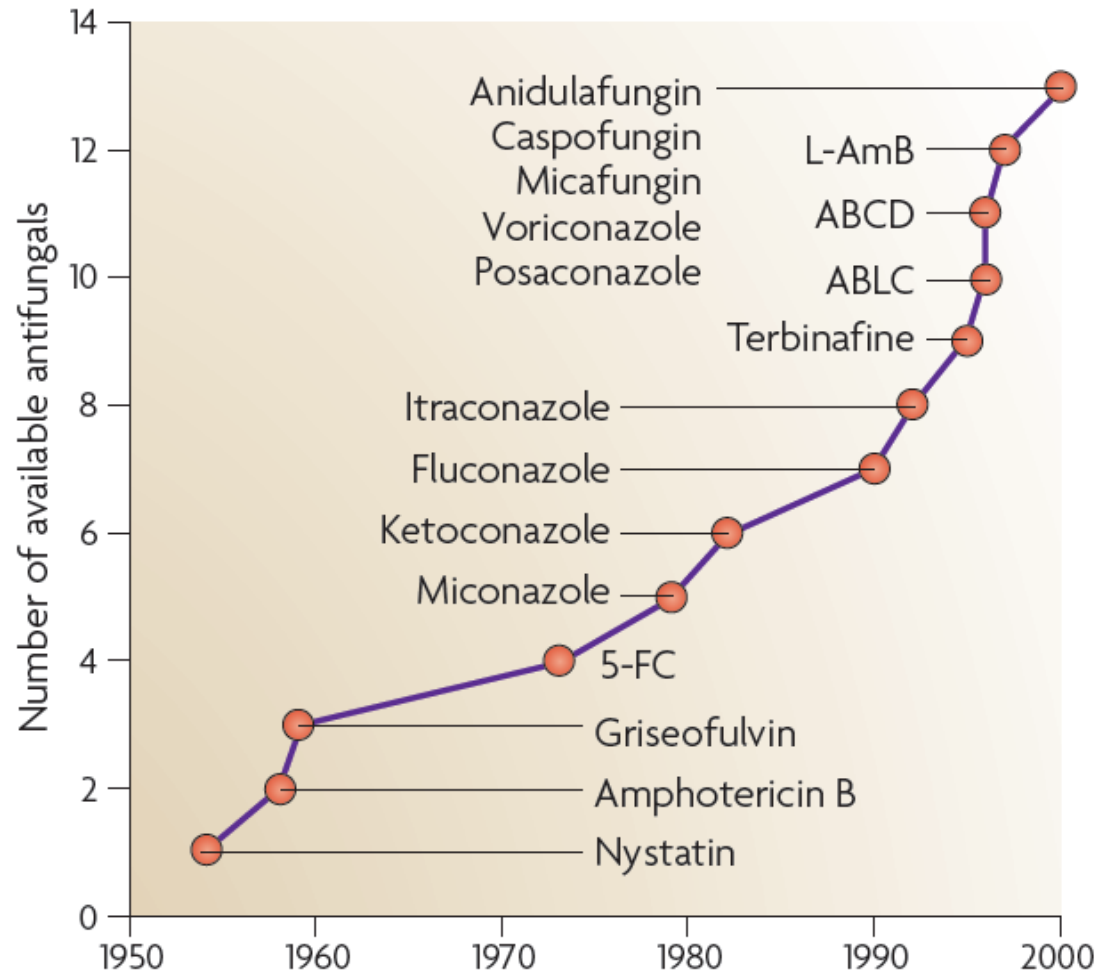
Arbeitsgruppe Klinische Pharmakokinetik

Gemeinsame Einrichtung Internistische Intensiv- und
Notfallmedizin

Universitätsklinik für Innere Medizin I

Medizinische Universität Innsbruck

Alte und neuere Antimykotika



Antimykotika derzeit am Markt

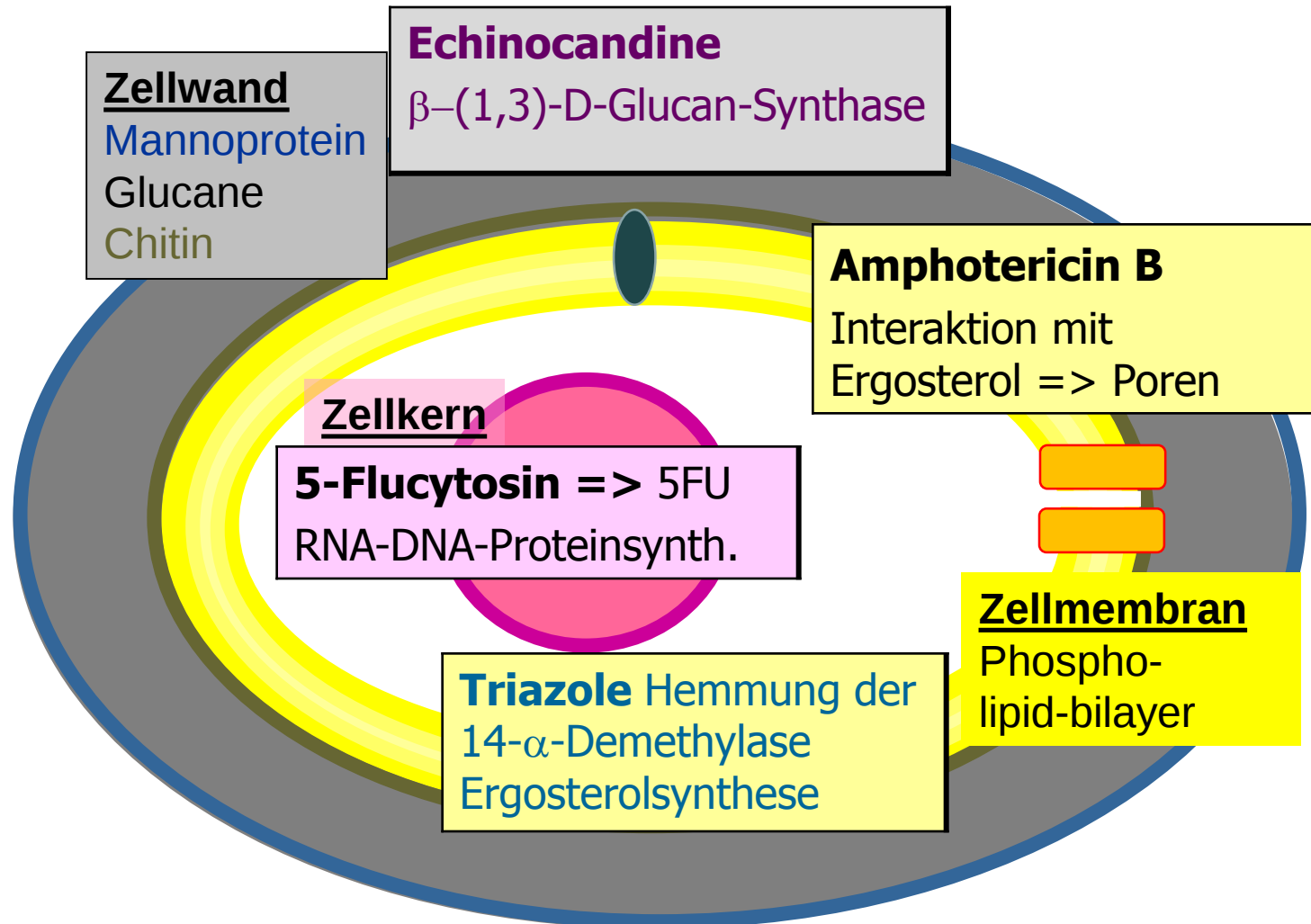
Gruppe	Wirkstoffe	<i>Handelsname</i>
Amphotericin B AMB	AMBdc, liposomales AMB kolloidales AMB AMB Lipidkomplex	Amphotericin B <i>AmBisome</i> <i>Amphocil</i> <i>Abelcet</i>
„Antimetabolite“	5-Flucytosin	<i>Ancotil</i>
Triazole	Fluconazol Itraconazol Voriconazol Posaconazol	<i>Diflucan</i> <i>Sporanox</i> <i>Vfend</i> <i>Noxafil</i>
Echinocandine	Caspofungin Anidulafungin Micafungin	<i>Cancidas</i> <i>Ecalta</i> <i>Mycamine</i>

Neue Antimykotika

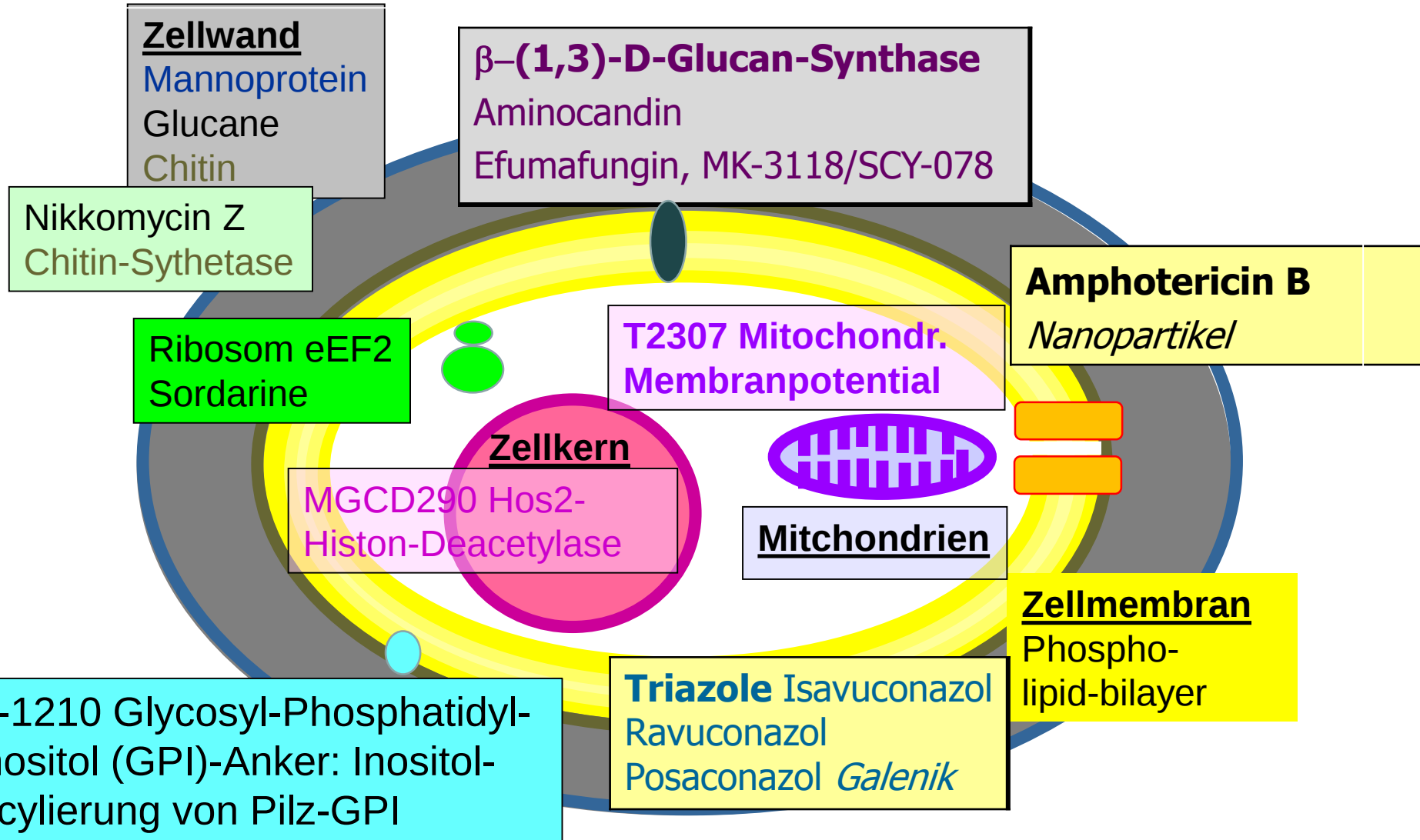
- Weiterentwicklungen bisheriger Substanzen durch Modifikation der Galenik
- Weiterentwicklungen bisheriger Substanzgruppen durch chemische Modifikationen
- Substanzen mit neuen Wirkmechanismen

- Substanzen in prä-klinischer Entwicklung
- Substanzen in klinischen Studien
- Neu zugelassene Präparate / kurz vor der Zulassung

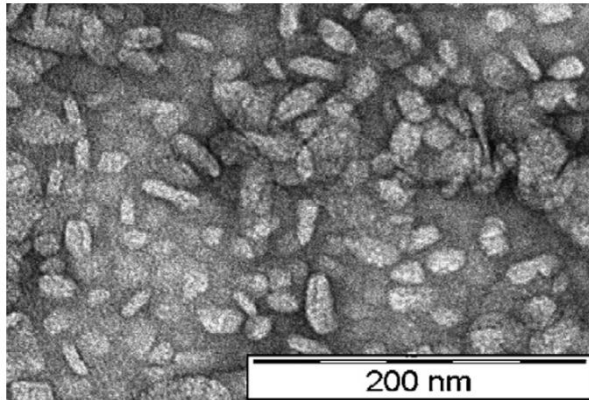
Zielstrukturen der „alten“ Antimykotika



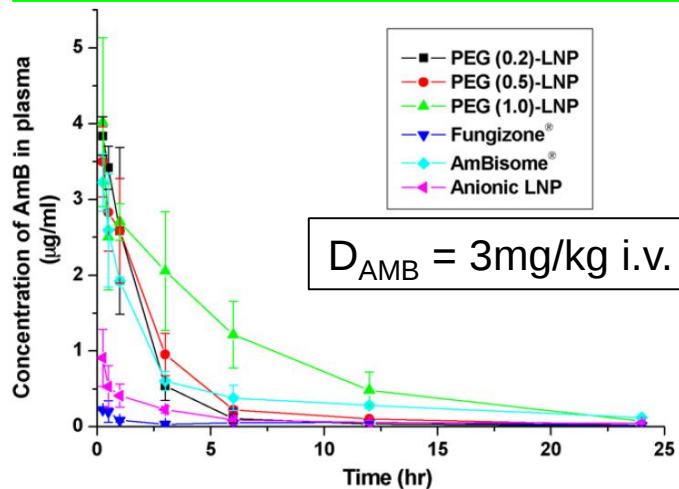
Zielstrukturen neuer Antimykotika



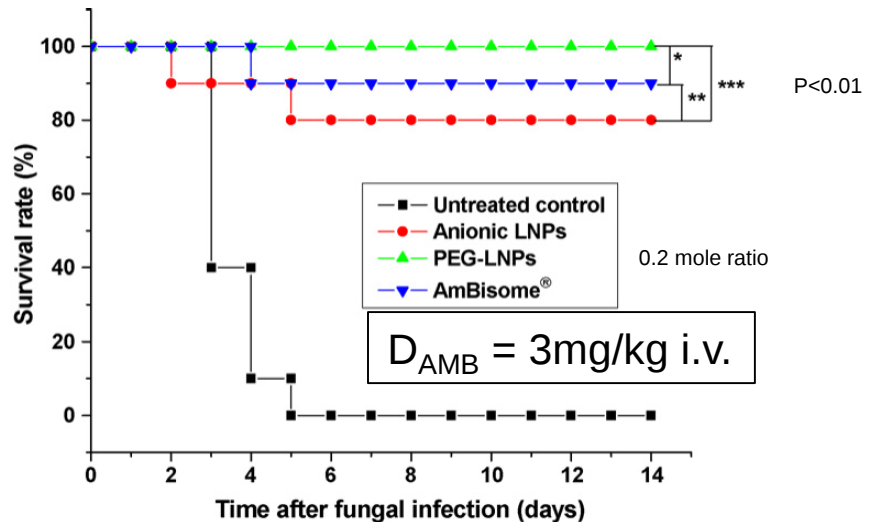
Amphotericin-B-Lipid-Nanopartikel



Distearylgylicero-Phosphoethanolamin-
Methoxy PEG 2000



Überleben *A. fum.* -infizierter Mäuse

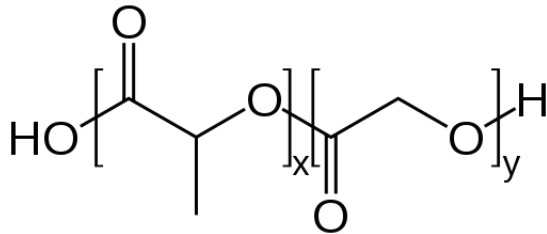


Geringe Toxizität, weniger schnelle
Aufnahme in Makrophagen

Jung et al. 2009 Eur J Pharm Sci 37:313-21

Orales Amphotericin B: PLGA-Nanopartikel

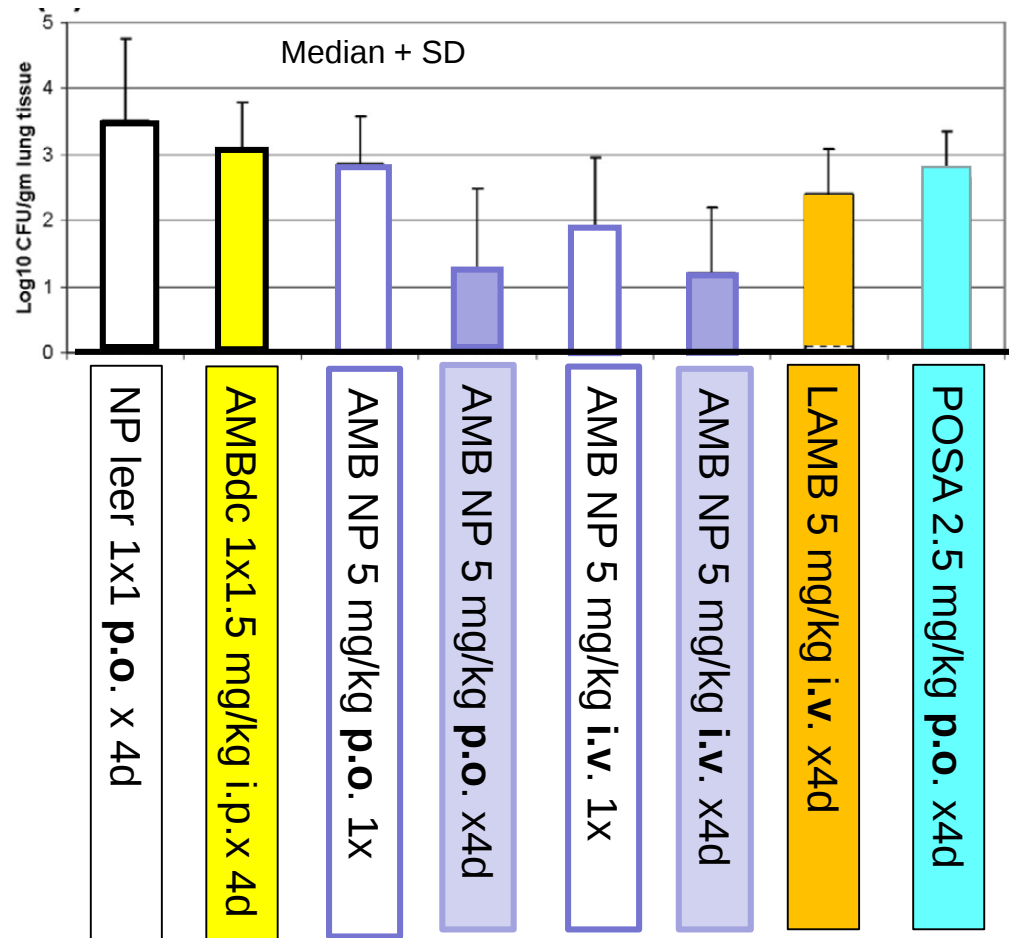
Poly(lactid-co-Glycolid) PLGA
113 ± 20 nm



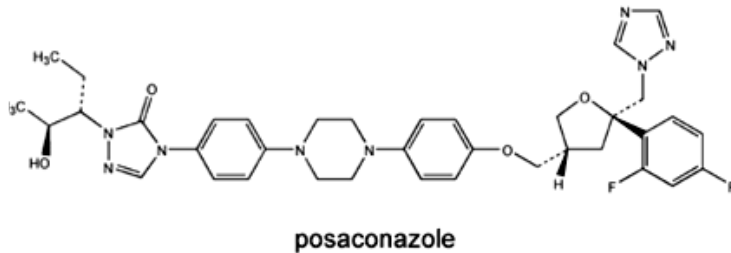
Milchsäure-Reste Glycolsäure-Reste

Invasive pulmonale
Aspergillose bei
neutropenen Mäusen

Italia et al. 2011 PLoS ONE 6(10): e25744



Neue Posaconazol-Tabletten- und Kapsel-Formulierung



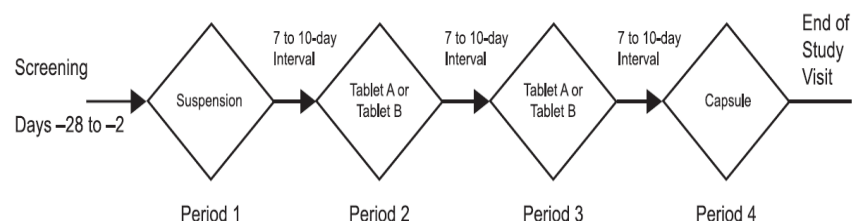
- Salvage-Ther. inv. Aspergillose, Fusariose, Chromoblastomykose, Myzetom, Kokzidioidomykose,
- Oropharyngeale Candidose
- AML, MDS längerd. Neutropenie
- HSCT + GvHD

- POSA + Hydroxypropyl-Methylcellulose-Acetat-Succinat (HMPCAS) + Ascorbinsäure 1:3:0.08 (Kapsel)
 - Tabletten A zusätzlich: Hydroxypropyl-Cellulose
 - **Tabletten B zusätzlich: Polyvinyl-Pyrrolidon + Crosscarmellose**
- ⇒ Hemmt Freisetzung im Magen und Re-Kristallisation
- Dosis 1 x 3 Tabl. /Kps. à 100 mg (LD 2x 3 Tabl.)

Krishna et al. 2012 AAC 56:4196-201

Neue Posaconazol-Tabletten- und Kapsel-Formulierung

Phase I: Pharmakokinetik n=16



- Treatment A: Single 100-mg dose of POS oral suspension
- Treatment B: Single 100-mg dose of POS Tablet A
- Treatment C: Single 100-mg dose of POS Tablet B
- Treatment D: Single 100-mg dose of POS capsule
- Subjects were randomized to receive either Tablet A-B or B-A in periods 2 and 3

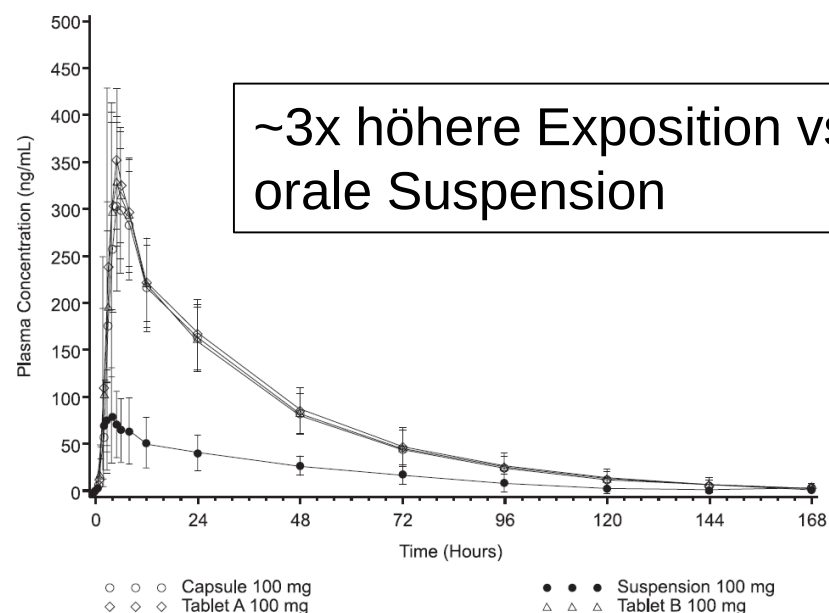


TABLE 2 Plasma pharmacokinetic parameters of 100 mg posaconazole under fasted conditions^a

Formulation	AUC _{0-t} (ng · h/ml)	AUC _{0-∞} (ng · h/ml)	C _{max} (ng/ml)	T _{max} ^b (h)	t _{1/2} (h)	CL/F (liters/h)	V/F (liters)
Oral suspension	2,970 (50)	3,420 (44) ^c	84.0 (62)	4.00 (2.00, 8.00)	29.2 (31) ^c	34.0 (38) ^c	1,450 (54) ^c
Tablet A	11,400 (26)	11,700 (26)	385 (28)	5.00 (3.00, 6.00)	26.1 (28)	9.16 (29)	345 (45)
Tablet B	11,000 (22)	11,300 (22)	358 (23)	5.00 (2.00, 8.00)	25.0 (25)	9.25 (22)	331 (34)
Capsule	10,700 (26)	11,000 (25)	335 (27)	5.00 (4.00, 8.00)	25.1 (27)	9.67 (26)	349 (36)

^a Data are arithmetic means (percent CV) for 16 subjects. AUC_{0-t}, area under the curve from time zero to the time of the final quantifiable sample; AUC_{0-∞}, area under the curve

Neue Posaconazol-Tabletten-Formulierung

Phase I: Pharmakokinetik an Probanden n=24

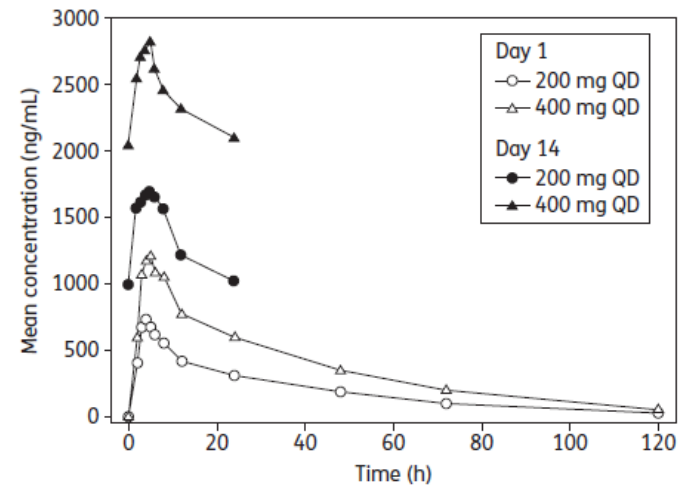
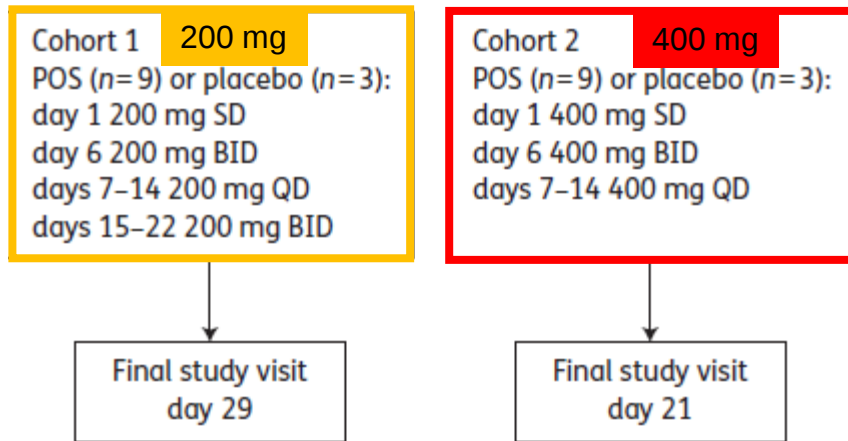


Table 2. Mean (%CV) of posaconazole pharmacokinetic parameters after single oral tablet administration of 200 or 400 mg of posaconazole

Dose (mg)	Day	n	C _{max} (ng/mL)	T _{max} ^a (h)	AUC ₀₋₂₄ ^b (ng·h/mL)	AUC _{0-∞} (ng·h/mL)	CL/F (L/h)	t _{1/2} (h)
200 mg (Cohort 1)	1	10	778 (29)	4.0 (3–8)	10 500 (23)	23 000 (23)	8.80 (26)	25.1 (20)
400 mg (Cohort 2)	1	9	1290 (29)	5.0 (3–8)	18 900 (34)	42 800 (35)	9.55 (34) ^c	26.1 (22) ^c

^aMedian (range).

^bt_{au}=24 h.

^cn=8.

Krishna et al. 2012 JAC 67:2725-30

Neue Posaconazol-Tabletten-Formulierung

- Einfluss des Magen-Milieus und der -Motilität? Probanden n=20
- POSA 1 x 4 Tbl. à 100 mg

POS tablet + treatment listed compared with POS tablet alone	C _{max} GMR (90% CI)	AUC _{0-inf} GMR (90% CI)	AUC _{0-last} GMR (90% CI)
Antacid 1x Al(OH) ₃ 2g Mg(OH) ₂ 2g	1.06 (0.90–1.26)	1.03 (0.88–1.20)	1.04 (0.90–1.20)
Ranitidine 2x150 mg	1.04 (0.88–1.23)	0.97 (0.84–1.12)	0.97 (0.84–1.12)
Esomeprazole 1x40 mg	1.05 (0.89–1.24)	1.01 (0.87–1.17)	1.02 (0.88–1.17)
Metoclopramide 4x15 mg	0.86 (0.73–1.02)	0.93 (0.79–1.09)	0.93 (0.80–1.07)

GMR, geometric mean ratio;

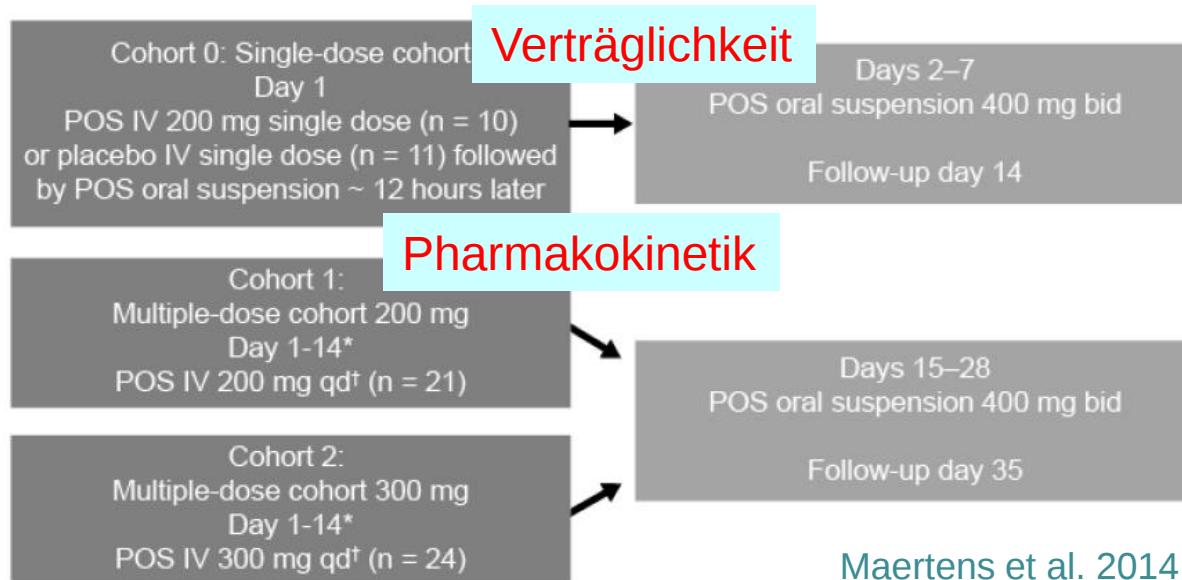
Resorption unabhängig von Antacidum, H₂ Blocker, PPI und Prokineticum

Kraft et al. 2014 AAC 5 May Epub ahead of print

Posaconazol-Formulierung für i.v. Gabe

Phase I B Dosisfindungsstudie n=66

- Lösungsvermittler Sulfobutyl-Ether- β -Cyclodextrin *SBEC*
- Erwachsene Pat. mit AML, MDS, sek. Leukämie
- Aplasierende Chemotherapie vorauss. $\geq 7d < 500$ Neutrophile
- Infusion über ZVK in Gluc 5% / NaCl 0.9%



UAW:

Unruhe, Übelkeit
LFP-Anstieg

Durchbruchsinfektionen

Maertens et al. 2014 AAC 14 April Epub ahead of print

Posaconazol i.v. Pharmakokinetik

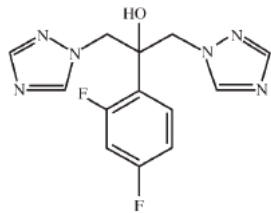
Dosis mg	N	C _{max} µg/mL	AUC _{0-24h} µg·h/mL	C _{avg} µg/mL	C _{min} µg/mL	Accum. ratio	% C _{avg} 0.5-2.5 µg/mL
Tag 1							
2 x 200	20	0.99 (47)	5.39 (29)	-	-	-	-
2 x 300	22	1.59 (61)	8.24 (26)	-	-	-	-
Tag 14							
1 x 200	15	1.95 (50)	28.20 (51)	1.18 (51)	0.96 (63)	3.6 (44)	94
1 x 300	19	2.61 (39)	34.3 (42)	1.43 (42)	1.07 (50)	2.8 (31)	95

Mean (CV%)

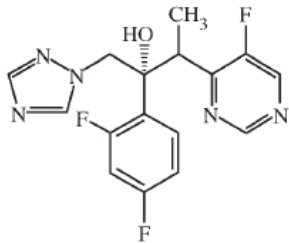
Dosis für die Phase III Studie: 1 x 300 mg i.v.

Maertens et al. 2014 AAC14 April Epub ahead of print

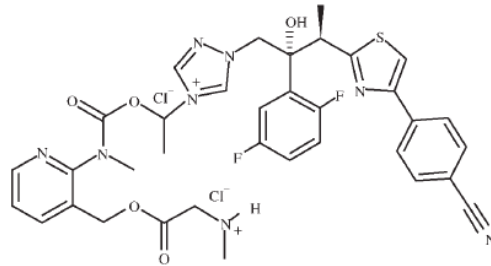
Neue Azole



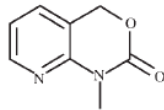
Fluconazole



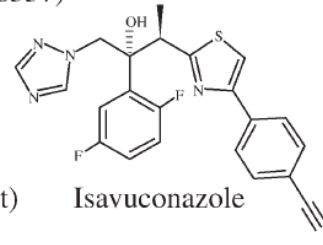
Voriconazole



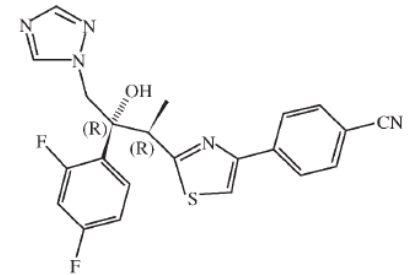
Isavuconazonium (pro-drug BAL-8557)



BAL-8728 (pro-drug cleavage product)



Isavuconazole



Ravuconazole

Pasqualotto & Denning 2008 JAC 61 suppl i19-30

Isavuconazol BAL 4815

- Wasserlösliche Pro-drug: Isavuconazonium BAL 8557
- **Spektrum in-vitro:** Candida, inklusive non-albicans, Aspergillus, Zygomyceten
- unwirksam gegen Fusarium und Sporotrix Schenkii
- **Dosis** iv. und p.o 1x200mg i.v. ü. 1h, LD 3x200mg x 2d
- $t_{1/2}$ i.v. 76-104 h, Vd ~300-500L, Proteinbindung 98%
- Metabolisierung CYP3A4, geringer CYP3A4-Inhibitor
- $\frac{1}{2}$ Dosis bei mild-mäßig eingeschränkter Leberfunktion

Schmitt-Hoffmann 2006 AAC 50:279; Schmitt-Hoffmann 2009 AAC 53:4885

Isavuconazol BAL 4815: klinische Studien

- **ISV**: Aspergillose und seltene Pilze, Niereninsuffizienz, Ph.III offen, nicht kontrolliert, n=150 NCT00634049
Abschluss April 2014? Keine Ergebnisse publiziert.
- Invas. Candidiasis **ISV vs. Caspofungin** gefolgt von **VRC** n=526 NCT00413218 Rekrutierung läuft
- **ISV** Prophylaxe bei AML n=18 NCT00413439, Resultate?
- **ISV** Dosis: 3x200 mg iv/p.o.x2d => 1x200mg

Isavuconazol BAL 4815 gegen Voriconazol: Phase III Studie

Aspergillose und andere Schimmelpilze **ISV vs. VRC**

n=516 NCT00412893 „SECURE“ Double Blind, Non-Inferiority,

Aspergillose 85%, Lungenbefall 92%, maligne hämatolog. GK 84%

Neutropenie 65% HSCT 20%

ISV d 1,2: 3x200iv => 1x200 iv/po 258 ITT	42-d Mortalität	18.6%
VRC d 1: 2x 6 mg/kg d 2: 2x4 mg/kg iv => 2x4 mg/kg iv / 2x200mg po 258 ITT	42-d Mortalität	20.2%

Maertens et al. 2014 ECCMID O230a

Ravuconazol BMS 207147, ER 30346

- Spektrum: Candida, Cryptococcus neoformans, Aspergillus, ~50% Mucorales
- Kreuzresistenz mit anderen Azolen
- i.v. Ravuconazol-Dilysin-Phosphoester (keine Akkumulation bei NI wie bei Cyclodextrin)
- Metabolisierung: CYP 3A4, geringer Inhibitor 2C9, 2C19?
- $t_{1/2}$ = 76-202 h, Proteinbindung 98%

Pasqualotto & Denning 2008 JAC 61 suppl i19-30; Bellmann 2007 CCP 2, 37-58

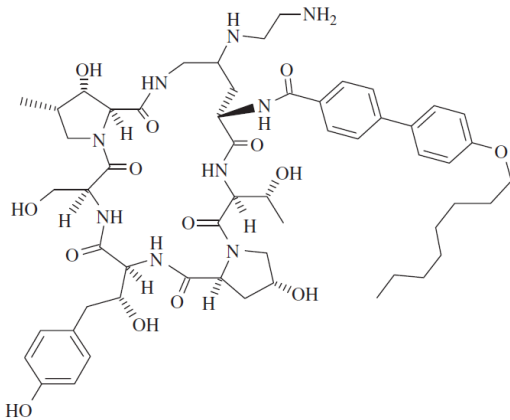
Ravuconazol bei Stammzelltransplantation und anderen Indikationen

- RAV in preventing FIs in allogeneic SCT n=24
RAV po. d -2 v. Chemotherapie – Take / - CYA
Durchbruchsinfektionen? Phase II, NCT00064311 Chair: T.Walsh
⇒ abgeschlossen 2012?, Resultate noch nicht publiziert
- RAV bei Chagas Krankheit *T. cruzi* Phase II NCT01489228,
in-vitro- und Tierexperimente
- RAV bei Onychomycose n=151
 - 1x200 mg/d => 56% Heilungsrate n. 48 Wo
 - 100 mg/Wo => 10% Heilungsrate
 - 400 mg/Wo => 8% Heilungsrate
 - 15% Heilungsrate unter Placebo

Gupta et al. 2005 J Eur Acad Dermatol
Venereol. 19:437-43.

Hemmung der β -(1,3)-D-Glucan-Synthase

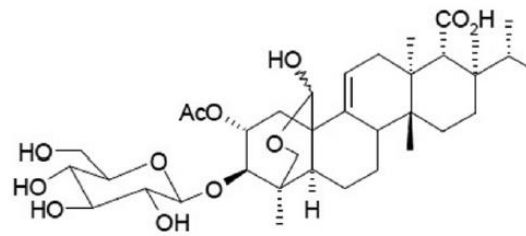
Aminocandin (IP960/HMR-3270)



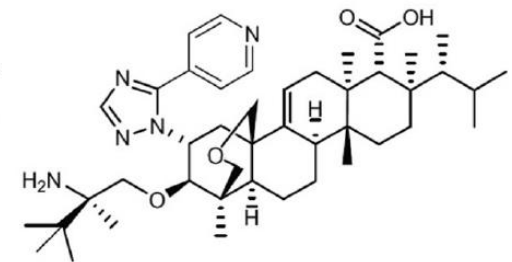
Halbsynthetisches
Fermentierungsprodukt von
Aspergillus sydowi

Warn et al 2005 JAC 56:, 590–3

Efumafungin und MK-3118/ SCY-078:



Efumafungin



MK-3118

Triterpenoid-Glycosid Fermentierungs-
produkt von *Homonema Sp.*

Jiménez-Ortigosa et al. 2014 AAC 58:1248-51

Aminocandin HMR-3270: Phase I und Tiermodell

- 12 männliche Probanden
- Spektrum: Candida, Aspergillus
- Dosis 75-300 mg $C_{\max}$ 4.9-16.1 µg/ml, Proteinbg. 99.9%
- $t_{1/2}$ = 48-58h, antimykotischer Effekt noch 168 h nach 300 mg Dosis, V_d ~25L
- Gut verträglich in Phase I
- MEC *A. fumigatus* 0.06 µg/ml
- Relevanter PK/PD-Parameter: $C_{\max}/MIC$

Sandage et al 2005 ECCMID P1115

Andes et al 2003 AAC 47:1187-92

MK-3118/SCY-078: halbsynthetisches Efumafungin-Derivat

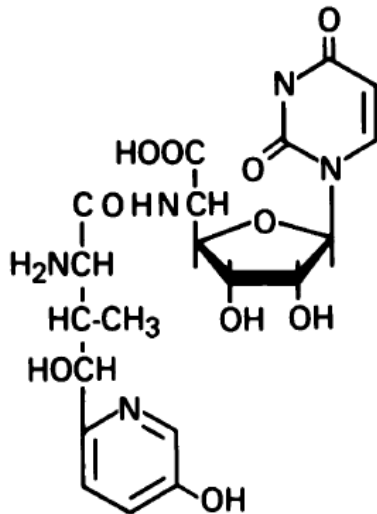
- Keine publizierten Daten über Tierversuche oder Phase I
- Entwickelt für orale Gabe

				Species		MEC/MIC (μg/ml) ^a		
				(no. of isolates tested)	Antifungal agent	Range	50%	90%
				<i>A. flavus</i> SC (23)	MK-3118	0.06–0.12	0.06	0.12
					Amphotericin B	1–2	2	2
					Caspofungin	≤0.008–0.03	0.015	0.03
		Mode value and MEC ₅₀ range (mg/liter) ^a						
Species	Phenotype (no. of isolates)	Caspofungin	MK-3118	<i>A. fumigatus</i> SC (21)	MK-3118	0.03–1	0.12	0.25
<i>A. flavus</i>	WT (10)	0.12 (0.06–2)	8 (2.0–16)		Amphotericin B	1–2	1	2
					Caspofungin	0.015–0.25	0.03	0.06
<i>A. fumigatus</i>	WT (1)	0.12	0.12	<i>A. terreus</i> SC (18)	MK-3118	0.03–0.25	0.06	0.12
	ER (1)	>16	0.12		Amphotericin B	1–4	2	2
	WT (6 [ITR ^s]) ^c	0.12 (0.12–0.25)	8 (0.12–8)		Caspofungin	≤0.008–0.06	0.015	0.06
	WT (8 [ITR ^r]) ^b	0.12 (0.06–0.25)	0.25 (≤0.03–8)					
<i>A. niger</i>	WT (10)	0.12 (0.06–0.12)	0.12 (≤0.03–0.25)	<i>A. niger</i> SC (9)	MK-3118	0.03–0.25	0.06	ND ^b
<i>A. terreus</i>	WT (6)	0.06 (0.06–0.25)	0.12 (0.06–0.12)		Amphotericin B	1	1	ND
					Caspofungin	≤0.008–0.06	0.03	ND

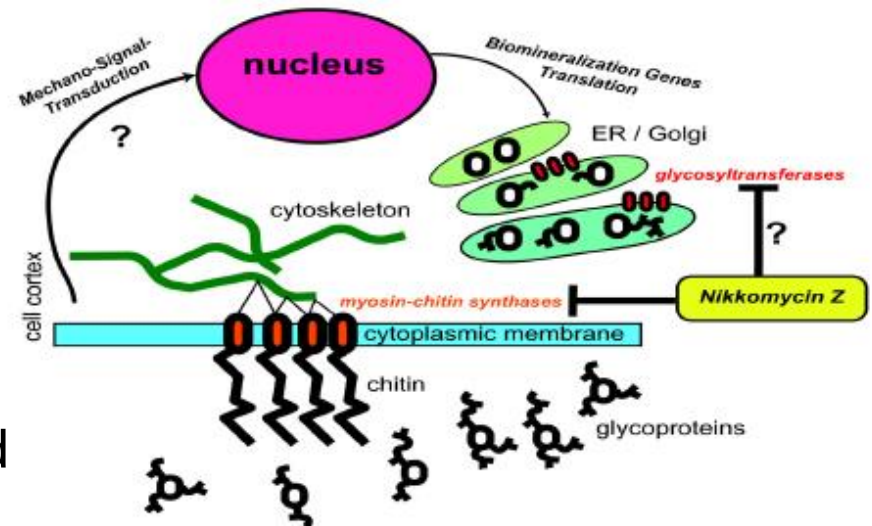
Jiménez-Ortigosa et al. 2014 AAC 58:1248-51

Pfaller et al. 2013 AAC 57:1065-68

Hemmung der Chitin-Synthese: Nikkomycin Z

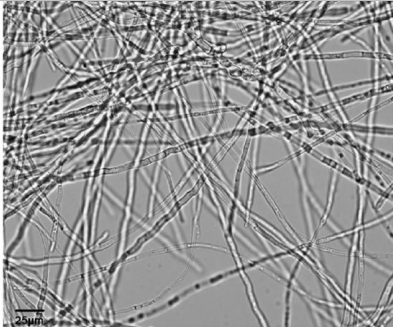


Peptidyl-Nukleosid

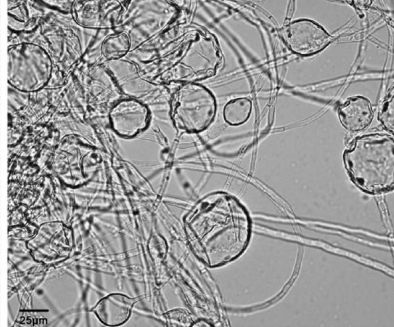


Cabib 1991 AAC 35: 170–173

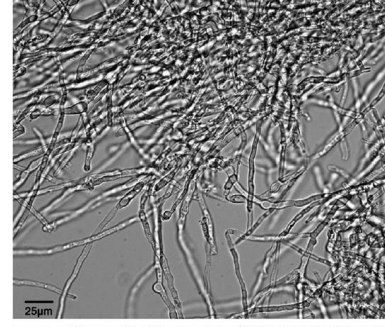
Nikkomycin Z gegen Aspergillus?

Kontrolle *A. fumig.*

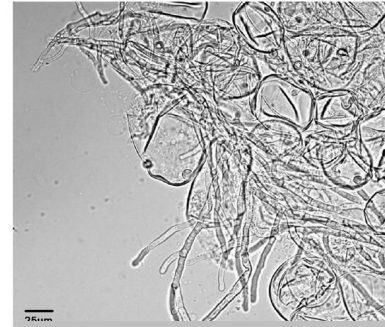
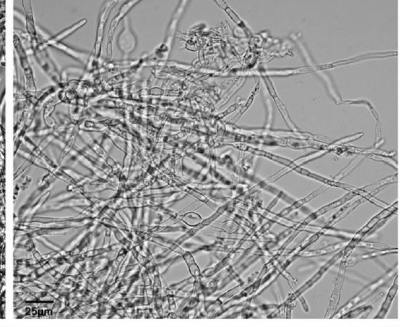
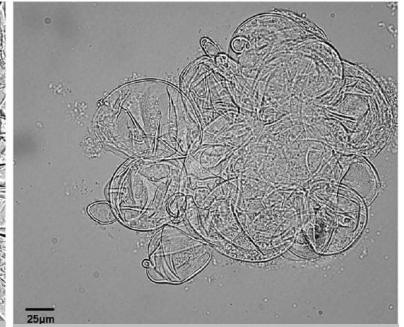
Nikko 8 µg/ml



CAS 0,125 µg/ml



CAS 4 µg/ml

CAS 0,125 µg/ml
+ Nikko 8 µg/mlCAS 4 µg/ml
+ Nikko 8 µg/ml

<i>A. fumigatus</i>	10 Stämme	FICI
Caspofungin	MEC 0.25 (0.006-0.5)	
Nikkomycin Z	MIC >64	0.15

FICI Fractional inhibitory concentration index

$$FICI = [(MIC_{A \text{ in combination}}) / MIC_A] + [(MIC_{B \text{ in combination}}) / MIC_B]$$

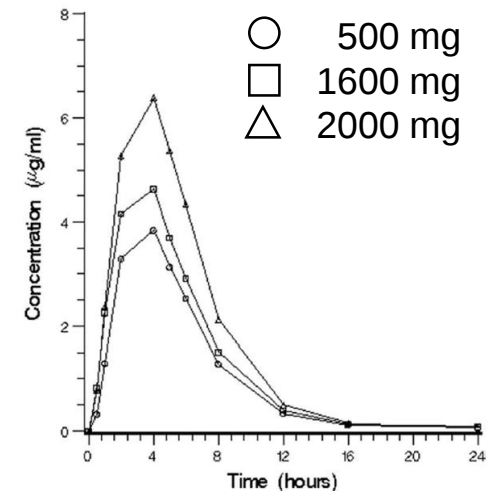
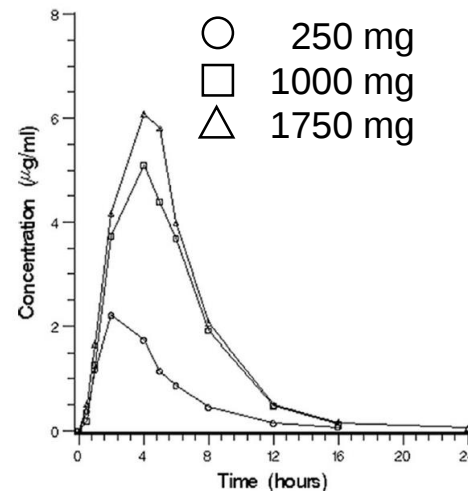
Schwache Wirkung allein, in-vitro synergistisch mit Echinocandin

Nikkomycin Z in klinischen Studien

• Pharmakokinetik in 12 Probanden

Dosis	250-2000 mg po
$t_{1/2}$	~2.5 h
$T_{\max}$	2-4 h
F rel.	40-70%

Keine ernsten Nebenwirkungen



Nix et al. 2009 AAC 53:2517

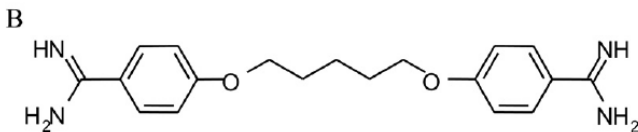
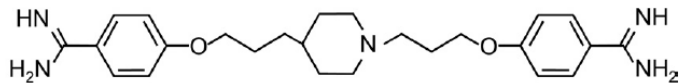
• Phase I/II Coccidioidomycose NCT00614666

2x50-3x750 mg p.o. x 2 Wo n=40

Vorzeitig abgebrochen "Recruitment challenges and lack of funding caused an early end to this study"

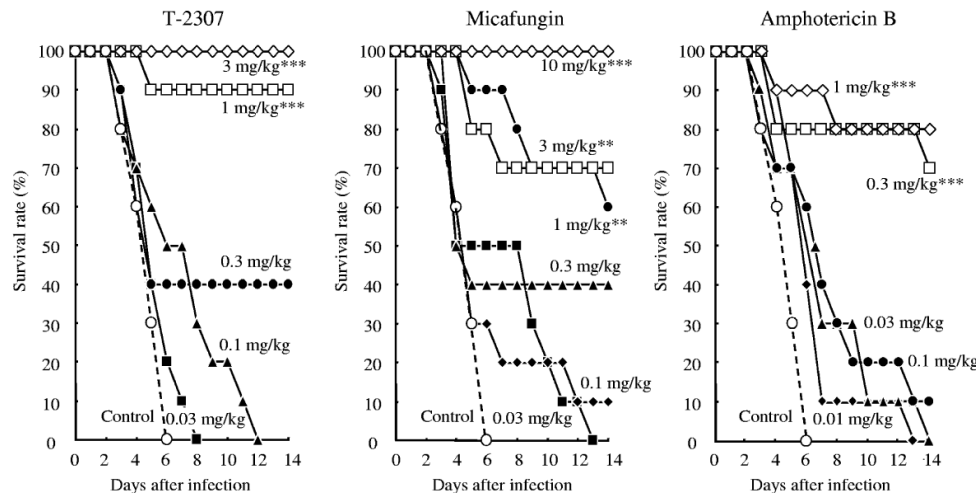
Ziel fungale Mitochondrien: T-2307 (Arylamidin)

T-2307



Pentamidin

Species (no. of isolates)	Antifungal agent	MIC ($\mu\text{g/liter}$)		
		Range	50%	90%
<i>Aspergillus fumigatus</i> (20)	T-2307	0.125–4	1	2
	Fluconazole	64–>64	>64	>64
	Voriconazole	0.25–1	1	1
	Micafungin	0.0313	0.0313	0.0313
	Amphotericin B	1–2	2	2



Störung der Mitochondrienfunktion in Hefen, nicht aber in Ratten-Mikrosomen:
Zusammenbruch des Membran-Potentials

Laufende Phase I Studie

Invas. Aspergillose der Maus *A. fumigatus*

Mitsuyama et al. 2008 AAC 52:1318-24

R. Bellmann, Innsbruck

Shibata et al. 2012 AAC 56: 5892-07

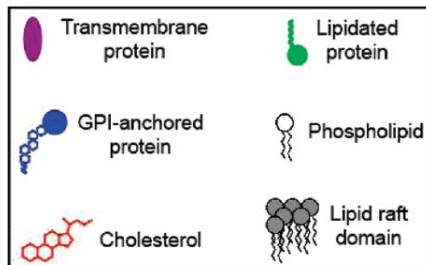
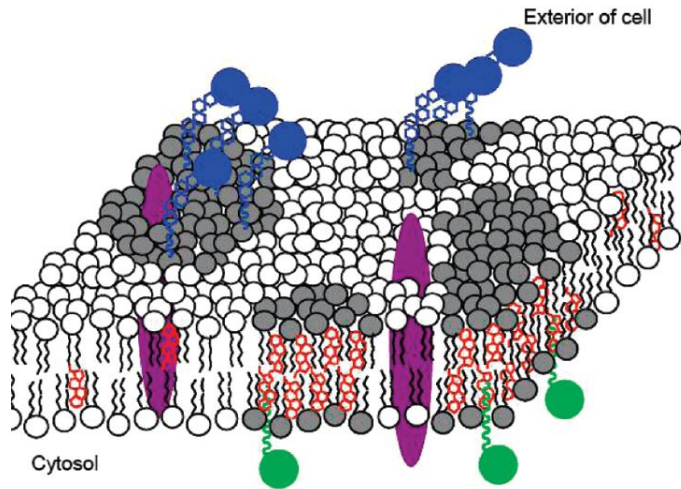
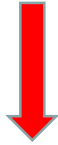
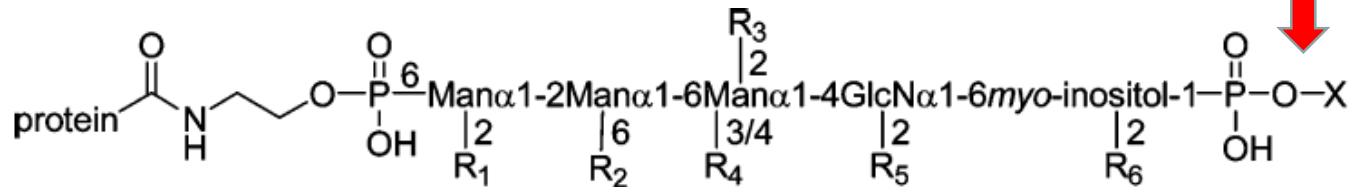
Histon-Hos2-Deacetylase-Hemmer: MGCD-290

Species	No. of isolates tested	Antifungal agent	MIC ($\mu\text{g/ml}$)		
			Range	50%	90%
<i>A. fumigatus</i>	3	Fluconazole	>256	>256	
		Posaconazole	0.25–0.5	0.25	
		Voriconazole	0.25–0.5	0.25	
		MGCD290	8.0–>32	16	
<i>C. glabrata</i>	14	Fluconazole	2–>256	64	128
		Posaconazole	0.25–>8.0	2.0	>8
		Voriconazole	0.03–8.0	1.0	4.0
		MGCD290	0.5–4.0	2.0	4.0

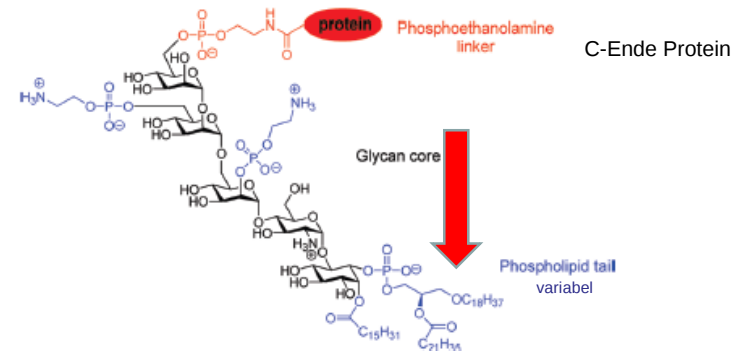
Species	Strain no.	Antifungal agent	MIC ($\mu\text{g/ml}$) of each agent:	
			Alone	With MGCD
<i>A. niger</i>	20546.100	Fluconazole	>256	16 (16)
		Posaconazole	2.0	0.25 (16)
	20552.002	Fluconazole	>256	16 (16)

=> Schwach wirksam gegen *Aspergillus*, Kombinationspartner?

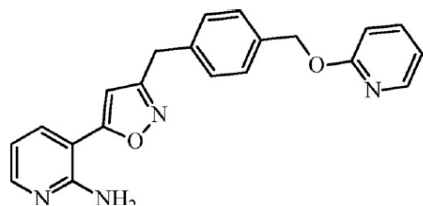
Glycosyl-Phosphatidyl-Inositol-Anker von Zellmembranproteinen als Ziel



Struktur des GPI-Ankers



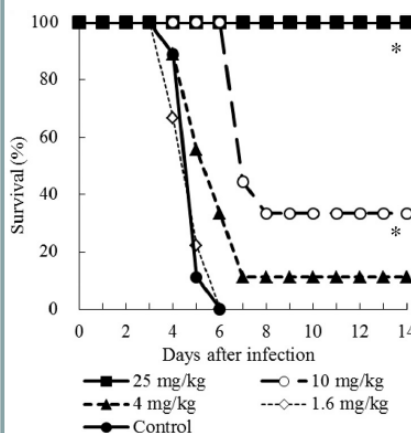
Hemmung der Synthese des GPI-Ankers von Membranproteinen: E-1210 *Eisai*



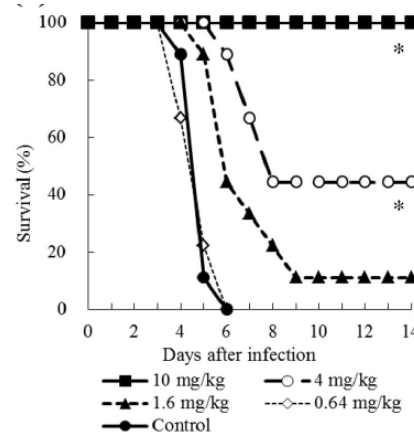
1-(4-butylbenzyl) isoquinoline (BIQ)-Derivat
E-1210, verträglich bis 300mg/kg in Ratten

Species	Isolate no.	MIC/MEC (µg/ml) for ^a :						E1210
		ITR	PSC	VRC	AMB	ANF	CSF	
<i>A. fumigatus</i> SC	8686	>8	1	2	1	0.015	0.12	0.12
	8687	>8	1	2	1	0.015	0.12	0.06
	8688	>8	1	1	1	0.008	0.12	0.03
	8689	>8	1	2	1	0.015	0.12	0.06
	8690	>8	2	8	1	0.008	0.12	0.06
	8737	4	1	2	1	0.015	0.12	0.03
	8737	>8	1	0.25	1	0.008	0.12	0.03
<i>A. niger</i> SC	8698	4	1	2	1	0.008	0.12	0.008
	301	4	1	2	0.5	0.008	0.12	0.008
<i>A. terreus</i> SC	8731	4	2	>8	2	0.008	0.12	0.015

E-1210 p.o.



Voriconazol p.o.



Pulmonale Aspergillose, Maus, *A. flavus*

Hemmung der Synthese von
Glycosyl-phosphatidylinositol (GPI):
=> GPI-verankerte Zellwandproteine
=> Hyphenverlängerung,
Wachstumshemmung

Hata et al. 2011 AAC 55:4543-51

Pfaller et al. 2011 AAC 55:5155-58

Zusammenfassung

- POSA Tabletten (bald) verfügbar, bessere Resorption
POSA i.v. derzeit Phase III
- ISV i.v./p.o. vergleichbar mit VRC: Zulassungsantrag bald
- RAVU: derzeit Phase III
- AMB-Nanopartikel-Präparate u. a. orale: tierexperimentell
- Aminocandin HMR-3270 Phase I als Abstract
- MK-3118/SCY-078 Phase I? Phase II geplant
- Nikkomycin Z in-vitro Synergismus mit ECHI
- Pilz-Mitochondrien: T-2307
- Histon-Deacetylase: MGCD-290 in-vitro
- Glycosyl-Phosphatidyl-Inositol-Protein-Anker: E-1210