Generation of Broad-Spectrum Antifungal Drug Candidates from the Natural Product Aureobasidin A

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Kalexsyn
a Dipharma Francis S.r.l. company

Aureobasidin A (AbA)

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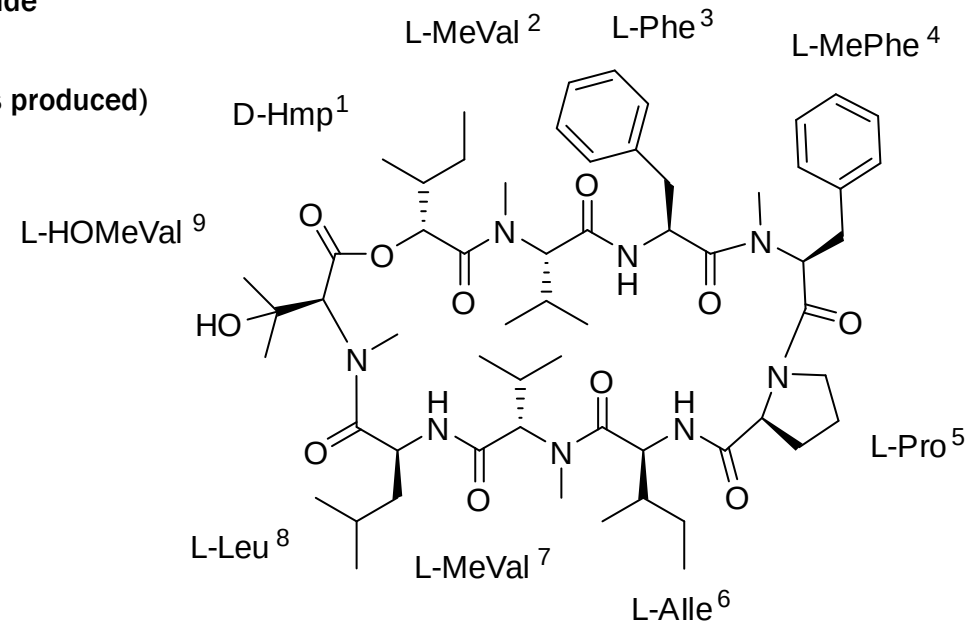
AureoGen Biosciences, Inc.

- AbA is an inhibitor of inositol phosphorylceramide synthase (IPC) which is absent in mammals
- Produced by low cost fermentation (100s kilos produced)
- Novel target and MoA
- Very specific and cidal
- No resistant strains
- Efficacious and well tolerated
- IV and PO
- Phase I clinical trials
- Limited spectrum



Takesako, K.; *et al. J. Antibiot.* **1993**, *46*, 1414-1420.
Aeed, P. A.; *et al. Biochemistry* **2004**, *43*, 8483-8493.

AbA Analogs in the Literature

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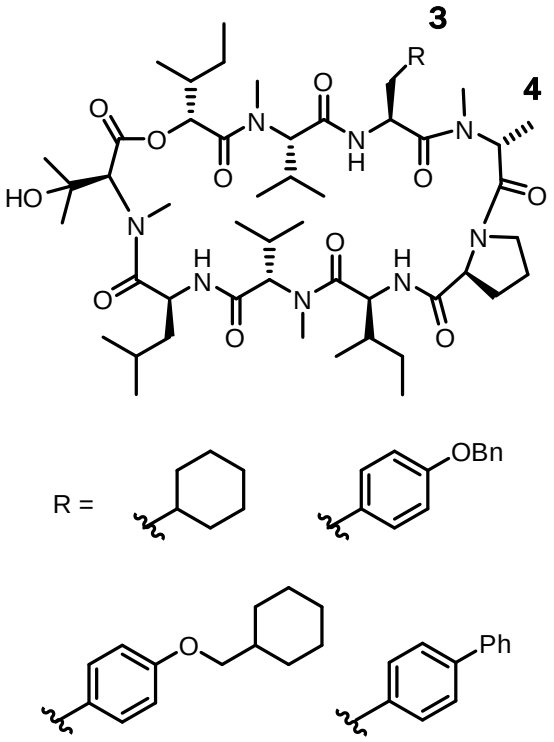
Compounds synthesized by TakaraBio

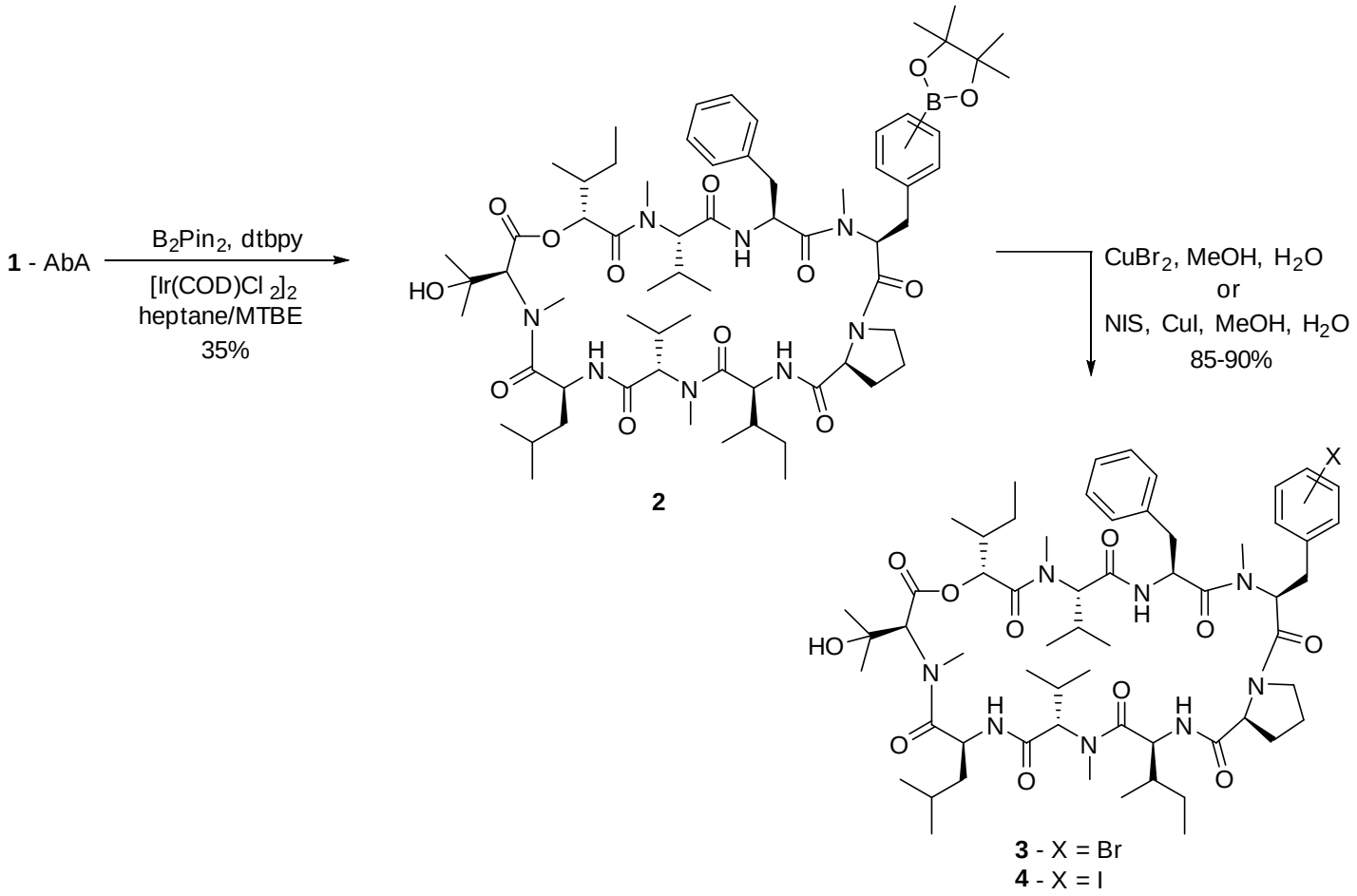
Residue #		MIC (µg/ml)	
3	4	C. albicans	A. fumigatus
L-cha	D-me-Ala	0.013	3.1
L-Tyr(bzl)	D-me-Ala	0.05	1.6
L-Tyr(chm)	D-me-Ala	0.1	1.6
L-bph	D-me-Ala	0.1	0.8
Native aureobasidin A		<0.05	>25



Prepared by partial degradation and re-synthesis in low yield

Kurome, T. and Takesako, K. *Curr. Opin. Anti-Infect. Invest. Drugs*, **2000**, *2*, 375-386.

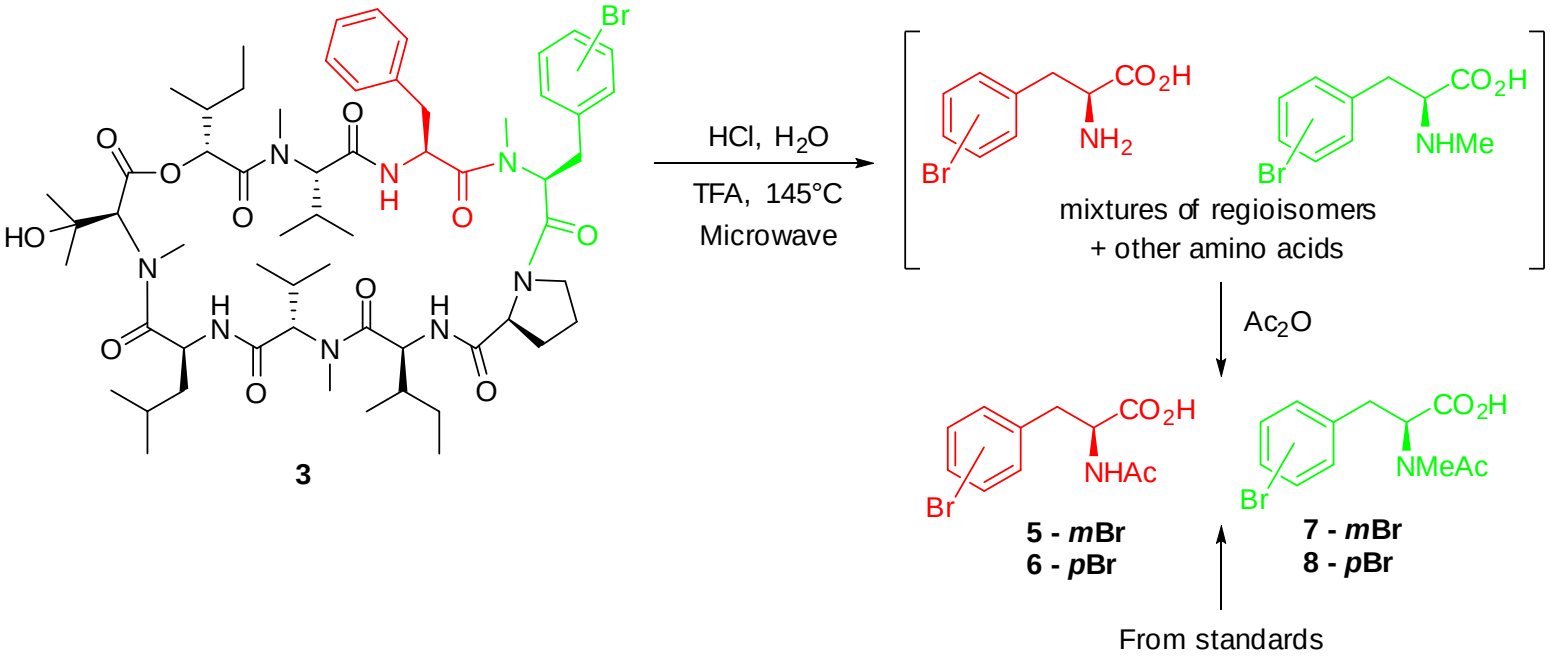
Borylation of AbA



Meyer, F. -M.; Liras, S.; Guzman-Perez, A.; Perreault, C.; Bian, J.; James, K. *Org. Lett.* **2010**, *12*, 3870-3873.

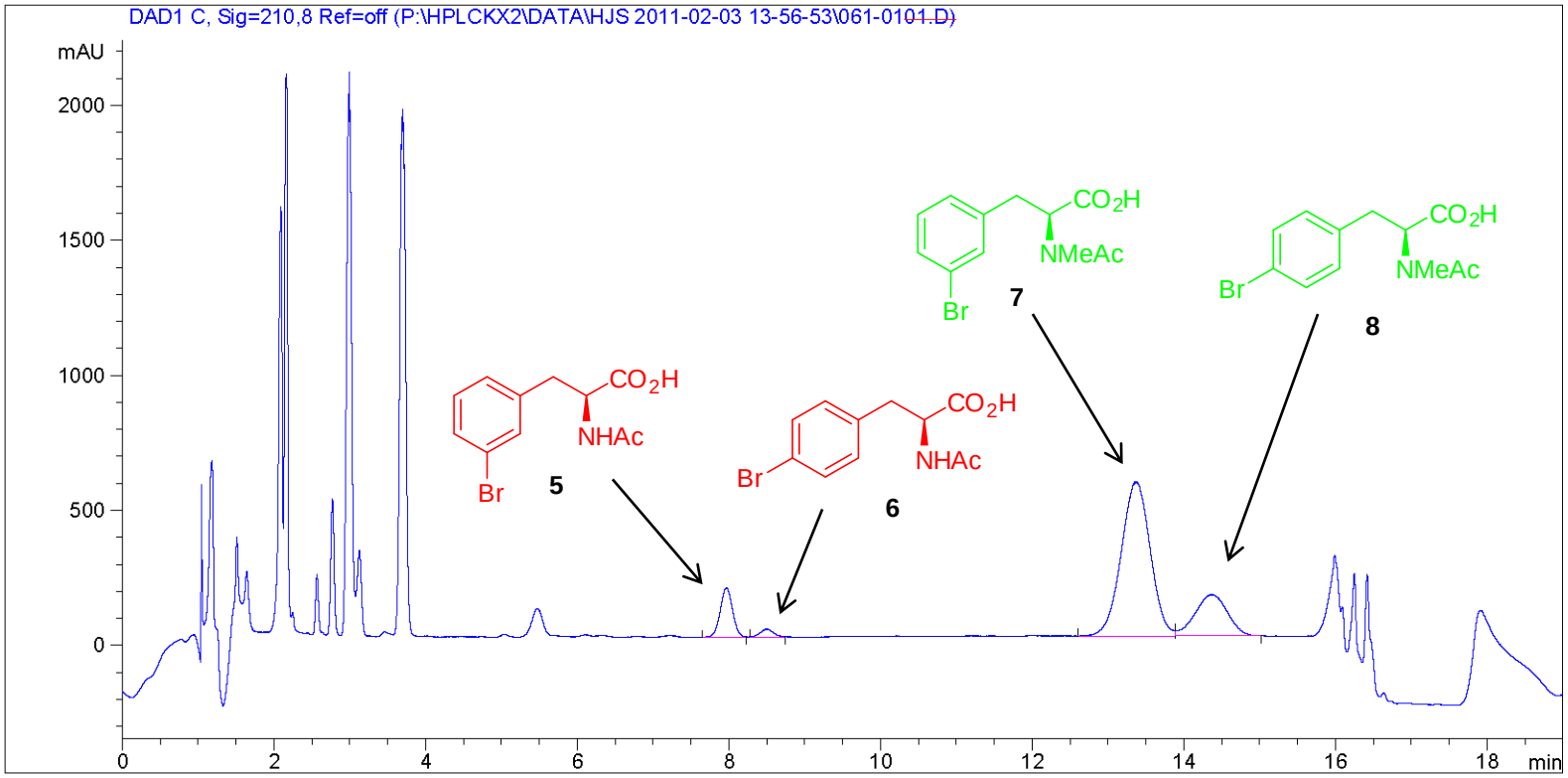
Wuts, P. G.M.; Simons, L. J.; Metzger, B. P.; Sterling, R. C.; Slightom, J. L.; and Elhammer, A. P. *ACS Med. Chem. Lett.* **2015**, *6*, 645−649.

Determination of Isomeric Ratio



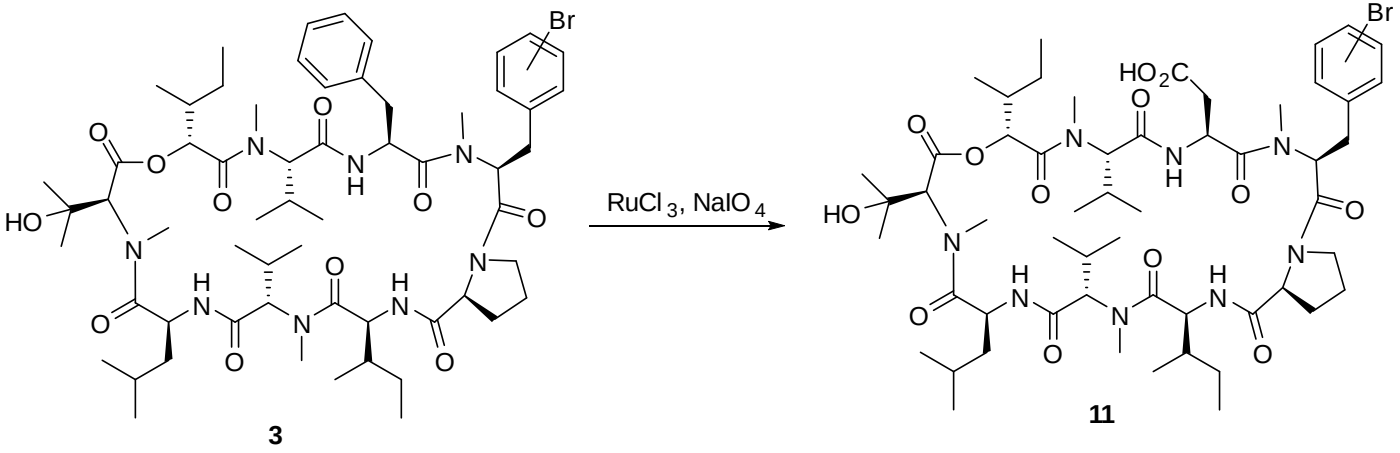
Tsugita, A. and Scheffler, J.-J. *Eur. J. Bicochem.* **1982**, *124*, 585.

Determination of Isomeric Ratio

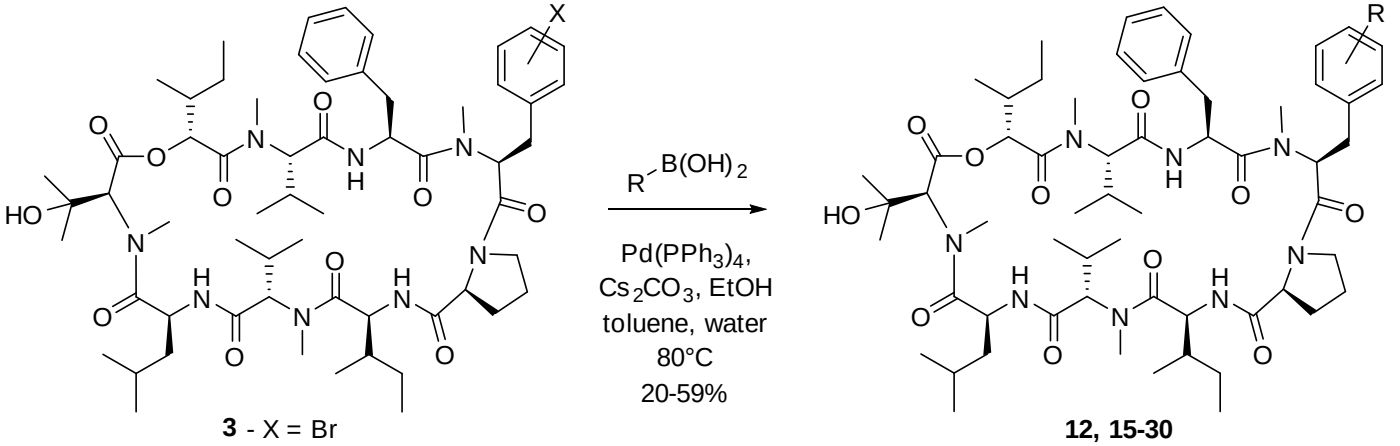


The ratio of **5:6:7:8** was 9:2:62:27. No ortho substitution was detected.

Synthesis of Analogs



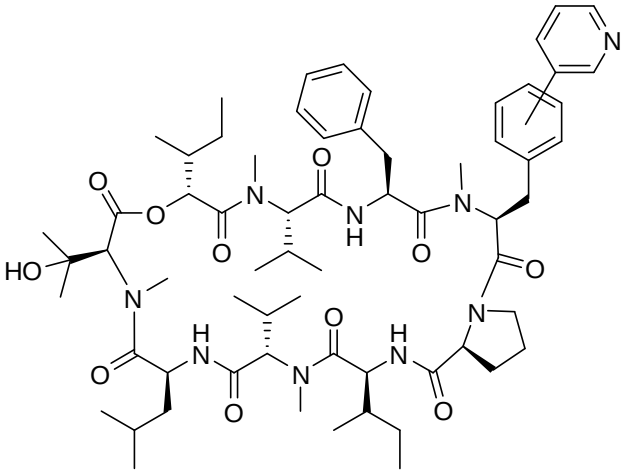
3 **11**



3 - X = Br
4 - X = I

12, 15-30

In vitro Activity of Analogs



20

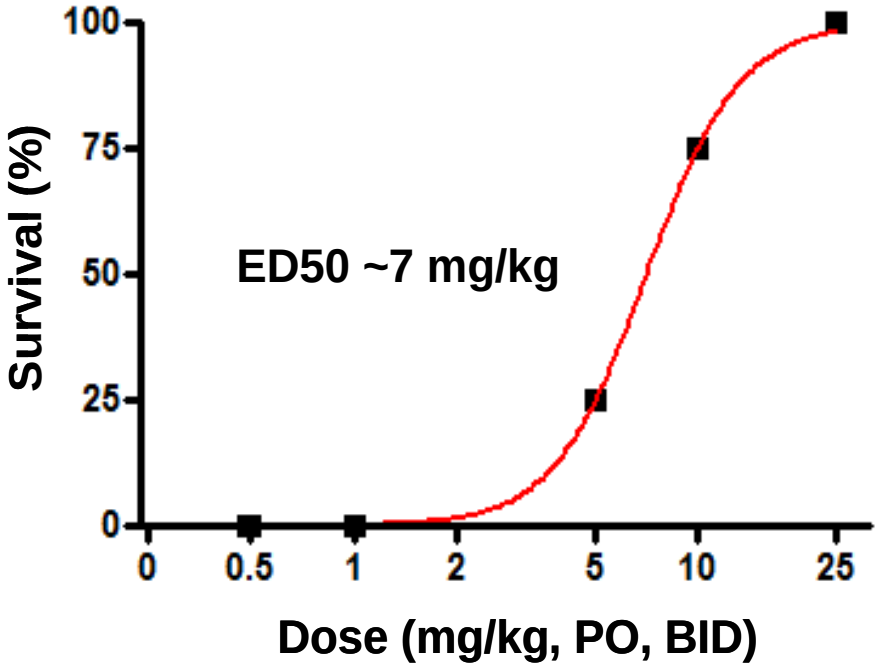
Cmpd	Modification	MIC (µg/ml)	
		C. albicans	*A. fumigatus*
1	AbA (native)	<0.05	>25
2	Boronate-mPhe^4	<0.5	10
3	Br-mPhe^4	0.031	2.5
4	I-mPhe^4	2.5	>5
10	B(OH)$_2$-mPhe^4	<0.05	>100
11	Asp^3-Br-mPhe^4	5	10
13	Br-Phe^3-Br-mPhe^4	5	>100
14	Asp^3-mAsp^4	10	>100
15	**Phenyl-mPhe^4**	**<0.05**	**<0.94**
20	**3-pyrid-1-yl-mPhe^4**	**<0.05**	**<0.94**
21	1-Cyclohexenyl-mPhe^4	ND	>5
22	4-acetamidophenyl-mPhe^4	ND	>5
25	2-Cl-Phenyl-mPhe^4	<0.5	<1.25
26	4-Cl-Phenyl-mPhe^4	<0.5	<2.5
27	4-pyridyl-mPhe^4	<0.025	<1.25
28	3-biphenyl-mPhe^4	<5	>5
30	2-chloropyridin-5-yl-mPhe^4	<0.025	<1.25

In vitro Activity of Compound 20

Organism	MIC (µg/ml)	
	Compound 20	Amphothericin B
C. albicans (ATCC 90029)	0.5	0.03
C. albicans (ATCC 10231)	1	0.03
C. albicans (ATCC 204276)	0.03	0.06
C. albicans (ATCC MYA-2732)	0.03	0.06
C. albicans (ATCC 24433)	0.125	0.03
C. guilliermondii (ATCC 34134)	0.03	0.008
C. krusei (ATCC 14243)	0.06	0.125
C. lusitaniae (ATCC 66035)	0.125	0.015
C. parapsilosis (ATCC 90018)	0.03	0.06
C. parapsilosis (ATCC 22019)	0.06	0.125
C. glabrata (ATCC 90030)	0.03	0.03

Organism	MIC (µg/ml)	
	Compound 20	Amphothericin B
A. fumigatus (ATCC 204305)	1	0.25
A. fumigatus (ATCC MYA-32626)	2	0.25
A. flavus (ATCC 204304)	1	0.25
A. flavus (ATCC 22546)	2	0.25
A. candidus (ATCC 13686)	0.008	0.03
A. clavatus (ATCC 10058)	0.03	0.004
A. niger (ATCC 64028)	0.03	0.015
T. rubrum (ATCC MYA-4438)	2	0.03
Cryptococcus neoformans (ATCC 90112)	0.03	0.015
Saccharomyces cerevisiae (ATCC 7754)	0.03	0.06

Compound 20 Efficacy in a Mouse Candidiasis Model



Acknowledgements

Kalexsyn

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