

# Supporting information

## The antifungal potential of (Z)-ligustilide and the protective effect of eugenol demonstrated by a chemometric approach

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**Table S1** Botanical identification, anticandidal activity (minimum inhibitory concentrations (MIC),  $\mu\text{g}/\text{mL}$ ) and antifungal activity score (AAS) measured for the selected essential oils. The antifungal activity score is calculated based on the measured minimum inhibitory concentrations (MICs), according to the following scheme:  $> 512 \mu\text{g}/\text{mL} = 0$ ;  $512 \mu\text{g}/\text{mL} = 1$ ;  $256 = 2$ ;  $128 = 3$ ;  $64 = 4$ . The final score is obtained by adding together the values obtained for each fungal strain.

**Table S2** Full data table of essential oil bioactivity chemometric analysis by OPLS

**Figure S1.** Permutations plot (100 permutations) displaying  $R^2$ -values (green circles) and  $Q^2$ -values (blue squares). The solid line represents the  $R^2$  regression line and the dashed line represents the  $Q^2$  regression line.

**Figure S2.** OPLS summary plot obtained using R *rop/s* package. Top left: significance diagnostic using permutation plots displaying  $R^2$ -values (light grey) and  $Q^2$ -values (dark grey). The solid line represents the  $R^2$  and  $Q^2$  regression lines. Top right: inertia barplot. The graphic indicates that 1 orthogonal component may be sufficient to capture most of the inertia. Bottom left: observation diagnostic. Bottom right: scores plot. The number of components and the cumulative  $R^2X$ ,  $R^2Y$  and  $Q^2Y$  are indicated below the plot.

**Figure S3.** OPLS loading scatter plot obtained using SIMCA 15.

**Table S3.** Full factorial design and results obtained for antifungal and cytotoxic activities. The anticandidal activity (minimum inhibitory concentrations (MIC),  $\mu\text{g}/\text{mL}$ ) and cytotoxicity ( $\text{IC}_{50}$ ,  $\mu\text{g}/\text{mL}$ ) are indicated for each combination. The antifungal activity score is calculated based on the measured minimum inhibitory concentrations (MICs), according to the following scheme:  $> 512 \mu\text{g}/\text{mL} = 0$ ;  $512 \mu\text{g}/\text{mL} = 1$ ;  $256 = 2$ ;  $128 = 3$ ;  $64 = 4$ . The final score is obtained by adding together the values obtained for each fungal strain.

**Table S1** Botanical identification, anticandidal activity (minimum inhibitory concentrations (MIC), µg/mL) and antifungal activity score (AAS) measured for the selected essential oils. The antifungal activity score is calculated based on the measured minimum inhibitory concentrations (MICs), according to the following scheme: > 512 µg/mL = 0; 512 µg/mL = 1; 256 = 2; 128 = 3; 64 = 4. The final score is obtained by adding the values obtained for each fungal strain.

Botanical identification, origin* and herbarium voucher number**	MIC C.a. LMG0 103***	MIC C.p. ATCC 22020***	MIC C.p. LMG0 06***	Antifungal Activity Score
<i>Thymus vulgaris</i> var1 (c)	64	64	64	12
<i>Levisticum officinale</i> (c)	64	64	128	11
<i>Cymbopogon citratus</i> (c)	128	128	64	10
<i>Protium heptaphyllum</i> (l, PS20)	128	64	128	10
<i>Cymbopogon citratus</i> (l, sample 1, PS40)	128	256	64	9
<i>Cymbopogon citratus</i> (l, sample 2, PS40)	256	128	128	8
<i>Syzygium aromaticum</i> (c,)	256	128	128	8
<i>Backhousia citriodora</i> (c)	256	256	128	7
<i>Leptospermum petersonii</i> (c)	256	>512	128	5
<i>Melissa officinalis</i> (c)	256	512	256	5
<i>Pelargonium graveolens</i> var2 (c)	512	256	512	5
<i>Pimenta racemosa</i> (c)	256	256	512	5
<i>Sphagneticola trilobata</i> (l, PS4))	512	256	256	5
<i>Pelargonium graveolens</i> var1 (c)	512	256	512	4
<i>Pimenta racemosa</i> (l, PS26)	512	512	256	4
<i>Cryptocarya agathophylla</i> var2 (c)	512	256	512	4
<i>Cymbopogon winterianus</i> (c)	>512	256	512	3
<i>Mentha x piperita</i> var1(c)	512	512	512	3
<i>Daucus carota</i> (c)	>512	512	512	2
<i>Thymus mastichina</i> (c)	>512	512	512	2
<i>Cedrus atlantica</i> (c)	>512	512	>512	1
<i>Citrus clementina</i> (c)	>512	512	>512	1
<i>Eucalyptus dives</i> (c)	>512	>512	512	1
<i>Lavandula angustifolia</i> (c)	>512	>512	512	1
<i>Mentha arvensis</i> (c)	512	>512	>512	1
<i>Thymus vulgaris</i> var2 (c)	512	>512	>512	1
<i>Piper aduncum</i> (l, PS22)	>512	512	>512	1
<i>Unxia camphorata</i> (l, PS7)	512	>512	>512	1
<i>Cinnamomum camphora</i> (c)	>512	>512	>512	0
<i>Cinnamomum tamala</i> (c)	>512	>512	>512	0
<i>Citrus aurantiifolia</i> (c)	>512	>512	>512	0
<i>Citrus aurantium</i> var1 (c)	>512	>512	>512	0
<i>Citrus aurantium</i> var2 (c)	>512	>512	>512	0
<i>Citrus reticulata</i> var1 (c)	>512	>512	>512	0

<i>Citrus reticulata</i> var2 (c)	>512	>512	>512	0
<i>Citrus sinensis</i> (c)	>512	>512	>512	0
<i>Citrus x bergamia</i> (c)	>512	>512	>512	0
<i>Citrus x limonum</i> (c)	>512	>512	>512	0
<i>Copaifera officinalis</i> (c)	>512	>512	>512	0
<i>Corymbia citriodora</i> (c)	>512	>512	>512	0
<i>Croton nuntians</i> (l, PS11)	>512	>512	>512	0
<i>Cupressus sempervirens</i> (c)	>512	>512	>512	0
<i>Eucalyptus globulus</i> (c)	>512	>512	>512	0
<i>Eucalyptus polybractea</i> (c)	>512	>512	>512	0
<i>Eucalyptus radiata</i> (c)	>512	>512	>512	0
<i>Eucalyptus smithii</i> (c)	>512	>512	>512	0
<i>Lavandula hybrida</i> (c)	>512	>512	>512	0
<i>Lavandula latifolia</i> (c)	>512	>512	>512	0
<i>Lavandula x intermedia</i> (c)	>512	>512	>512	0
<i>Licaria canella</i> (l, fresh bark, PS16)	>512	>512	>512	0
<i>Licaria canella</i> (l, wood, PS16)	>512	>512	>512	0
<i>Licaria cannella</i> (l, dry bark, PS16)	>512	>512	>512	0
<i>Melaleuca ericifolia</i> (c)	>512	>512	>512	0
<i>Mentha x piperita</i> var2 (c)	>512	>512	>512	0
<i>Mikania micrantha</i> (l, PS12)	>512	>512	>512	0
<i>Pinus caribaea</i> (l, PS14)	>512	>512	>512	0
<i>Piper hispidum</i> (l, sample 1, PS23)	>512	>512	>512	0
<i>Piper hispidum</i> (l, sample 2, PS23)	>512	>512	>512	0
<i>Piper marginatum</i> (l, PS21)	>512	>512	>512	0
<i>Cryptocarya agathophylla</i> (c)	>512	>512	>512	0
<i>Rosmarinus officinalis</i> (c)	>512	>512	>512	0
<i>Thymus vulgaris</i> var3 (c)	>512	>512	>512	0
<i>Turnera odorata</i> (l, PS38)	>512	>512	>512	0
<i>Varronia curassavica</i> (l, PS5)	>512	>512	>512	0
<i>Vouacapoua americana</i> (l, AR6)	>512	>512	>512	0
<i>Zingiber officinale</i> (c)	>512	>512	>512	0

\* (c): commercial; (l): laboratory

\*\* for the plants collected in French Guiana; plant collectors: Pierre Silland (PS) and Alice Rodrigues (AR)

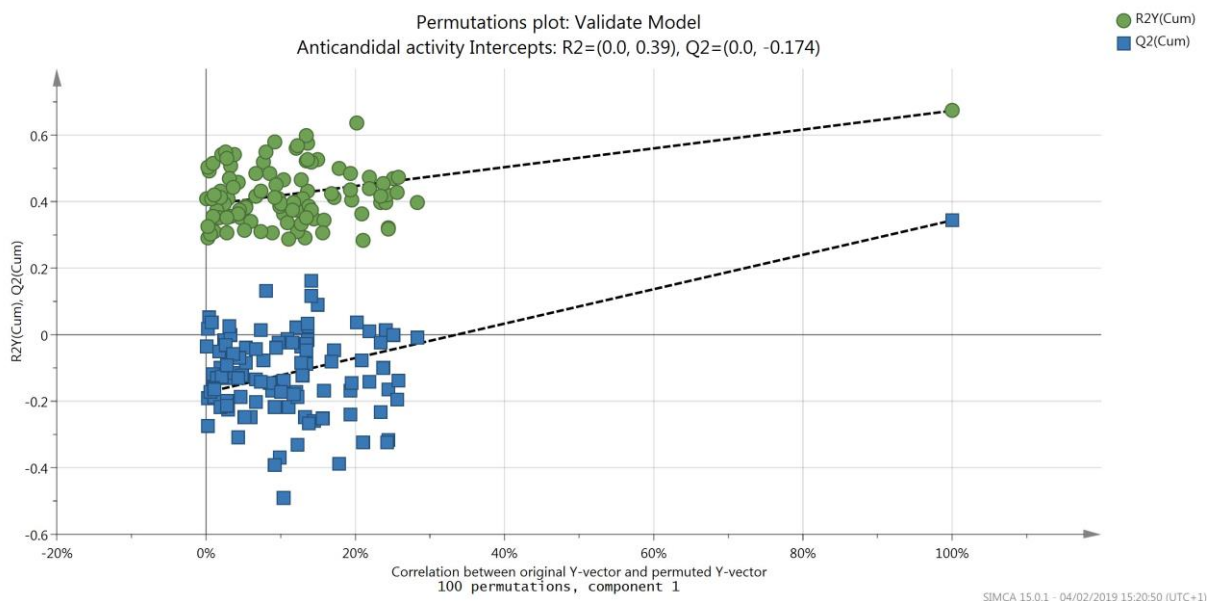
\*\*\* *C.a. Candida albicans*; *C.p. Candida parapsilosis*

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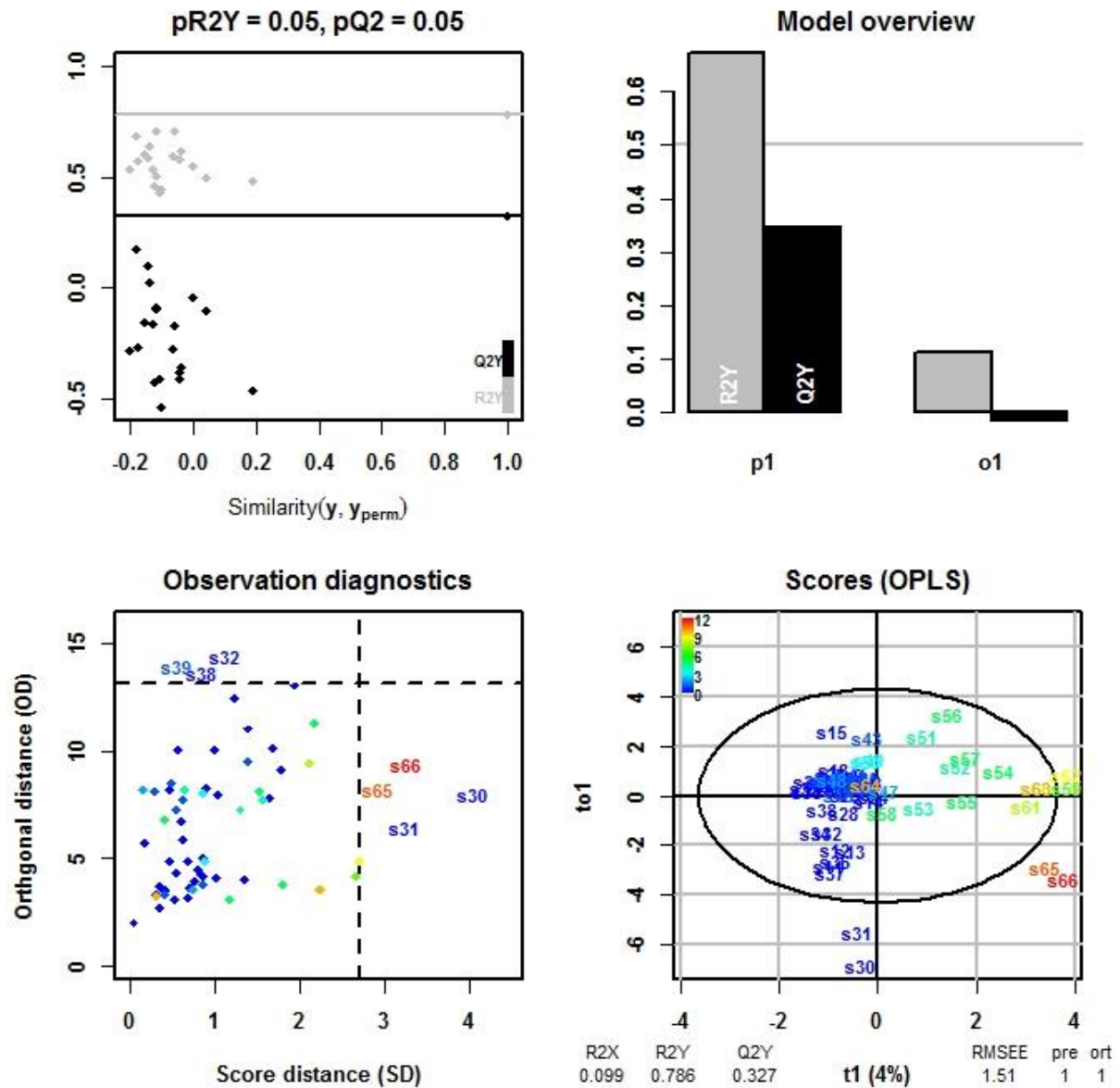
<b>Var ID (Primary)</b>	<b>M1.CoeffCS[1] (Anticandidal activity)</b>	<b>2.44693 * M1.CoeffCS[1] (Anticandidal activity)cvSE</b>
FU	0.226922	0.133096
FF	0.222602	0.120642
GI	0.160261	0.370596
PS	0.14514	0.338895
HL	0.109145	0.159558
MH	0.0969221	0.227263
AT	0.0769188	0.149939
FA	0.0655938	0.0892951
FV	0.0590428	0.0963044
JN	0.0496585	0.111952
FO	0.0407129	0.0893108
EL	0.0323164	0.0784412
DR	0.0280096	0.0659178
DG	0.0072838	0.0124753
BC	0.00566723	0.153568
OK	0.000487046	0.00437213
EE	-0.0000164412	0.00648229
IB	-0.00212655	0.053949
DF	-0.00324156	0.076832
FP	-0.00596497	0.0471081
AI	-0.0147207	0.101058
KA	-0.0155855	0.0338889
KU	-0.0155855	0.0338889
LV	-0.0155855	0.0338889
OO	-0.0168079	0.0393681
BK	-0.018436	0.136655
DB	-0.0212132	0.079684
MC	-0.0297421	0.0723836
BE	-0.0298598	0.076742
MN	-0.0316515	0.0763212
EQ	-0.031658	0.0725101
GD	-0.031658	0.0712443
HV	-0.031658	0.0712443
KE	-0.031658	0.0712443
LO	-0.031658	0.0762484
OB	-0.031658	0.0762484
RF	-0.031658	0.0748603
BL	-0.032161	0.0744401
OW	-0.033809	0.0743698
GB	-0.0380244	0.0694962
NX	-0.0381101	0.069763
AF	-0.0391985	0.0691309

KW	-0.0399454	0.0744402
AY	-0.0404889	0.0319635
LL	-0.0451194	0.0725257
JJ	-0.0461541	0.0573595
LR	-0.0528982	0.0679319
BD	-0.0560966	0.124701
LF	-0.0593095	0.0641676
AN	-0.0604593	0.0745833
NN	-0.0605584	0.0657862
IA	-0.0632474	0.0686619
DA	-0.0640168	0.0646835
AP	-0.0657449	0.102099
IV	-0.0700415	0.0753341
KD	-0.0701151	0.0678144
BF	-0.0746817	0.0687898
FM	-0.0762967	0.0784396
EF	-0.0767521	0.0873149
CE	-0.0881575	0.0646603

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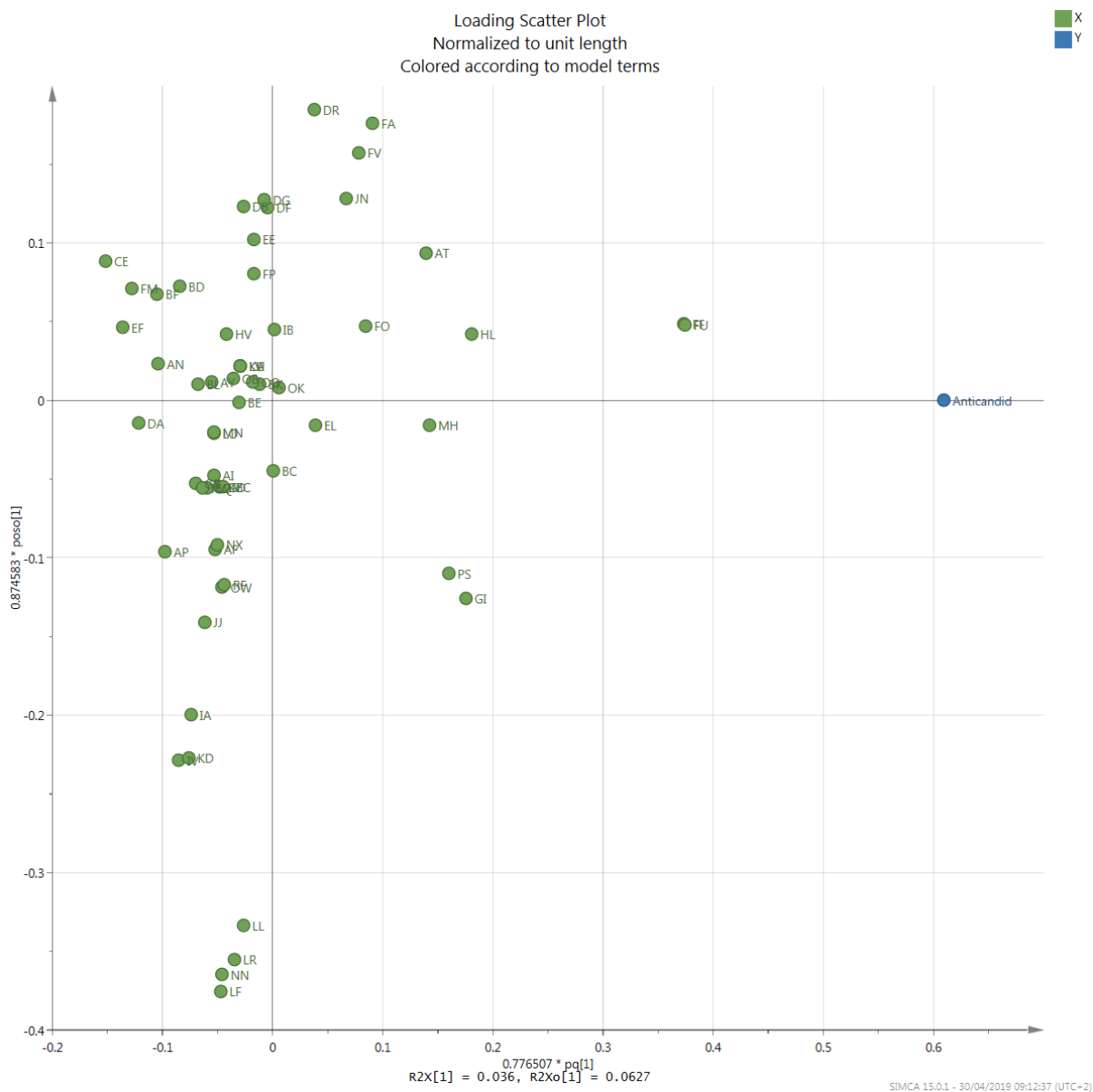


**Figure S1.** Permutations plot (100 permutations) obtained using SIMCA software and displaying  $R^2$ -values (green circles) and  $Q^2$ -values (blue squares). The solid line represents the  $R^2$  regression line and the dashed line represents the  $Q^2$  regression line.



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**Figure S3.** OPLS loadings plot obtained using SIMCA 15. Letters indicate compounds from the analysis. Points for compounds FF and FU are superimposed. FF: (*Z*)-Citral; FU: (*E*)-Citral; GI: Thymol; PS: (*Z*)-Ligustilide; HL: Eugenol; MH: Eugenyl acetate; AT:  $\beta$ -Pinene; FA: (*-*)-Citronellol; FV: (*-*)-Citronellyl formate; JN: Aristolene; FO: (*E*)-Anethole; EL: Estragol.

**Table S3.** Full factorial design and results obtained for antifungal and cytotoxic activities. The anticandidal activity (minimum inhibitory concentrations (MIC),  $\mu\text{g/mL}$ ) and cytotoxicity ( $\text{IC}_{50}$ ,  $\mu\text{g/mL}$ ) are indicated for each combination. The antifungal activity score is calculated based on the measured minimum inhibitory concentrations (MICs), according to the following scheme:  $> 512 \mu\text{g/mL} = 0$ ;  $512 \mu\text{g/mL} = 1$ ;  $256 = 2$ ;  $128 = 3$ ;  $64 = 4$ . The final score is obtained by adding the values obtained for each fungal strain.

StdOrder	RunOrder	Ligustilide	Eugenol	Citral	Thymol	Eugenyl acetate	$\beta$ -Citronellol	MIC C.a. ATCC10231	MIC C.p. ATCC22019	Antifungal activity score	$\text{IC}_{50}$ MRC5	Average SI
1	16	-1	-1	-1	-1	-1	-1	> 512	> 512	0	-	-
2	5	1	-1	-1	-1	-1	-1	32	64	9	4.5	0.09
3	22	-1	1	-1	-1	-1	-1	512	256	3	45.0	0.12
4	18	1	1	-1	-1	-1	-1	16	32	11	13.5	0.56
5	2	-1	-1	1	-1	-1	-1	64	64	8	8.0	0.12
6	57	1	-1	1	-1	-1	-1	32	32	10	6.0	0.19
7	29	-1	1	1	-1	-1	-1	64	64	8	13.0	0.20
8	1	1	1	1	-1	-1	-1	32	32	10	10.5	0.33
9	25	-1	-1	-1	1	-1	-1	128	64	7	9.0	0.09
10	9	1	-1	-1	1	-1	-1	64	64	8	6.5	0.10
11	64	-1	1	-1	1	-1	-1	128	128	6	13.0	0.10
12	59	1	1	-1	1	-1	-1	64	64	8	11.0	0.17
13	26	-1	-1	1	1	-1	-1	64	64	8	9.5	0.15
14	30	1	-1	1	1	-1	-1	64	64	8	10.5	0.16
15	4	-1	1	1	1	-1	-1	64	64	8	12.0	0.19
16	10	1	1	1	1	-1	-1	64	64	8	13.5	0.21
17	27	-1	-1	-1	-1	1	-1	512	128	4	47.5	0.15
18	46	1	-1	-1	-1	1	-1	64	64	8	11.5	0.18
19	52	-1	1	-1	-1	1	-1	256	128	5	37.5	0.19
20	39	1	1	-1	-1	1	-1	64	64	8	20.0	0.31
21	56	-1	-1	1	-1	1	-1	512	128	4	13.0	0.04
22	32	1	-1	1	-1	1	-1	64	64	8	10.5	0.16

23	8	-1	1	1	-1	1	-1	128	128	6	15.5	0.12
24	24	1	1	1	-1	1	-1	64	64	8	13.5	0.21
25	12	-1	-1	-1	1	1	-1	128	128	6	10.5	0.08
26	58	1	-1	-1	1	1	-1	64	64	8	12.5	0.19
27	13	-1	1	-1	1	1	-1	256	128	5	17.5	0.09
28	14	1	1	-1	1	1	-1	128	64	7	16.5	0.17
29	7	-1	-1	1	1	1	-1	128	128	6	11.5	0.09
30	20	1	-1	1	1	1	-1	64	64	8	11.5	0.18
31	40	-1	1	1	1	1	-1	128	128	6	11.0	0.08
32	54	1	1	1	1	1	-1	64	64	8	13.5	0.21
33	63	-1	-1	-1	-1	-1	1	256	256	4	8.0	0.03
34	38	1	-1	-1	-1	-1	1	64	32	9	8.5	0.18
35	3	-1	1	-1	-1	-1	1	512	128	4	18.5	0.06
36	43	1	1	-1	-1	-1	1	64	64	8	14.5	0.23
37	41	-1	-1	1	-1	-1	1	128	128	6	10.5	0.08
38	49	1	-1	1	-1	-1	1	64	32	9	9.5	0.20
39	11	-1	1	1	-1	-1	1	256	128	5	15.0	0.08
40	17	1	1	1	-1	-1	1	64	64	8	15.5	0.24
41	48	-1	-1	-1	1	-1	1	128	64	7	11.5	0.12
42	42	1	-1	-1	1	-1	1	64	64	8	9.0	0.14
43	35	-1	1	-1	1	-1	1	256	128	5	15.5	0.08
44	44	1	1	-1	1	-1	1	128	64	7	13.5	0.14
45	6	-1	-1	1	1	-1	1	256	128	5	8.5	0.04
46	15	1	-1	1	1	-1	1	64	32	9	11.5	0.24
47	61	-1	1	1	1	-1	1	128	16	9	15.0	0.21
48	28	1	1	1	1	-1	1	64	32	9	16.0	0.33
49	37	-1	-1	-1	-1	1	1	512	64	5	18.0	0.06
50	53	1	-1	-1	-1	1	1	128	32	8	25.0	0.31
51	33	-1	1	-1	-1	1	1	512	128	4	17.0	0.05
52	31	1	1	-1	-1	1	1	128	64	7	15.0	0.16

53	34	-1	-1	1	-1	1	1	256	64	6	13.0	0.08
54	23	1	-1	1	-1	1	1	128	64	7	16.5	0.17
55	51	-1	1	1	-1	1	1	256	128	5	20.5	0.11
56	21	1	1	1	-1	1	1	128	64	7	18.0	0.19
57	62	-1	-1	-1	1	1	1	128	64	7	16.0	0.17
58	55	1	-1	-1	1	1	1	128	64	7	16.5	0.17
59	50	-1	1	-1	1	1	1	256	128	5	17.5	0.09
60	19	1	1	-1	1	1	1	128	64	7	16.5	0.17
61	47	-1	-1	1	1	1	1	256	64	6	16.5	0.10
62	60	1	-1	1	1	1	1	128	64	7	16.5	0.17
63	45	-1	1	1	1	1	1	256	128	5	17.5	0.09
64	36	1	1	1	1	1	1	128	64	7	17.0	0.18

\* *C.a. Candida albicans*; *C.p. Candida parapsilosis*