Supporting Information

1-(3-Aryloxy-3-arylpropyl)-1*H*-imidazoles, New Imidazoles with Potent Activity against *Candida albicans* and dermatophytes. Synthesis, Structure-Activity Relationship and Molecular Modeling Studies

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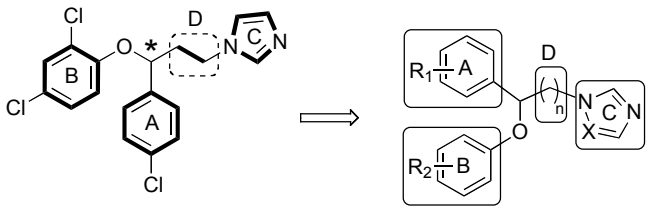
TOC Graphic



10 **11**, **15-28**, **30-37**, **39-50**

R_1 = H, 4-Cl, 4-F, 4-Me, 4-Me, 2,4-Cl_2; R_2 = H, 2-Cl, 4-Cl, 4-Me, 4-Et, 4-i-Pr, 4-t-Bu, 2,4-Cl_2, 2,6-Cl_2, 3.5-Cl_2, 2,4-Me_2; n = 1-4; X = CH, N.

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Computational Investigations – Additional Information

The spread of the MIC values among derivatives **48**, **49** and **50**, about one order of magnitude, roughly corresponded to the acceptable prediction uncertainty by MOD3.[15] At the same time, the measured antifungal values pointed to **50** as the less active derivative within this series and to **49** as the very most potent compound. MOD3 did not reproduced the trend of the measured MIC values of these compounds, even if it correctly predicted their antifungal activities within the measured order of magnitude. Figure 1S shows that the chain connecting the imidazole to the chiral carbon atom of **50** does not superimpose the corresponding shorter chain of **49**. This event might be consistent with the steric clashes of the former derivative within the catalytic cavity of the enzyme. Loosing torsional entropy (further to binding) might magnify this hypothetical effect determining the lower activity of **50** with respect to **49**.

Compound **52**, even sharing structural similarity with **4** (Figure 2A), was 20-fold less potent than **4** (see Table 7). According to MOD3, this result was caused by the prolonged chain connecting ring C to ring B. The first mapping (corresponding to a predicted MIC = 0.11 μM) proposed an orientation of the imidazole ring which was inconsistent with those adopted by the whole set of compounds (Figure 2A). Such an orientation, that was automatically selected by Catalyst to counterbalance the exceeding distance between the rings, would prevent the coordination bond with the heme moiety of the cytochrome (results not shown). Conversely, the second mapping (Figure 2SA) showed an apparently appropriate alignment of **52**, corresponding to an higher MIC value (0.89 μM) due to a slightly worse mapping of the pharmacophoric features onto the corresponding structural functions.

The trend of antifungal activities shown by compounds **53-56** was reproduced fairly well by MOD3 (Table 7). Figure 2SB displays the superposition of MOD3 with compounds **54** (white) and **55** (yellow). The different antifungal activity of these compounds is determined by the common structural scaffold, showing two phenyl rings too close each other. As a consequence, mapping of MOD3 is variable, depending on the substitution pattern of the two rings. The case of **53** has been already discussed as due to the impossibility of this derivative to match three pharmacophoric features.

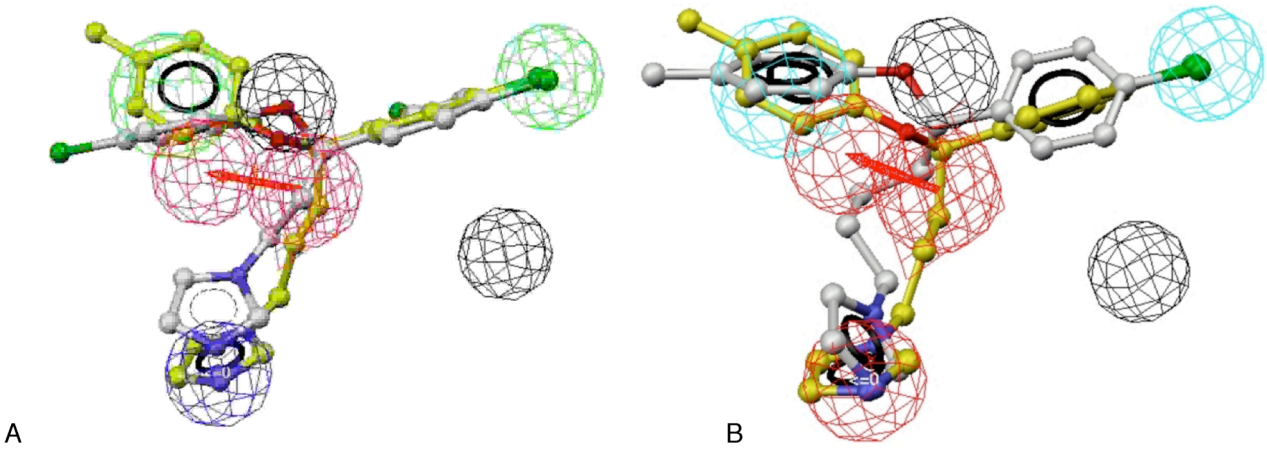

Figure 1S. (A) Superposition of MOD3 with **49** (yellow) and **44** (white). The fourth mapping of **44** is shown in the figure. (B) Superposition of MOD3 with **49** (yellow) and **50** (white).

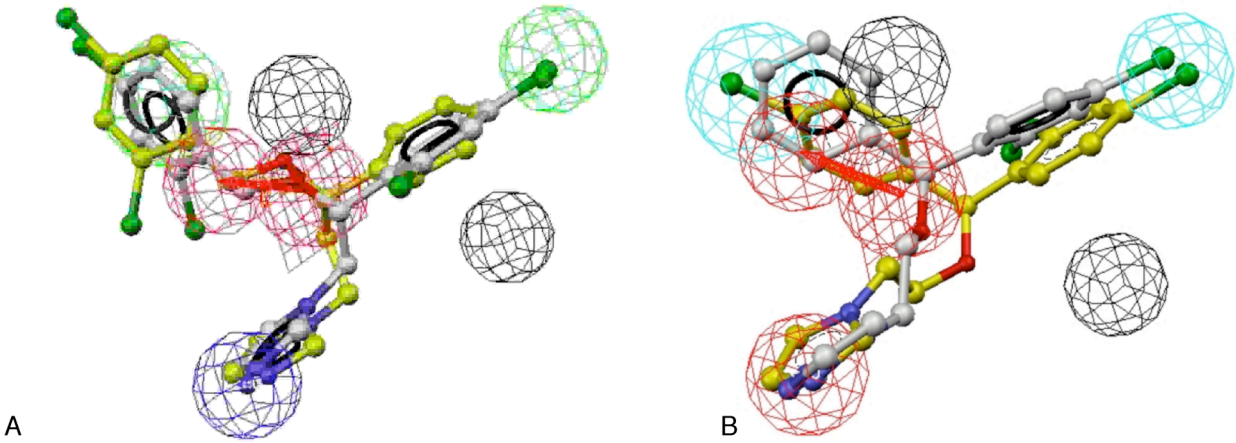

Figure 2S. (A) Superposition of MOD3 with **52** (yellow) and **4** (white). The second mapping of **52** is shown in the figure. (B) Superposition of MOD3 with **55** (yellow) and **54** (white).

On the contrary, in addition to UNA, **54** could partially map HY1 with the unsubstituted phenyl ring and HY2 with the para-chloro of the other ring (Figure 2SB). Compound **55** might map both HY1 and HY2 with two para-chlorine atoms. The MIC values estimated by Catalyst for **54** (2.6) and **55** (0.4) highlighted their different behaviour. Finally, the software was actually unable to rationalize the complete inactivity of **56**.

Figure 3S. Difference Spectra and Determination of Binding Constants of Compounds **5**, **10** and **33**.

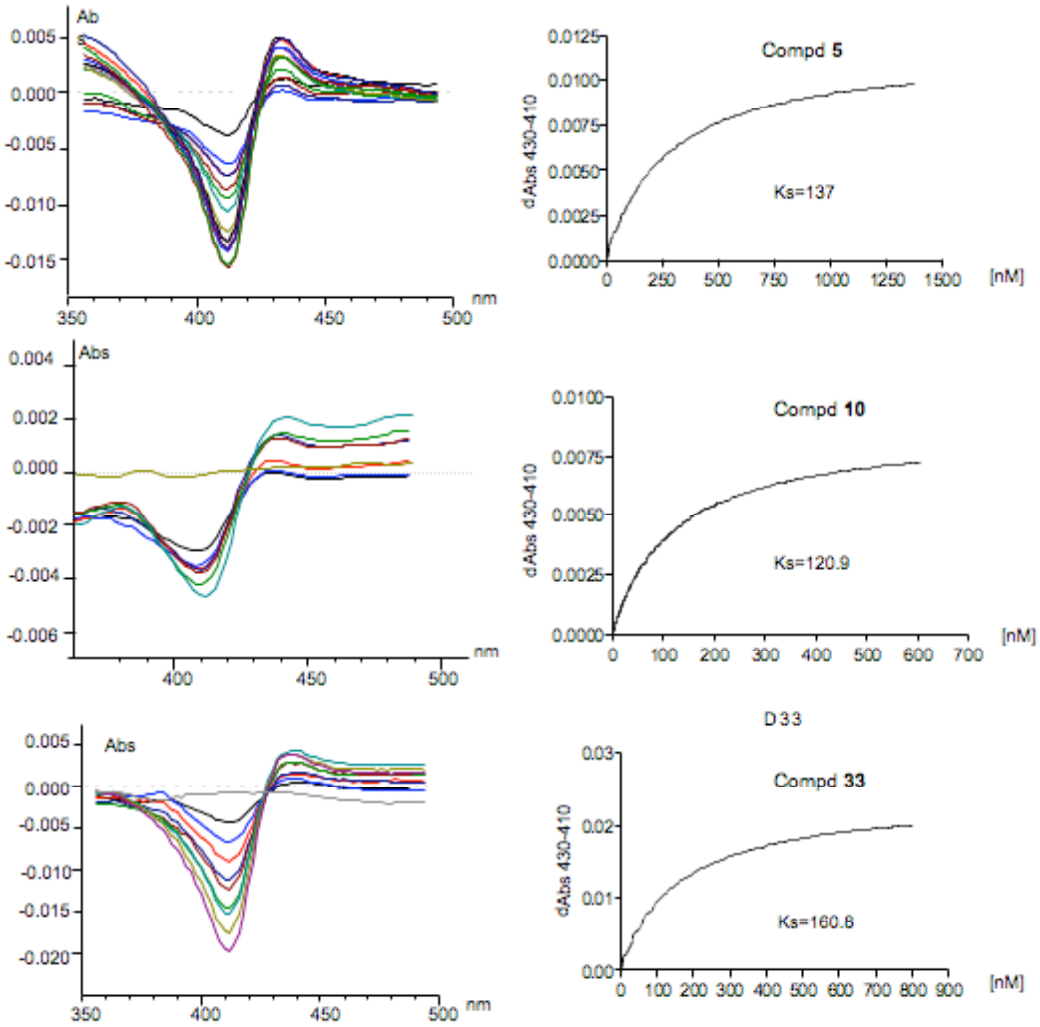

Table 1S. Elemental Analyses of Compounds **11**, **15-28**, **30-37**, **39-52** and **56**.

Compd	Calcd	Found
11	C, 77.67; H, 6.52; N, 10.06.	C, 77.52; H, 6.49; N, 9.94.
15	C, 62.26; H, 4.64; Cl, 20.42; N, 8.07.	C, 62.07; H, 4.51; Cl, 20.22; N, 7.84.
16	C, 62.26; H, 4.64; Cl, 20.42; N, 8.07.	C, 62.12; H, 4.55; Cl, 20.30; N, 7.97.
17	C, 69.12; H, 5.48; Cl, 11.33; N, 8.96.	C, 68.91; H, 5.35; Cl, 11.12; N, 8.74.
18	C, 62.26; H, 4.64; Cl, 20.42; N, 8.07.	C, 61.97; H, 4.49; Cl, 20.08; N, 7.79.
19	C, 62.26; H, 4.64; Cl, 20.42; N, 8.07.	C, 62.04; H, 4.52; Cl, 20.27; N, 7.95.
20	C, 69.83; H, 5.86; Cl, 10.85; N, 8.57.	C, 69.72; H, 5.80; Cl, 10.62; N, 8.48.
21	C, 70.48; H, 6.21; Cl, 10.40; N, 8.22.	C, 70.27; H, 6.18; Cl, 10.28; N, 8.09.
22	C, 71.07; H, 6.53; Cl, 9.99; N, 7.89.	C, 70.92; H, 6.44; Cl, 9.86; N, 7.71.
23	C, 71.63; H, 6.83; Cl, 9.61; N, 7.59.	C, 71.51; H, 6.79; Cl, 9.45; N, 7.40.
24	C, 56.64; H, 3.96; Cl, 27.87; N, 7.34.	C, 56.45; H, 3.86; Cl, 27.72; N, 7.16.
25	C, 56.64; H, 3.96; Cl, 27.87; N, 7.34.	C, 56.55; H, 3.90; Cl, 27.75; N, 7.18.
26	C, 70.48; H, 6.21; Cl, 10.40; N, 8.22.	C, 70.32; H, 6.08; Cl, 10.28; N, 8.10.
27	C, 72.95; H, 5.78; F, 6.41; N, 9.45.	C, 72.77; H, 5.71; F, 6.32; N, 9.28.
28	C, 73.53; H, 6.17; F, 6.12; N, 9.03.	C, 73.38; H, 6.13; F, 5.96; N, 8.87.
30	C, 59.19; H, 4.14; Cl, 19.41; F, 5.20; N, 7.67.	C, 58.92; H, 4.07; Cl, 19.24; F, 5.04; N, 7.41.
31	C, 59.19; H, 4.14; Cl, 19.41; F, 5.20; N, 7.67.	C, 59.01; H, 4.11; Cl, 19.36; F, 5.12; N, 7.52.
32	C, 78.05; H, 6.89; N, 9.58.	C, 77.88; H, 6.78; N, 9.32.
33	C, 69.83; H, 5.86; Cl, 10.85; N, 8.57.	C, 69.70; H, 5.78; Cl, 10.71; N, 8.39.
34	C, 78.40; H, 7.24; N, 9.14.	C, 78.28; H, 7.18; N, 9.02.
35	C, 78.71; H, 7.55; N, 8.74.	C, 78.53; H, 7.48; N, 8.55.
36	C, 79.00; H, 7.84; N, 8.38.	C, 78.84; H, 7.78; N, 8.12.
37	C, 79.27; H, 8.10; N, 8.04.	C, 79.08; H, 8.02; N, 7.91.
39	C, 63.17; H, 5.02; Cl, 19.63; N, 7.75	C, 63.05; H, 4.96; Cl, 19.45; N, 7.59
40	C, 63.17; H, 5.02; Cl, 19.63; N, 7.75	C, 62.65; H, 4.91; Cl, 19.38; N, 7.38
41	C, 70.48; H, 6.21; Cl, 10.40; N, 8.22.	C, 70.36; H, 6.16; Cl, 10.28; N, 8.08.
42	C, 70.48; H, 6.21; Cl, 10.40; N, 8.22.	C, 70.29; H, 6.10; Cl, 10.18; N, 7.92.
43	C, 78.71; H, 7.55; N, 8.74.	C, 78.66; H, 7.48; N, 8.61.
44	C, 51.95; H, 3.39; Cl, 34.08; N, 6.73.	C, 51.82; H, 3.31; Cl, 33.74; N, 6.52.
45	C, 58.63; H, 4.34; Cl, 20.36; N, 12.07.	C, 58.48; H, 4.30; Cl, 20.13; N, 11.84.
46	C, 53.36; H, 3.69; Cl, 27.79; N, 10.98.	C, 53.21; H, 3.61; Cl, 27.62; N, 10.84.
47	C, 59.68; H, 4.73; Cl, 19.57; N, 11.60.	C, 59.44; H, 4.65; Cl, 19.31; N, 11.48.
48	C, 69.12; H, 5.48; Cl, 11.33; N, 8.96.	C, 68.95; H, 5.44; Cl, 11.24; N, 8.80.
49	C, 70.48; H, 6.21; Cl. 10.40; N, 8.22.	C, 70.26; H, 6.13; Cl. 10.28; N, 8.09.
50	C, 71.07; H, 6.53; Cl, 9.99; N, 7.89.	C, 70.87; H, 6.41; Cl, 9.74; N, 7.70.
51	C, 77.67; H, 6.52; N, 10.06.	C, 77.52; H, 6.46; N, 9.90
52	C, 57.67; H, 4.33; Cl, 26.88; N, 7.08.	C, 57.44; H, 4.26; Cl, 26.55; N, 6.85.
56	C, 51.95; H, 3.39; Cl, 34.08; N, 6.73.	C, 51.82; H, 3.30; Cl, 33.87; N, 6.62.