# Microwave-assisted synthesis and antifungal activity of calix[4]aldimines

**Cleiton M. da Silva[1]*, Thais F.F. Magalhães[2], Danielle L. da Silva[2], Rosemeire B. Alves[1], Maria A. de Resende-Stoianoff[2], Ângelo de Fátima[1]**

[1]*Grupo de Estudos em Química Orgânica e Biológica (GEQOB), Departamento de Química, ICEx, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil.*
[2]*Departamento de Microbiologia, ICB, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil.*

**E-mail corresponding author*: cleitonms@ufmg.br

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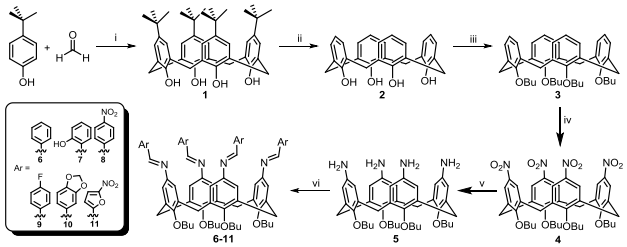
## INTRODUCTION

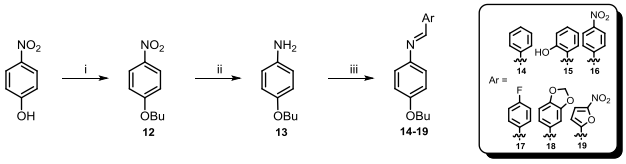
Calixarenes are macrocyclic compounds formed of phenolic units linked by methylene bridges in *ortho* positions. In last decades these compounds have received increasing attention due to its technological and biological applications, particularly as platforms for the development of new drugs[1]. Aldimines are organic substances known to exhibit a broad range of biological properties that includes antifungal, antibacterial, antimalarial, anti-inflammatory and antiviral activities[2]. Here we report the microwave-assisted synthesis of six calix[4]aldimines and their respective monomeric units. The antifungal activities of such compounds against six strains of *Candida* species are also described.

## RESULTS AND DISCUSSION

The calix[4]aldimines **6**-**11** and the aldimines **14**-**19** were obtained according to the synthetic approach shown in Schemes 1 and 2.



**Scheme 1.** Synthesis of calix[4]aldimines **6**-**11**. i) diphenyl ether, NaOH, 260°C, 56%; ii) $AlCl_3$, toluene, r.t., 80%; iii) NaH, *n*-BuBr, DMF, 80°C, 60%; iv) $HOAc/HNO_3$, r.t., 54%; v) $N_2H_4.H_2O$, Pd/C, EtOH, 80°C, 99%; vi) ArCHO, EtOH, microwave irradiation, 52-90%.



**Scheme 2.** Synthesis of the aldimines **14**-**19**. i) $K_2CO_3$, *n*-BuBr, MeCN, 80°C, 94%; ii) $N_2H_4.H_2O$, Pd/C, EtOH, 80 °C, 99%; iii) ArCHO, EtOH, microwave irradiation, 69-88%.

The minimum inhibitory concentration (MIC) for each synthesized compound was determined according to the protocol M27-A2[3]. The results are shown in Table 1. In general, both the calix[4]aldimines and aldimines presented moderate activity against the fungi studied. Among all the compounds evaluated, the calix[4]aldimine **11**, derived from 5-nitrofurfuraldehyde, was the most active, with MIC values of 0.05 $mmol.L^{-1}$ against *C. albicans*, *C. krusei*, *C. tropicalis*, *C. parapsilosis and C. dubliniensis.*

**Table 1.** Minimal inhibitory concentration (MIC; $mmol.L^{-1}$) of the compounds **6**-**11** and **14**-**19** against fungal strains

| Fungal strains[a] | Compounds | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **6** | **7** | **8** | **9** | **10** | **11** | **14** | **15** | **16** | **17** | **18** | **19** | **Flu[b]** |
| *C.a.* | 0.48 | 0.45 | 0.41 | 0.45 | 0.41 | 0.05 | 2.02 | 1.90 | 1.72 | 3.77 | 3.44 | 1.78 | 0.0008 |
| *C.k.* | 0.48 | 0.23 | 0.21 | 0.23 | 0.21 | 0.05 | 1.01 | 1.90 | 0.86 | 3.77 | 1.72 | 0.22 | 0.10 |
| *C.t.* | 0.48 | 0.45 | 0.41 | 0.45 | 0.41 | 0.05 | 4.04 | 3.80 | 3.43 | 3.77 | 3.44 | 1.78 | 0.0008 |
| *C.p.* | 0.24 | 0.11 | 0.21 | 0.23 | 0.41 | 0.05 | 1.01 | 0.48 | 0.43 | 3.77 | 1.72 | 1.78 | 0.007 |
| *C.g.* | 0.48 | 0.23 | 0.21 | 0.45 | 0.41 | 0.11 | 4.04 | 0.95 | 3.43 | 3.77 | 3.44 | 1.78 | 0.03 |
| *C.d.* | 0.24 | 0.45 | 0.21 | 0.23 | 0.41 | 0.05 | 2.02 | 1.90 | 1.72 | 3.77 | 1.72 | 0.89 | 0.0008 |

[a]Fungal strains: *C. albicans* (C.a.); *C. krusei* (C.k.); *C. tropicalis (C.t.)*; *C. parapsilosis* (C.p.); *C. glabrata* (C.g.); *C. dubliniensis* (C.d.). [b]Flu stands for fluconazole (positive control).

## CONCLUSION

Six calix[4]aldimines, as well as the respective monomeric units were synthesized and evaluated for their antifungal activities. *In vitro* assays showed that calix[4]aldimine **11** is an interesting lead compound for the development of new antifungal agents.

## ACKNOWLEDGEMENTS

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## REFERENCES

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