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ANA DE ARAÚJO SATHLER

NEW PROMISING LEADS FROM NATURAL SOURCES AGAINST *Cryptococcus* sp. AND *Candida* sp.: AN 8 YEARS REVIEW

Governador Valadares - MG

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Trabalho de conclusão de curso, apresentado no formato de artigo, como requisito parcial para obtenção de título de bacharel em Farmácia, na Universidade Federal de Juiz de Fora – *Campus* Governador Valadares

Orientadora: Prof.ª Dra. Karen Luise Lang

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New promising leads from natural sources against *Cryptococcus* sp. and *Candida* sp.: an 8 years review

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Abstract: Systemic fungal infections caused by fungal species of the genus *Candida* sp. and *Cryptococcus* sp. have important epidemiological significance, because they affect immunocompromised patients and present high mortality rates. The available drugs used for the treatment of the diseases caused by these fungi species are restricted of three classes of antifungals. Besides the limited number of therapeutic alternatives, these drugs are associated with several factors that limiting its use, such as the incidence of serious adverse effects, drug interactions, development of resistance and high cost, justifying the search for new chemical entities. Natural products are historically relevant sources of compounds for the development of new drugs, and studies with these organisms has resulted in the discovery of new molecules with anti-cryptococcus and anti-candida activity. In this review, 125 molecules with minimal inhibitory concentration (MICs) in the range of 0.63 to 50 μg mL^{-1} were compiled. 88% of these molecules were active against the different species of *Candida* sp. and 35.2% were active against fungi of the genus *Cryptococcus* sp.. 77.6% were molecules isolated from plants, 8% isolated from microorganisms and 13.6% isolated from algae and marine sponges.

Key-words: *Cryptococcus, Candida*, antifungals, natural products.

Conflict of interest: The authors declare no conflicts of interest.

Introduction

More than 2 million invasive fungal infections are estimated to occur globally every year and are responsible for ~ 1.5 million deaths, particularly in immunocompromised individuals. This population mainly includes HIV-infected individuals, those undergoing organ transplants or receiving anticancer chemotherapy. The introduction of highly active antiretroviral therapy (HAART) for HIV has reduced rates of fungal diseases, but the increasing number of transplant recipients and patients receiving immunosuppressive medications has created an at-risk population with a high incidence of fungal infection (George et al., 2017). Approximately 90% of invasive mycoses are caused by species that belong to one of four genera: *Aspergillus*, *Candida*, *Cryptococcus* and *Pneumocystis.* However, epidemiological data for fungal infections are notoriously poor because fungal infections are often misdiagnosed (Brown et al., 2012).

C. albicans is part of the normal microbiota and is therefore the most common etiologic agent of fungal infections not only in immunocompromised patients but also in patients who have undergone some invasive clinical procedure or who have suffered some kind of extensive trauma whose treatment involves permanence in intensive care units - being therefore one of the main agents of nosocomial infection (Brown et al., 2012). In addition to *C. albicans* other species of the genus also involved in candidemia are *C. krusei, C. parapsilosis* and *C. glabrata*. The incidence of candidemia ranges from 1 to 14 per 100,000 inhabitants, depending on the population studied, and mortality at 30 days of infection may reach 60% (Enoch et al., 2017). Commonly prescribed drugs for the treatment of candidiasis include a variety of imidazole and triazole drugs that disrupt biosynthesis of ergosterol, a fungal-specific sterol of cellular membranes, and the echinocandins (caspofungin, micafungin, anidulafungin) which inhibit synthesis of cell wall β-(1,3)-glucans. Formulations of amphotericin B are given less often due to the risk of toxicity. Both the echinocandins and the azoles are better tolerated than amphotericin B formulations (Mellinghof et al., 2018).

Cryptococcosis is one of the most serious fungal diseases worldwide and afflicts not only immunocompromised individuals but also apparently immunocompetent individuals (Park et al. 2009). Cryptococcal meningitis is a disease considered neglected in HIV carriers, which causes over 600,000 deaths per year worldwide (Armstrong-James et al., 2014). Caused by *Cryptococcus neoformans* and *Cryptococcus gattii* species complexes, this infection presents substantial therapeutic challenges (Kwon-Chung et al., 2017). The antifungal arsenal for treatment against cryptococcosis currently is largely limited to three old and off-patent drugs, used singly or in combination: amphotericin B, which complex with membrane sterols resulting in cellular leakage, 5-fluorocytosine (5FC), which interacts as 5-fluorouridinetriphosphate with RNA biosynthesis thus disturbing the building of certain essential proteins, and azoles (Perfect and Bicanic., 2015).

Despite the increasing importance of opportunistic fungal pathogens, there is a limited number of effective antifungal drugs available for the treatment of systemic fungal infections. Therefore, the development of new antifungal agents with novel chemical scaffolds and new mechanisms of action is vital due to increased incidence and mortality of invasive fungal infections and severe drug resistance, and the severe side effects, limited spectrum of action and drug–drug interactions of conventional drugs (Liu et al., 2016).

Natural products have attracted considerable attention and have been introduced on the research of new drugs over the past decades. Due to chemical diversity, they are advantageous sources for the discovery of various bioactive molecules (Thammasit et al., 2018).

In view of this, the aim of this review is not only to list promising anti-candida or/and anti-cryptococcal candidates or natural compounds that can be use as prototype for the development of new antifungal drugs, but also to explore the diverse sources that may provide more effective and less toxic antifungal compounds. We've searched for original results from peer-reviewed papers published between 2010 and 2018 by international journals using five databases (PubMed, SienceDirect, Web of Science, Scopus and Scielo) using the key words "Cryptococcus" "Candida" "antifungal" "natural products". Inclusion criteria were papers reporting metabolites that have potentially useful antifungal activity, namely those with minimum inhibitory concentration (MIC) ≤ 50 μg mL^{-1}. These compounds, which total 125 from 7 structural classes, are arranged according to class and then source.

Alkaloids

Alkaloids are a group of naturally occurring chemical compounds that contains mostly basic nitrogen atoms. This group also includes some related compounds with neutral and even weakly acidic properties (Roy, 2017). They have a wide distribution which includes bacteria, fungi, plants and animals (Fattorusso, 2008; Hesse, 2003; Tadeusz, 2007). Many of these compounds possess potent pharmacological effects and several alkaloids from natural sources are reported to possess potent antimicrobial properties and could therefore be good candidates to new drugs or will be useful as prototype for new drugs development.

Isolated from *Prosopis glandulosa* Torrey var. *glandulosa* (Fabaceae) and *Prosopis juliflora*, the indolizidine alkaloids $\Delta^{1,6}$–juliprosopine (**1**) and juliprosine (**2**) showed strong anti-cryptococal activity with MIC value of 1.25 μg mL^{-1} and 0.63 μg mL^{-1} respectively, against *C. neoformans* ATCC 90113 (positive control amphotericin B MIC 1.25 μg mL^{-1}). Compound **2** also exhibited antifungal activity against *C. albicans* ATCC 90028 with MIC value of 20 μg mL^{-1} and *C. krusei* ATCC 6258 with MIC value of 10 μg mL^{-1} (Rahman et al., 2011).

The apomorphine alkaloids *O*-methylmoschatoline (**3**) and liriodenine (**4**) isolated from *Guatteria blepharophylla* (Annonaceae) bark exhibited antifungal activity against *Candida dubliniensis* ATCC 777 and ATCC 778157 with MIC value of 12.5 μg mL^{-1} and 25 μg mL^{-1} for **3** and 50 μg mL^{-1} and 100 μg mL^{-1} for **4**, respectively (Costa et al., 2010). The difference in activity level and structural features suggest that substitutions in ring A may be important for the antifungal activity of these alkaloids. Compound **4** was also active against *C. albicans* (MIC of 6.25 μg mL^{-1}) and *C. neoformans* (MIC of 12.5 μg mL^{-1}) (Zhang et al., 2002). Isolated from the same source, isomoschatoline (**5**) showed MIC value of 50.8 μM (14.8 μg mL^{-1}) against *C. albicans* (Costa et al., 2011). Tripathi and collaborators (2017) observed that liriodenine methiodide (**4a**), a methiodide salt of **4**, mediate it antifungal activities by disrupting mitochondrial iron-sulfur (Fe-S) cluster biosynthesis. The compound targets a cellular pathway that is distinct from the pathways commonly targeted by clinically used antifungal drugs and is considered a new potential target for the development of new antifungal therapies.

The new apomorphine alkaloid 2-hydroxy-9-methoxyaporphine (**6**), isolated from *Beilschmiedia alloiophylla* (Lauraceae), inhibited the growth of *C. albicans* with MIC of 8 μg mL^{-1}. In this same study, other known alkaloids such as laurotetanine (**7**), boldine (**8**), secoboldine (**9**), isoboldine (**10**), asimilobine (**11**), 6-epioreobeiline (**12**) and (S)-3-methoxynordomesticine (**13**), also showed activity against *C. albicans* with MIC ranging from 16 to 32 μg mL^{-1} (Mollataghi et al., 2012).

The alkaloid 6-methoxyldihydrochelerythrine (**14**), found in plants of the genus *Macleaya*, presented activity against *C. albicans* CMCC (F) 98001 exhibiting an MIC value of 8.27 μg mL^{-1} (Sai et al., 2016). In a previous study, using the disk-diffusion method, compound **14** did not show activity against *C. albicans* EDCL (Islam et al., 1997). This can be explained, in part, by the fact that the disk-diffusion agar method is strongly dependent of physical-chemical properties of molecules, like molecular weight and lipophilicity. Therefore, lipophilic compounds would have problems to diffuse against solid agar which may be a cause of the discrepancy of the results observed in the two studies.

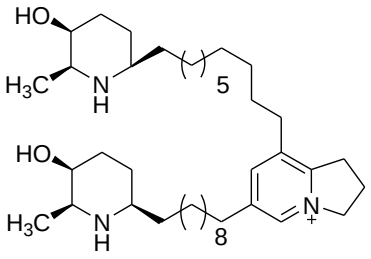
The study of the root bark of *Cordia alliodora* (Boraginaceae) yielded the isolation of the isoindoline alkaloid 5-O-[*β*-D-apiofuranosyl-(1→6)-*β*-D-glucopyranosyl]-1-isoindolinone (**15**) with anti-candida activity, which present an MIC range of 4.98 to 5.23 μg mL^{-1} against *C. albicans* ATCC 10231, *C. tropicalis* ATCC 13861 and *C. glabrata* ATCC 28838 (Fouseki et al., 2016).

Antifungal alkaloids have also been isolated from marine sources. From marine sponge *Pseudaxinella reticulata* (Axinellidae), four guanidine alkaloids analogues of crambescin A2 with anti-cryptococcal activity were obtained: (+)-crambescin A2 392 (**16**), (+)-crambescin A2 406 (**17**), (+)-crambescin A2 420 (**18**) and (+)-Sch 575948 (**19**). Compounds **16** and **17** showed MIC_{90} value

of 32 µM (12.6 µg mL^{-1}) and 26 µM (10.6 µg mL^{-1}), respectively, against *C. albicans* ATCC 14503 and an MIC value of 2.3 µM (0.9 µg mL^{-1}) and 2.2 µM (0.9 µg mL^{-1}), respectively, against *C. neoformans* var. *gattii*. Compounds **18** and **19** also demonstrated activity against *C. albicans, C. glabrata and C. krusei*, with an MIC_{90} range of 22 (9.3 µg mL^{-1}) to 27 µM (11.4 µg mL^{-1}) for compound **18** and 41 (14.9 µg mL^{-1}) to 59 µM (21.5 µg mL^{-1}) for compound **19**. Against *C. neoformans*, compound **18** exhibited an MIC_{90} of 2.6 µM and compound **19** had an MIC_{90} of 4.9 µM. Crambescins exhibited potent antifungal activity against *C. neoformans* var. *gattii* that showed a modest dependence upon the length of the alkyl side chains in the structures (Jamison et al., 2015). Compound **19** has previously been isolated from fungi of the genus *Aspergillus* sp., where demonstrated activity against *C. albicans* C43, with an MIC value of 32 µg mL^{-1} (Yang et al., 2005). Another natural source of compound **19** is the marine sponge *Ptilocaulis spiculifer* (Axinellidae) (Yang et al., 2003).

The alkaloids hyrtioseragamine A (**20**) and hyrtioseragamine B (**21**), isolated from the marine sponge *Hyrtios* sp., demonstrated antifungal activity against *C. neoformans* (unspecified strain) with MIC value of 33.3 and 16.6 µg mL^{-1}, respectively (Takahashi et al., 2011).

Isolate of the endophytic fungus *Penicillum vinaceum*, the quinazolinic alkaloid, (-)-(1*R*, 4*R*)-1,4-(2,3)-Indolmethane-1-methyl-2,4-dihydro-1*H*-pyrazino-[2,1-*b*]-quinazoline-3,6-dione (**22**), demonstrated antifungal activity against *C. albicans* ATCC 76615 (MIC_{80} 32 µg mL^{-1}) and against *C. neoformans* ATCC 32609 (MIC_{80} 16 µg mL^{-1}) (Zheng et al., 2012).



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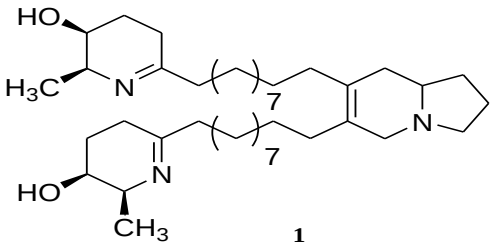

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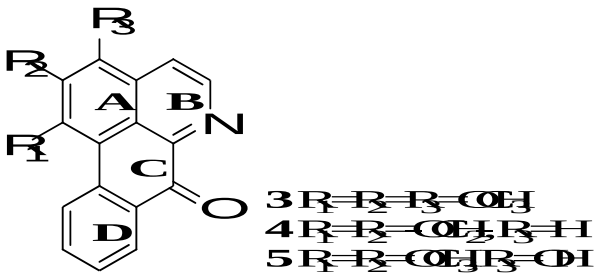
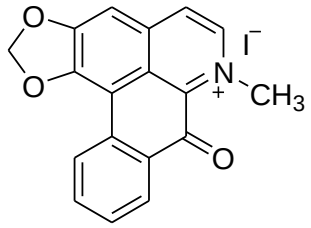
Several mechanisms have already been described for alkaloids, including changes in membrane permeability, impair mitochondrial function, production of oxidative stress, targeting cell wall integrity pathway, heme modulations and shock transcription factor HSF1 - a key determinant of virulence that protects the fungi cells during the fever (Khan et al., 2017).



3 $R_1=R_2=R_3=OCH_3$

4 $R_1=R_2=OCH_2O$, $R_3=H$

5 $R_1=R_2=OCH_3$, $R_3=OH$



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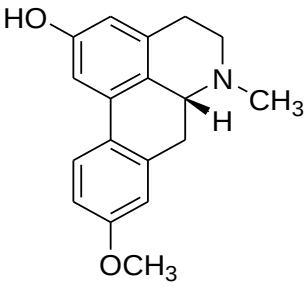

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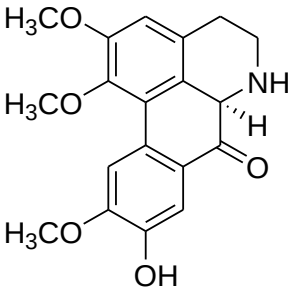

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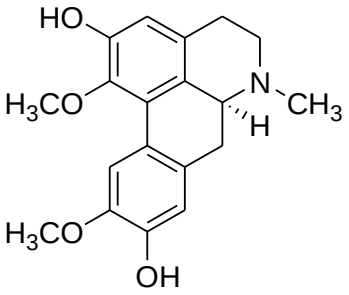

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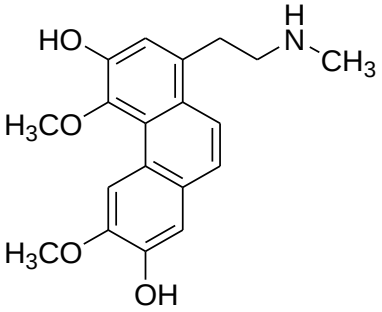

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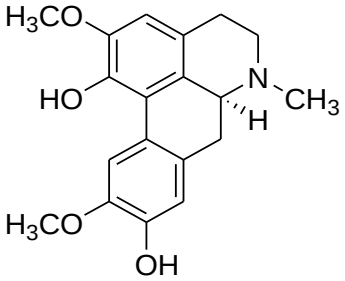

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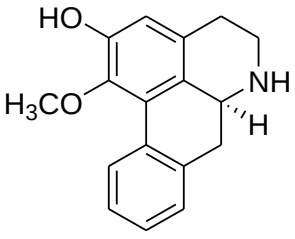

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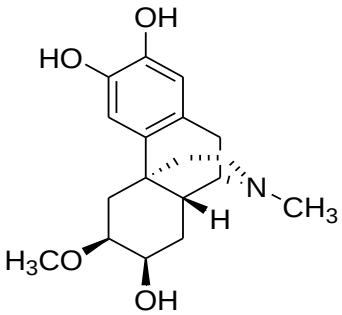

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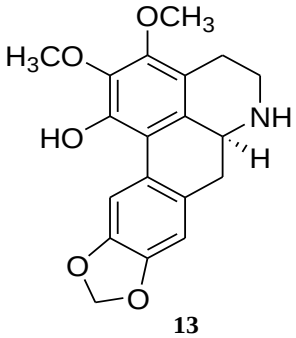

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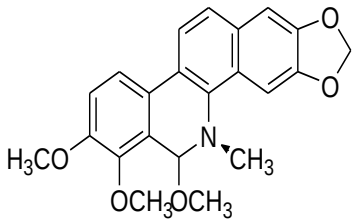

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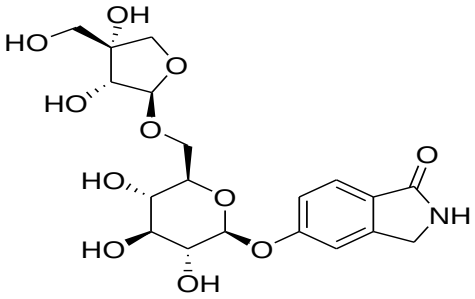

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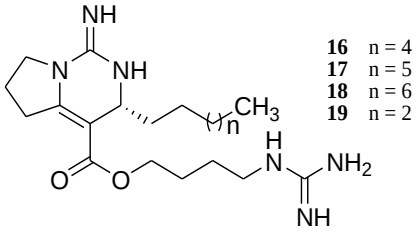

16 n = 4
17 n = 5
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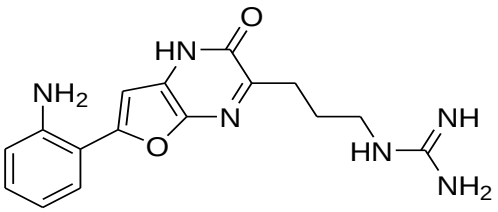

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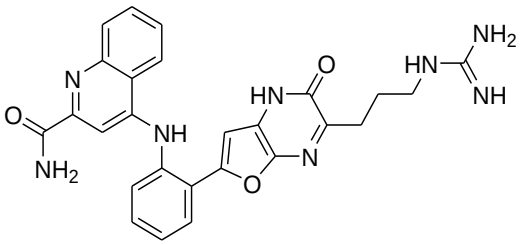

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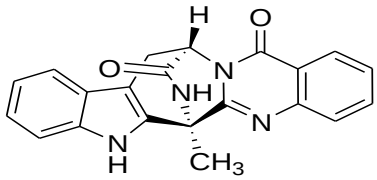

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Flavonoids

Flavonoids are one of the biggest classes of secondary metabolites compounds, which have a wide distribution in the plant kingdom. Several functions have been assigned to flavonoids, such as protection against UV radiation and other environmental stresses and significant antioxidant properties. They have also been identified as potent antitumor, anti-inflammatory, antiviral and antimicrobial agents (Mierziak et al., 2014).

The flavonoid sorbifolin (**23**) showed to be active against *C. albicans* ATCC 90028 (MIC 31.20 µg mL^{-1}), *C. gatti* 118 (MIC 3.9 µg mL^{-1}), *C. krusei* ATCC 6258 (MIC 7.8 µg mL^{-1}), *C. parapsilosis* ATCC 22019 (MIC 7.8 µg mL^{-1}) and *C. neoformans* ATCC 90012 (MIC 7.8 µg mL^{-1}) (Lima et al., 2016). Compound **23** has been isolated from various plants of the families Rutaceae (Chan et al, 1967; Zaitsev et al, 1969; Arisawa et al, 1970; Box and Taylor, 1973), Acanthaceae (Chothani et al, 2010), Lamiaceae (Corticchiato et al, 1995; Jin et al, 2015), Asteraceae (Eshbakova et al., 1996; Nazaruk and Galicka, 2014), Fabaceae (El-Hawiet et al., 2010) and Leguminosae (Lima et al., 2016).

The flavonoids pedalin (**24**), nitensoside B (**25**) and isoquercitrin (**26**), isolated from *Pterogyne nitens* (Fabaceae) showed activity against *C. neoformans* ATCC 90012, with an MIC of 7.8, 7.8 and 15 µg mL^{-1}, respectively. Compound **25** was also active against *C. krusei* ATCC 6258 with an MIC of 31.2 µg mL^{-1} (Lima et al., 2016). In the study performed by Tracanna et al. (2015), compound **26** showed no activity against *C. neoformans* H99 and neither against *C. albicans*. Compound **26** induces depolarization of membrane potencial, affecting permeability and leading to cell death (Yun et al., 2015).

From *Rhynchospora corymbosa* (Cyperaceae) was isolated the flavonoid tricin (**27**), which showed anti-cryptococcal activity against *C. neoformans* IP 90526 (MIC 8 µg mL^{-1}) and anticandida activity against *C. albicans* ATCC 9002 and *C. parapsilosis* (MIC 4 µg mL^{-1} for both) (Pagning et al., 2016). The C-7 monoacetyl semisynthetic analog of **27** (**27a**), presented better activity (4 µg mL^{-1}) against *C. neoformas* and 2 µg mL^{-1} for both *Candida* species tested, suggesting that these regions are important for the observed antifungal activity.

The flavonoids kaempferitrin (**28**) and kaempferol 3-*O*-α-L-(3-acetyl)rhamnopyranoside-7-*O*-α-L-rhamnopyranoside (**29**) both exhibited an MIC of 32 µg mL^{-1} against *C. albicans* ATCC9002 and an MIC of 16 µg mL^{-1} against *C. parapsilosis* ATCC22019 and *C. neoformans* IP 95026. Kaempferol 3-*O*-α-L-(4-acetyl)-rhamnopyranoside-7-*O*-α-L-rhamnopyranoside (**30**) and afzelin (**31**) exhibited an MIC of 32 µg mL^{-1} and 4 µg mL^{-1} against *C. parapsilosis* and *C. neoformans*, respectively. The flavonoid α-rhamnoisorobin (**32**) showed excellent activity against the three fungi tested, with MIC range of 1 to 2 µg mL^{-1}. Kaempferol 3-*O*-α-D-glucopyranoside-7-*O*-α-L-rhamnopyranoside (**33**) exhibited an MIC of 2 µg mL^{-1} against *C. parapsilosis* and *C. neoformans* and 8 µg mL^{-1} against *C. albicans*. All compounds were isolated from *Bryophyllum pinnatum* (Crassulaceae) (Tatsimo et al., 2012).

Two prenylisoflavones with antifungal activity were isolated from *Derris eriocarpa* (Fabaceae): 4'-hydroxy-5,7-dimethoxy-6-(3-methyl-2-butenyl)-isoflavone (**34**) and derrubon 5-methyl ether (**35**). Compound **34** showed activity against *C. neoformans* IP 90526 (MIC 50 µg mL^{-1}) and also against *C. albicans* ATCC 2091 and *C. guilliermondii* (MIC of 12.5 µg mL^{-1} for both fungi). Compound **35** exhibited activity only against *Candida* species, with an MIC of 25 µg mL^{-1} for *C. guilliermondii* and 50 µg mL^{-1} for *C. albicans* (Zhang et al., 2014).

Candida guilliermondii is one of the components of human microbiota. Although this yeast present low virulence and has been infrequently associated with human infections, reports suggest that *C. guilliermondii* may exhibit decreased susceptibility to several different classes of antifungal agents, such as fluconazole and echinocandins (Marcos-Zambrano et al., 2017).

Teodoro et al. (2015) reported the activity of the common phytochemical (-)-epicatequin (**36**) against *C. glabrata* ATCC 90030, with an MIC of 31 μg mL^{-1}. This compound demonstred no cytotoxicity on Vero Cells at the highest concentration tested (200 μg mL^{-1}) (Pendota et al., 2017).

From *Dorstenia mannii* (Moraceae), five flavonoids with activity against *C. albicans* ATCC 9002 were isolated. 6,8-diprenyleriodictyol (**37**) and dorsmanin I (**38**) exhibited MICs of 32 μg mL^{-1}, dorsmanin F (**39**) presented MIC of 16 μg mL^{-1} and dorsmanin E (**40**) exhibited MIC of 8 μg mL^{-1} (Mbaveng et al., 2012).

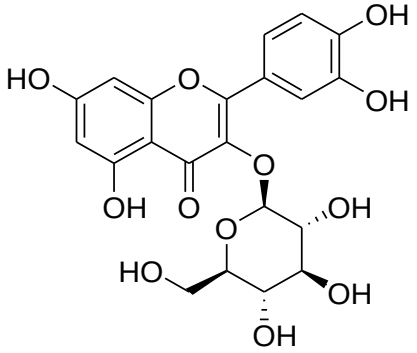
The common phytochemical, quercetin-3-O-α-L-rhamnopyranosyl-(1→6)-*β*-D-galactopyranoside (**41**), isolated from *Pyrostegia venusta* (Bignoniaceae), exhibited an MIC of 6 μg mL^{-1} against *C. albicans,* strains OF M7-19, OF M3-20 and USP 1 (Pereira et al., 2014). The unusual chlorinated flavonoid 7-*O*-methyl-8-chlorogenistein (**42**), isolated from *Streptomyces sp.* YIM GS3536 showed antimicrobial activity towards *C. albicans* with an MIC range of 23 to 35 μM (7.51 – 11.13 μg mL^{-1}) (Huang et al., 2013).

Funari et al. (2012) described the isolation of asebogenin (**43**), a dihydrochalcone active against *C. neoformans* 90012, with an MIC value of 15.6 μg mL^{-1}. Compound **43** can be found in several species of the family Piperaceae: *Piper aduncum* (Orjala et al., 1994), *Piper longicaudatum* (Joshi et al., 2001) and *Piper carpunya* (Quílez et al., 2010), besides in *Greyia flanaganii* (Francoaceae) (Mapunya et al., 2011), *Lippia salviaefolia* (Verbenaceae) (Funari et al., 2012), *Pityrogramma calomelans* (Pteridaceae) (Hitz et al., 1982) and *Pieris japonica* (Ericaceae) (Yao et al., 2005).

The neoflavonoid 5-O-methyllatifolin (**44**) showed activity against *C. albicans* ATCC 26555 with an MIC of 5 μg mL^{-1} (positive control fluconazole MIC 100 μg mL^{-1}). Compound **44** has been isolated from *Ficus drupacea* (Moraceae) (Yessoufou et al., 2015), *Belamcanda chinensis* (Iridaceae) (Lee et al., 2015) and from genus *Dalbergia* (Fabaceae)*: Dalbergia cochinchinensis* (Donnelly et al., 1968), *Dalbergia parviflora* (Muangnoicharoen and Frahm, 1982) and *Dalbergia odorifera* (Lee et al., 2013).

It is known that some flavonoids induce fungal apoptosis by mitochondrial damage in *C. albicans* by generation of ROS, metacaspases activation, cytochrome *c* release and mitochondrial membrane depolarization. ROS damage iron-sulfur clusters, making ferrous iron available for oxidation by the Fenton reaction, which leads to hydroxyl radical formation. The hydroxyl radicals damage DNA, proteins, and lipids, which results in cell death. The cytochrome *c* is an essential component of respiratory chain and a lethal factor involving the activation of apoptotic protease factor. The release of cytochrome *c* is due the increase of the mitochondrial outer membrane permeability. The increase of the mitochondrial transmembrane potential has been predicted to promote an osmotic matrix swelling (Hwang et al., 2012).

Besides, this class of compounds seems to damage the cell wall, structure that protects fungal protoplasts from external osmotic shocks and defines fungal morphogenesis. Changes in the organization or functional disruption of the cell wall induced by these antifungal agents are involved in fungal osmotic-induced death (Sitheeque et al., 2009).



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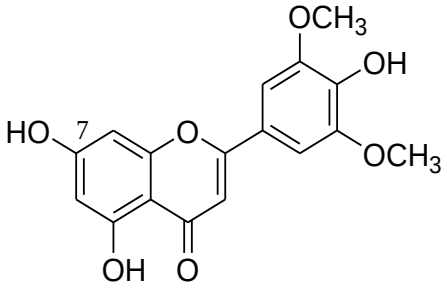

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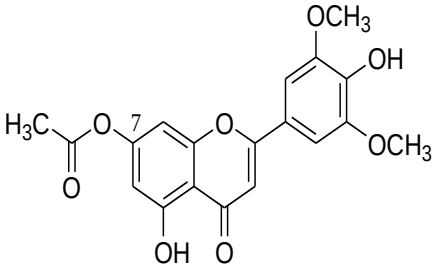

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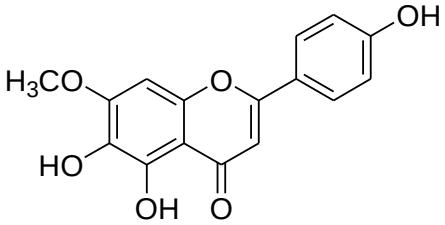

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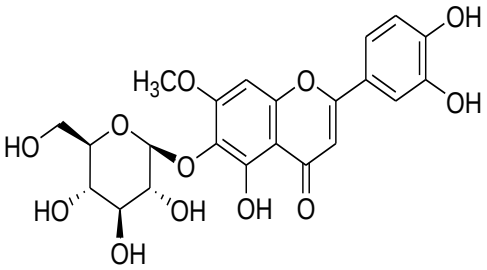

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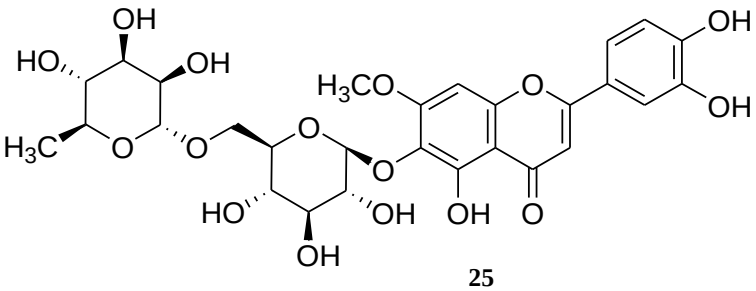

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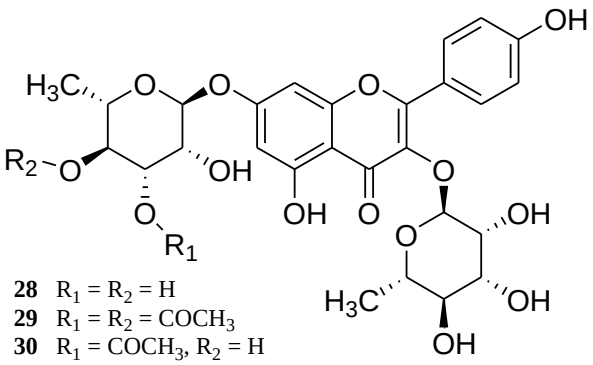
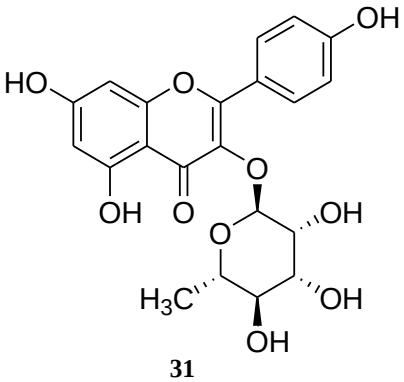


28 $R_1 = R_2 = H$
29 $R_1 = R_2 = COCH_3$
30 $R_1 = COCH_3$, $R_2 = H$



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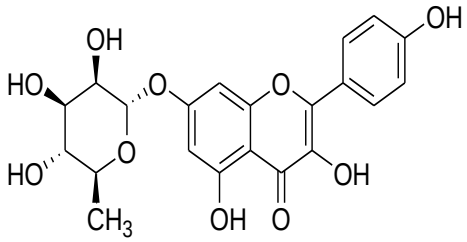

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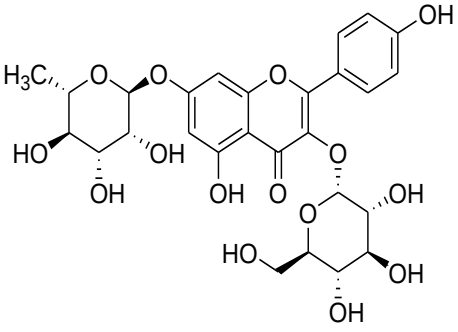

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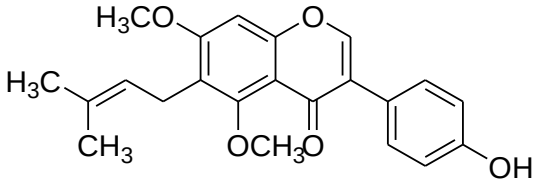

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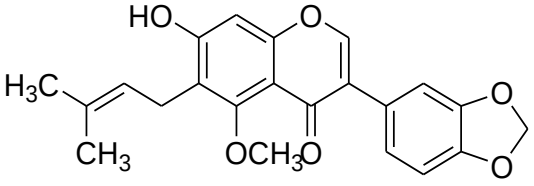

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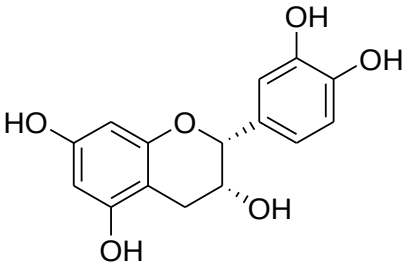

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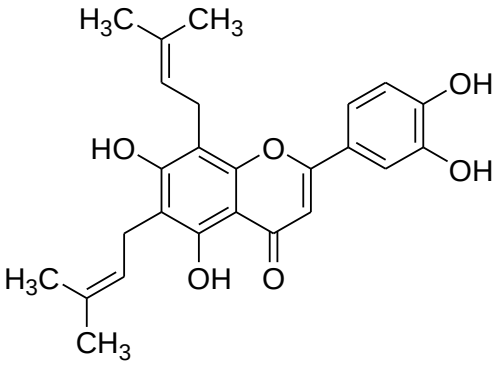

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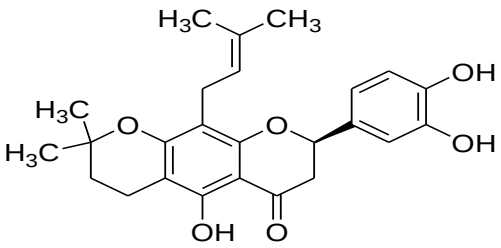

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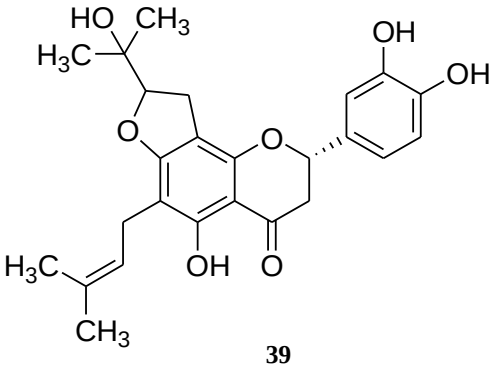

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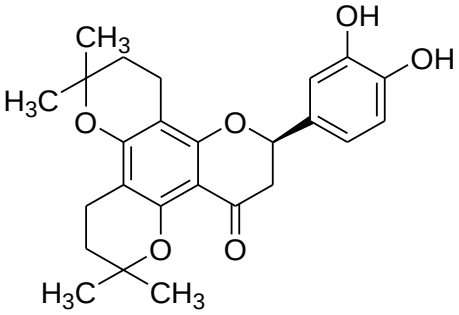

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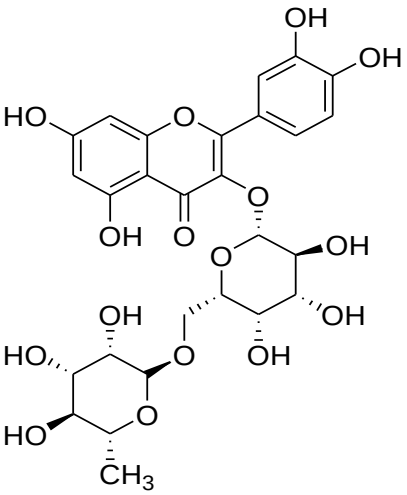

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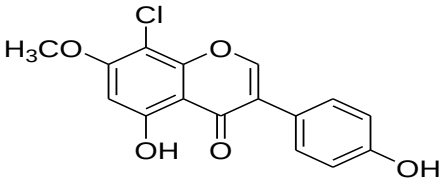

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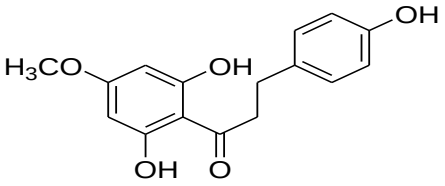

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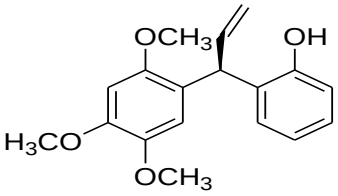


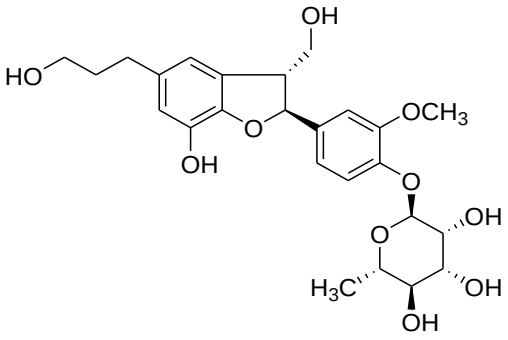
44

Lignans

Lignans are a large class of secondary metabolites in plants that have numerous biological effects in mammals, including antitumor, antioxidant and antimicrobial activity (Ono et al., 2010).

The lignans oxomatairesinol (**45**), massonianoside B (**46**), (2*R*, 3*R*)-2,3-dihydro-7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-5-benzofuranpropanol-4'-*O*-(3-*O*-methyl)-α-L-rhamnopyranoside (**47**) and lariciresinol-4'-*O*-*β*-D-glucoside (**48**) exhibited activity against *C. albicans* with range MIC_{90} of 9.90 to 33.58 μM (5 to 12.5 μg mL^{-1}). Compounds **45** to **48** were isolated from the branches of *Pseudolarix kaempferi* (Pinaceae) (He et al., 2011) and can also be found in *Cedrus deodara* (Pinaceae) (Wu et al., 2015), *Forsythia suspensa* (Oleaceae) (Chang et al., 2014), *Illicium henryi* (Schisandraceae) (Xiang et al., 2010), *Nepeta cadmea* (Lamiaceae) (Takeda et al., 1998), *Osmanthus asiaticus* (Oleaceae) (Sugiyama and Kikuchi et al., 1993), *Pedicularis artselaeri* (Scrophulariaceae) (Su et al., 1998), *Picea abies* (Pinaceae) (Pan and Lundgren, 1995), *Picea neoveitchii* (Chen et al., 2012), *Pinus massoniana* (Pinaceae) (Bi et al., 2001), *Pinus thunbergii* (Pinaceae) (Hong et al., 2014), *Stellera chamaejasme* (Thymelaeaceae) (Qiao et al., 2011), *Styrax perkinsiae* (Styracaceae) (Zhang and Zhang, 2015), *Taiwania flousiana* (Cupressaceae) (Xiang et al., 2004), *Taxus cuspidata* (Taxaceae) (Kawamura et al., 2004), *Taxus wallichiana* (Taxaceae) (Dang et al., 2017) and *Tsuga chinensis* (Pinaceae) (Fang et al., 1985).

A new lignanamide *N*-(2*E*)-3-[(2*S*,3*R*)-2-(4-hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-7-methoxy-2,3-dihydro-1-benzofuran-5-yl]acryloylglycine (**49**) was isolated from the methanolic extract of *Cordia alliodora* (Boraginaceae) root bark, and showed strong anti-candida activity with range MIC of 5.36 to 5.80 μg mL^{-1} against *C. albicans* ATCC 10231, *C. tropicalis* ATCC 13861 and *C. glabrata* ATCC 28838 (Fouseki et al., 2016).



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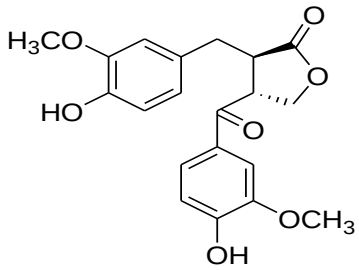

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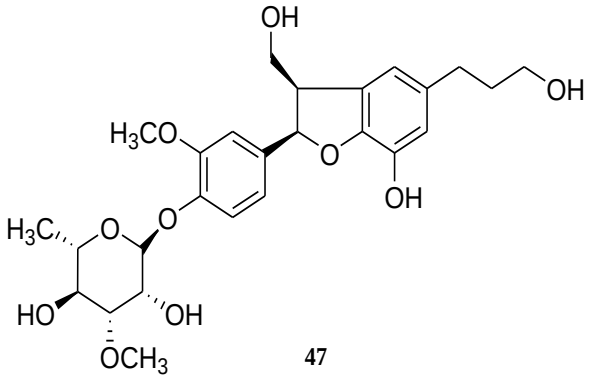

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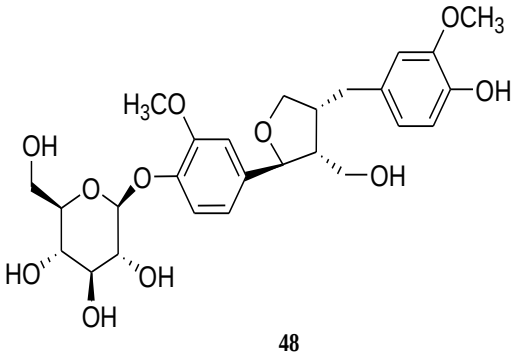

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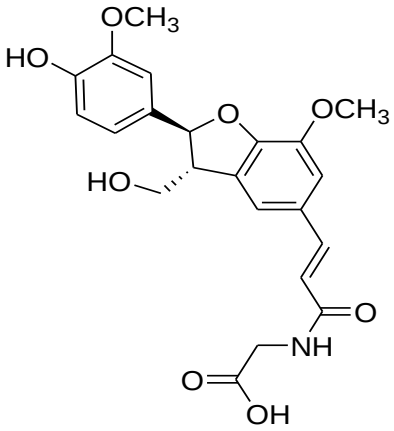

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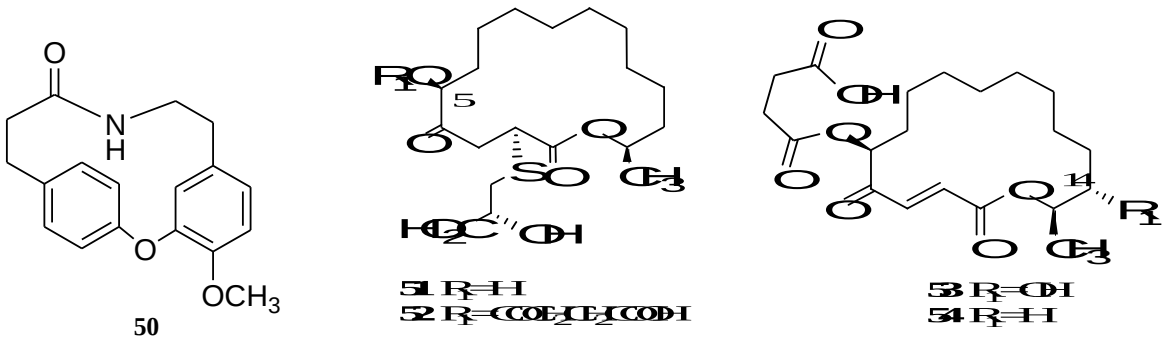
Macrolides

Macrolides are large and structurally diverse class of macrocyclic natural products that have a lactone ring (14-16 atoms) bonded to one or more deoxy sugar molecules. These compounds belong to the polyketides class of natural products and have been isolated from plants, insects and bacterias. Many members of this class exhibit antibiotic properties (Sanchez et al., 2007).

Laevicarpin (**50**) is a macrocyclic lactam isolated from the leaves of *Piper laevicarpu* (Piperaceae) that presented a strong activity against *C. gattii* FIOCRUZWM 178, with MIC value of 7.4 μg mL^{-1} (25 μM), IC_{50} = 2.3 μg mL^{-1} (7.9 μM). In this work, the gold-standard drug, amphotericin B, resulted in a MIC value for *C. gattii* strain of 1 μg mL^{-1} (1.1 μM). The cytotoxicity was tested agains mice conjunctive cells NCTC ATCC 929 and resulted in an IC_{50} of 100.3 μg/mL (337.7 μM). Thus, the selectivity index (SI) of laevicarpin, which is the ratio between the IC_{50} in mammalian cells and the IC_{50} against fungi resulted in a value of 42. Considering the elevated toxicity of amphotericin B and the selectivity index of laevicarpin observed in these trials, the obtained results suggest this compound as a possible scaffold for development of new drugs to be used against *C. gatti* (Maciel et al., 2016).

Co-culture of the fungi *Penicillium fuscum* and *Penicillium camembertii* yielded the isolation of three new 16-membered-ring macrolides with anti-candida activity: berkeleylactone A (**51**), berkeleylactone B (**52**), and berkeleylactone C (**53**), as well the known antibiotic macrolide A26771B (**54**). Compound **51** showed activity against *C. glabrata* with an MIC value of 6 μg mL^{-1} and an MIC of 26 μg mL^{-1} against *C. albicans*. Compounds **52** and **54** showed an MIC of 31 μg mL^{-1} and 48 μg mL^{-1}, respectively, against *C. glabrata*. Both were inactive against *C. albicans*. The absence of activity observed for **52** and **54** against *C. albicans* appears to be associated with the insertion of a substituent at C-5, suggesting that the α-cetol system may be involved in important interactions with the molecular target. Compound **53** had an MIC of 26 μg mL^{-1} against *C. glabrata* and 50 μg mL^{-1} against *C. albicans* (Stierle et al., 2017). The activity against *C. albicans* observed for **53** suggest that the hydroxyl at C-14 increments the activity against this specie of *Candida*, despite the absence of the α-cetol system. Compound **54** has already described for the fungi *Penicillium turbatum* (Michel et al., 1977).



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Phenolics (other than flavonoids and lignans)

Phenolic compounds are secondary metabolites ubiquitous in all higher plants. The role of these compounds in plants is not fully understood, but it is known that many of them act as defensive compounds, e.g. against plant pathogens, and they are often induced as a response to stress condition (Boudet, 2007).

The common phenolic acids ferulic acid (**55**) and chlorogenic acid (**56**) were isolated from the leaves of *Pterogyne nitens* (Leguminosae) and both exhibited an MIC of 31.2 µg mL^{-1} against *C. neoformans* ATCC 90012 and *C. gattii* (strain not specified) (Lima et al., 2016). Semisynthetic analogs of **56, 56a** and **56b,** have been synthesized and showed potent activity against *C. albicans* ATCC90028 (2 µg mL^{-1}) and *C. neoformans* ATCC32045 (1 µg mL^{-1}). Compound **56a** also demonstrad activity against *C. krusei* ATCC6258 with an MIC of 2 µg mL^{-1}). These results confirm the potential of the molecules to generate bioactive compounds (Ma et al., 2007).

The stilbenoids stemofuran E (**57**), stemofuran J (**58**), stemofuran M (**59**), stemofuran P (**60**) and stemofuran R (**61**) isolated from the roots of *Stemona aphylla* (Stemonaceae), showed activity against *C. neoformans*, with MIC value of 7.8 µg mL^{-1} for **57**, **58** and **60**, 31.3 µg mL^{-1} for **59** and 15.6 µg mL^{-1} for **61**. These compounds were also tested against *C. albicans*, were **57**, **58** and **59** presented an MIC of 31.3 µg mL^{-1}, and **60** and **61** showed an MIC of 15.6 µg mL^{-1} (Sastraruji et al. al., 2010).

The small molecule *N*-β-D-glucopyranosyl-*p*-hydroxyphenylacetamide (**62**) showed an MIC of 8 µg mL^{-1} against *C. albicans*, whereas the compounds *p*-hydroxyphenylacetic acid (**63**), *p*-hydroxyphenyl-acetonitrile (**64**), *p*-hydroxyacetophenone (**65**), 3,4,5-trimethoxyphenol (**66**) and dolichandroside A (**67**) showed a range MIC of 8 to 16 µg mL^{-1}. All of these compounds were isolated from the *Drypetes gossweileri* (Euphorbiaceae) tree (Ata et al., 2011). Compounds **64**, **66** and **67** have already been described from *Brassica campestris* (Brassicaceae) (Nagatsu et al., 2004), *Xylosma controversum* (Flacourtiaceae) (Xu et al., 2008), *Dolichandrone falcata* (Bignoniaceae) and *Odontonema cuspidatum* (Acanthaceae) (Aparna et al., 2009; Refaey et al., 2017). Compound **67** has also been isolated from the fungus *Cladosporium sp*. (Ding et al., 2008, Ata et al., 2011).

The caffeoyl phenylethanoid glycosides isoverbascoside (**68**) and verbascoside (**69**) presented strong antifungal activity against *C. albicans* (strains ATCC 10231, USP 1, USP 1565, OF M3-20, OF M7-19) with a range MIC of 0.7 to 3 µg mL^{-1}. These compouds are active against other *Candida* species, as compound **68** present an MIC of 1.5 µg mL^{-1} against *C. krusei* ATCC 6258 and *C. guilliermondii* USP 2234, and an MIC of 6 µg mL^{-1} against *C. tropicalis* USP B3. Compound **69** showed an MIC of 1.5 µg mL^{-1} towards *C. krusei*, *C. parapsilosis* USP 1933 and *C. tropicalis* and a potente activity against *C. guilliermondii* with an MIC of 0.7 µg mL^{-1}. In *C. albicans* strains USP 1, OF M3-20, OF M7-19, *C. guilliermondii* and *C. parapsilosis* species, the isolated compounds showed an MIC lower than the control drug amphotericin B (1 to 4 µg mL^{-1}) (Pereira et al., 2014). Funari et al. (2012) described for **69** no significant activity against *C. albicans* ATCC 90028, *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019 (MICs = 125 µg mL^{-1}), while the compound exhibited activity against *C. neoformans* 90012, with an MIC of 15.6 µg mL^{-1}. In general, compound **69** exhibit more potent activity than compound **68** against the fungals tested, indicating that the presence of the double bound between the C-7' and C-8' in verbacoside is important for the activity. Comparing the related compounds **67** and **69**, there is a decrease in activity towards *C. albicans*, probably associated with the methylation of the catechol system.

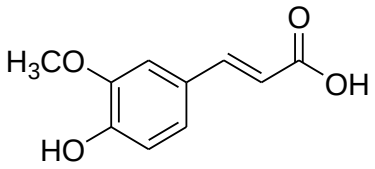
Compounds 4,5-(methylenedioxy)-*o*-coumaroylputrescine (**70**) and 4,5-(methylenedioxy)-*o*-coumaroyl-4'-*N*-methylputrescine (**71**) were isolated for the first time from bark and trunk of *Drypetes staudtii* (Putranjivaceae) and showed antifungal activity against *C. albicans* with an MIC value of 32 µg mL^{-1} (Grace et al., 2016).

The study of the essential oil of *Trachyspermum copticum* (Apiaceae) and the trunk of *Dendrobium denneanum* (Orchidaceae) yielded the isolation of two compounds with activity against *C. albicans* ATCC 10231: 2,5-dihydroxy-4-methoxy-phenanthrene-2-O-β-D-glucopyranoside (**72**), which exhibited MIC of 5.5 µg mL^{-1}, and 4-methoxy-2,5,7,9S-tetrahydroxy-9,10-dihydrophenanthrene (**73**) which exhibited MIC of 4.5 µg mL^{-1}. An additional compound was also isolated from the oil of *T. copticum*, trans-ethyl cinnamate (**74**), which obtained an MIC of 2 µg mL^{-1} (Moghadam, 2017; Lin et al., 2013). Isolation of compound **73** has also been described in the specie *Liparis regnieri* (Orchidaceae) (Ren et al., 2016).

Besides the previously mentioned flavonoids (compound **34** and **35**) were also isolated from the stems of *Derris eriocarpa* (Leguminosae) the phenolic compound 1-(3',4',5'-trimethoxyphenyl)-2-methoxy-2-(4''-methoxyphenyl)-ethane-1-ol (**75**), which presented activity against *C. albicans* ATCC 2091 and *C. guilliermondii* (clinically isolated), exhibiting an MIC of 50 µg mL^{-1} for both species (Zhang et al., 2014).

Buanmycin (**76**), isolated from the bacterium *Streptomyces sp*. SNR69, exhibited antifungal activity against *C. albicans* ATCC 10231 with MIC value of 21.1 µM (12.5 µg mL^{-1}) (Moon et al.,

2014). From *Bacillus* sp., were isolated the compounds 3,5-dihydroxy-4-ethyl-trans-stilbene (**77**) and 3,5-dihydroxy-4-isopropylstilbene (**78**), that showed an MIC of 8 µg mL^{-1} and 16 µg mL^{-1} against *C. albicans* MTCC 277, respectively (positive control amphotericin B presented an MIC of 32 µg mL^{-1}) (Kumar et al., 2014).



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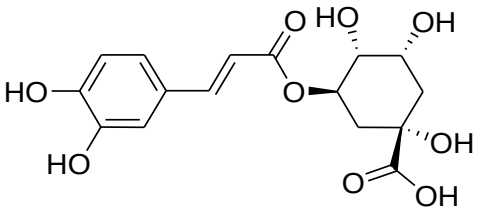

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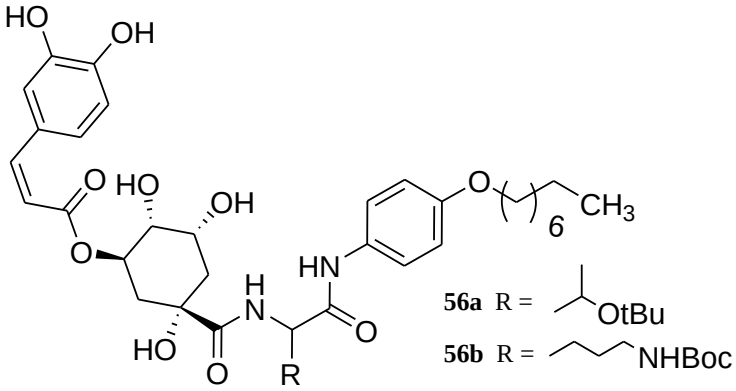
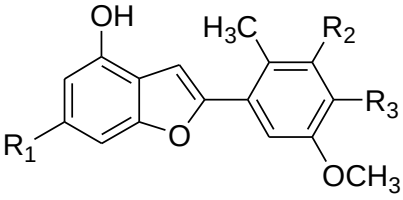
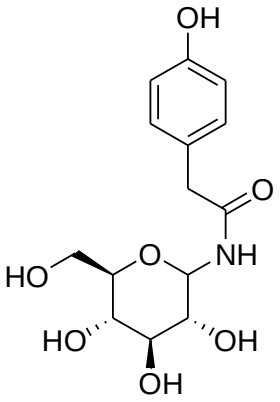


56a R = OtBu

56b R = NHBoc



57 R_1 = H, R_2 = OH, R_3 = CH_3
58 R_1 = H, R_2 = OCH_3, R_3 = CH_3
59 R_1 = OCH_3, R_2 = OH, R_3 = H
60 R_1 = OCH_3, R_2 = OCH_3, R_3 = H
61 R_1 = OCH_3, R_2 = OCH_3, R_3 = CH3



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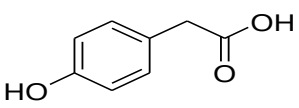

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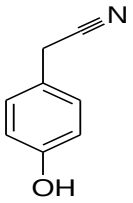

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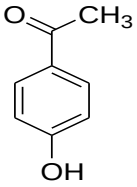

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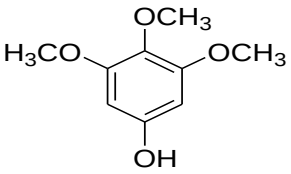

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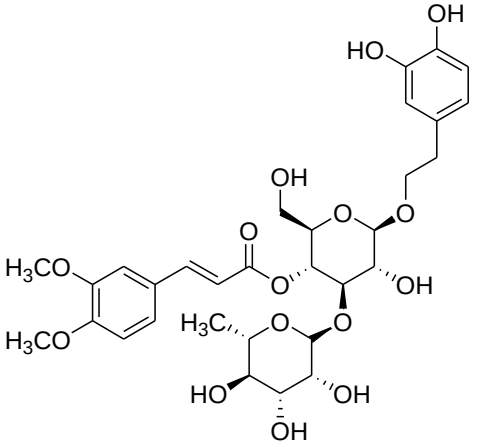

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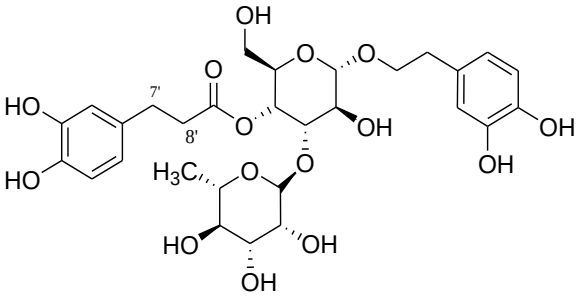

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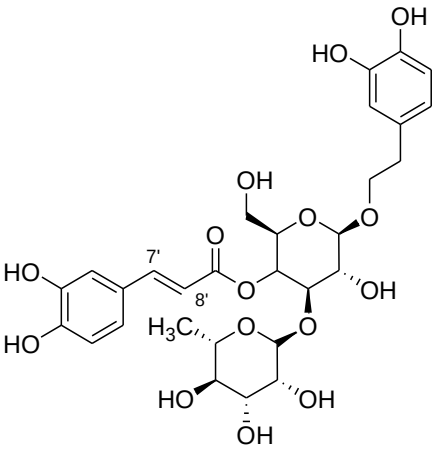

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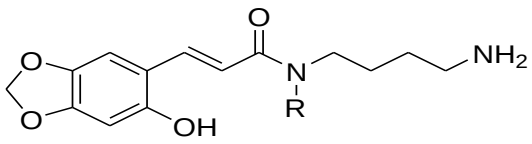
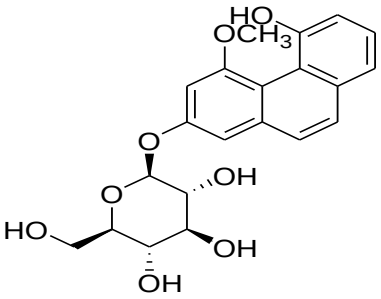


70 R = H
71 R = CH_3



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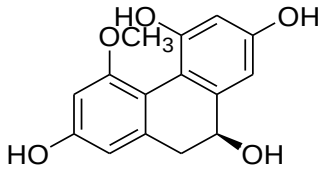

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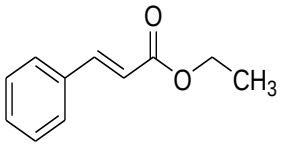

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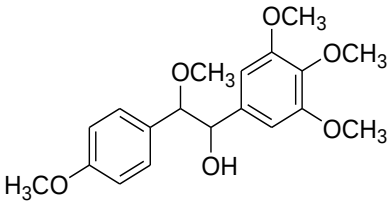

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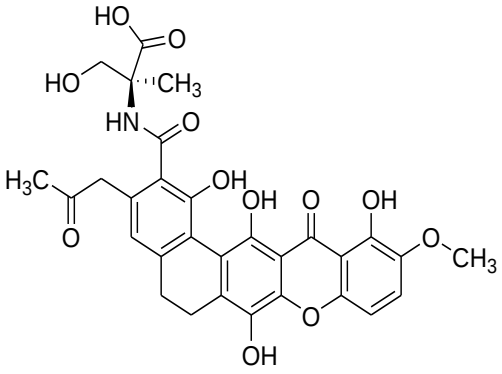

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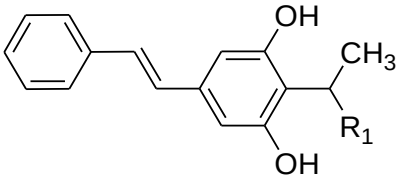


77 $R_1 = CH_3$
78 $R_1 = H$

Saponins

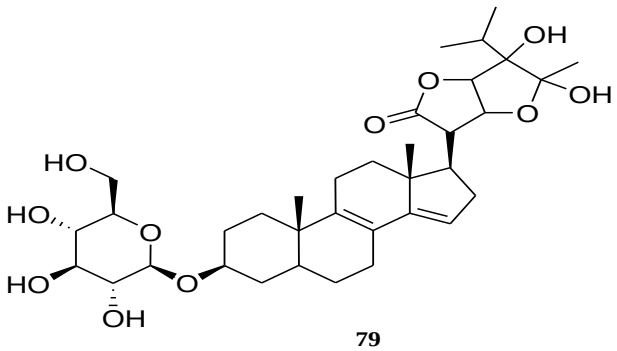
Saponins are steroid or triterpenoid glycosides common in a large number of plants that are important in human and animal health and nutrition. Concerning to antifungal activity, it is associated with the ability of saponins to cause disorganization of cell membranes in consequence of the complexation with steroids presents in membranes, causing the formation of pores and loss of membrane integrity (Coleman et al., 2010). This complexation are thought to be a micelle-like aggregation of saponins and cholesterol in the plane of the membrane, possibly with the saponin molecules arranged in a ring with their hydrophobic moieties combined with cholesterol around the outer perimeter (Mert-Türk, 2006).

The saponin vernoguinoside A (**79**) was active against *C. neoformans* IP 95026 and *C. parapsilosis* ATCC 22019 with an MIC of 7.81 µg mL^{-1} for both fungi and an MIC of 15.62 µg mL^{-}

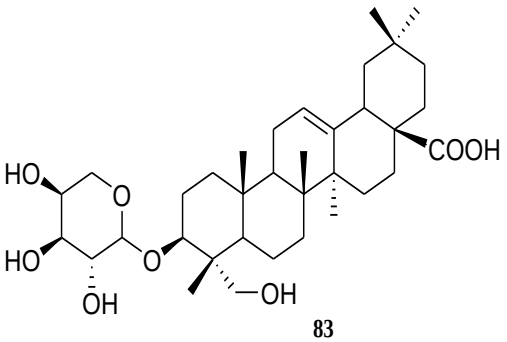
[1] against *C. albicans* ATCC 2091. Vernoguinoside (**80**) and stigmasterol 3-*O*-β-D-glucoside (**81**) are active only against *C. albicans* ATCC 2091, with an MIC of 31.25 µg mL^{-1}. This stigmastane saponins were isolated from *Vernonia guineensis* (Asteraceae) (Donfack et al., 2012). In addition, compound **81** has also been described in *Fagonia indica* (Zygophyllaceae), *Elephantopus scaber* (Asteraceae) (Kabeer, 2014) and *Acacia cochliacantha* (Fabaceae) (Manríquez-Torres et al., 2007).

Five triterpene pentacyclic saponins, 3-O-[α-L-rhamnopyranosyl(1-2)-α-L-arabinopyranosyl]-echinocystic acid (**82**), 3-O-α-L-arabinopyranosyl-hederagenin (**83**), 3-*O*-[*α*-L-rhamnopyranosyl(1-2)-*α*-L-arabinopyranosyl]-hederagenin (**84**), 3-*O*-[*α*-L-rhamnopyranosyl(1-2)-*α*-L-arabinopyranosyl]-28-*O*-[*O*-*α*-L-rhamnopyranosyl(1-4)-*O*-*β*-D-glucopyranosyl-(1-6)-*β*-D-glucopyranosyl]-hederagenin (**85**) and 3-*O*-[α-L-rhamnopyranosyl(1-2)-*α*-L-arabinopyranosyl]-28-*O*-[*α*-L-4-*O*-acetyl-rhamnopyranosyl (1-4)-*β*-D-glucopyranosyl-(1-6)-*β*-D-glucopyranosyl-hederagenin (**86**) were isolated from *Polyscias fulva* (Araliaceae) stem bark (Njateng et al., 2015) and presented antifungal activity. Both **82** and **84** inhibited the growth of *C. albicans* ATCC 1663 at concentration 50 µg mL^{-1} and 12.5 µg mL-1, respectively. Against *C. glabrata* IP 35, **83** and **84** showed an MIC of 12.5 µg mL^{-1} while **86** showed an MIC of 25 µg mL^{-1}. Both **83** and **84** exhibited an MIC of 50 µg mL^{-1} towards *C. lucitaniae* ATCC 200950. Against *C. parapsilosis* ATCC 22019, **84** showed an MIC of 50 µg mL^{-1}. Compounds **82** - **84** had a MIC value of 12.5 µg mL^{-1} against *C. guilliemondii* (clinical isolated), while compound **86** had a MIC of 50 µg mL^{-1} against this specie. Compound **84** display an MIC of 25 µg mL^{-1} towards *C. krusei* ATCC 6258. Both **84** and **85** display activity against *C. neoformans* AP 95026 (MIC 6.25 µg mL^{-1}), while compound **83** exhibited an MIC of 12.5 µg mL^{-1} (Njateng et al., 2015).

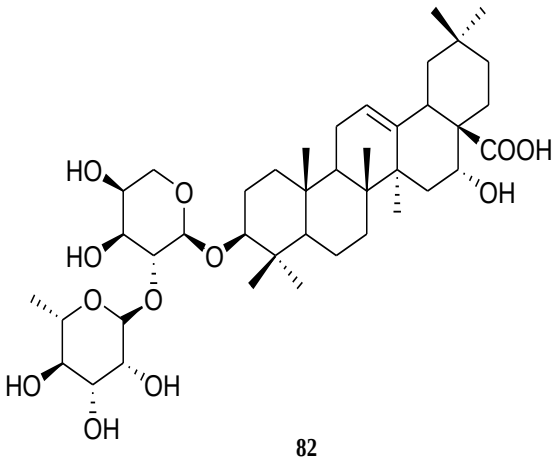
In vivo screening of natural compounds with antifungal activity made it possible to identify eleven saponins active against *C. albicans* DAY185: sakurasosaponin A2 (**87**) (MIC 27.5 µg mL^{-1}), aginoside A8 (**88**) (MIC 5.8 µg mL^{-1}), aginoside A16 (**89**) (MIC 47 µg mL^{-1}), aginoside A24 (**90**) (MIC 13.3 µg mL^{-1}), aginoside A11 (**91**) (MIC 38.9 µg mL^{-1}), aginoside A20 (**92**) (MIC 4.8 µg mL^{-1}) arvensoside B A7 (**93**) (MIC 3.1 µg mL^{-1}), barrigenol A19 (**94**) (MIC 26.5 µg mL^{-1}), barrigenol A25 (**95**) (MIC 28.7 µg mL^{-1}), maesabalide A17 (**96**) (MIC 31 µg mL^{-1}) and maesabalide A21 (**97**) (MIC 16.5 µg mL^{-1}). Compounds **94** and **96** were able to inhibit biofilm formation at the same MIC concentration (Coleman et al., 2010). Development of new antifungals that specifically disrupt the formation and/or maintenance of biofilms are interesting, once the microrganisms which produce biofilms are intrinsically resistant to conventional antifungal therapeutics and the host immune system, due to the upregulation of efflux pumps, the presence of the extracellular matrix and the presence of recalcitrant persister cells (Nobile and Johnson, 2015).


OH
OH
O
O
O
HO
HO
HO
O
O
OH

79


COOH
HO
HO
O
O
OH
OH

83


COOH
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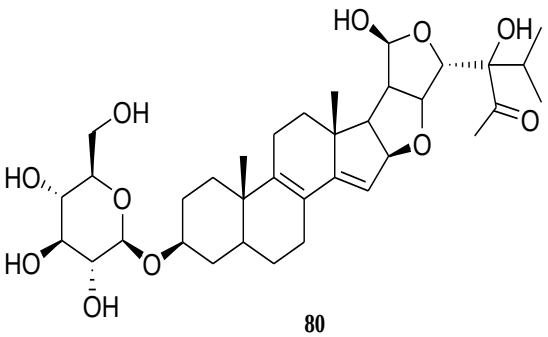
HO
O
O
O
HO
OH
OH

82


HO
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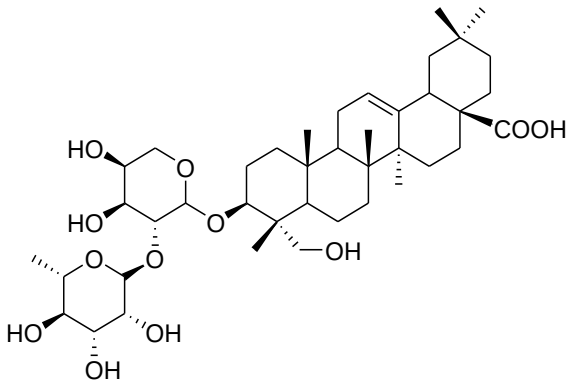
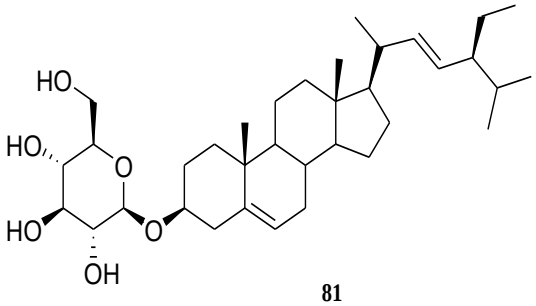
OH
O
O
OH
HO
HO
O
OH

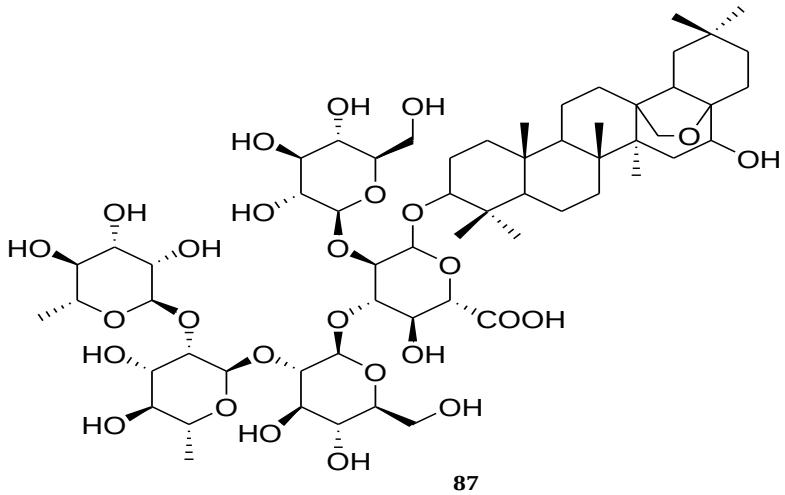
80


HO
HO
O
O
O
COOH
OH
HO
OH
OH

84


HO
HO
O
HO
O
OH

81


OH
OH
HO
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COOH
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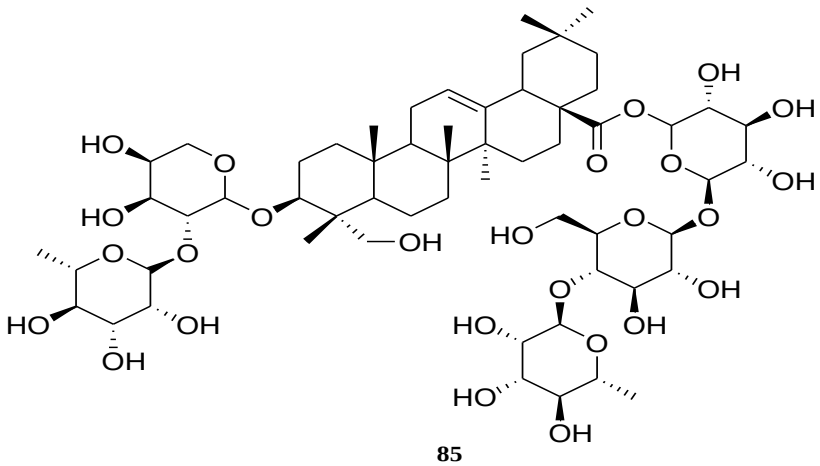
OH
HO
OH

87



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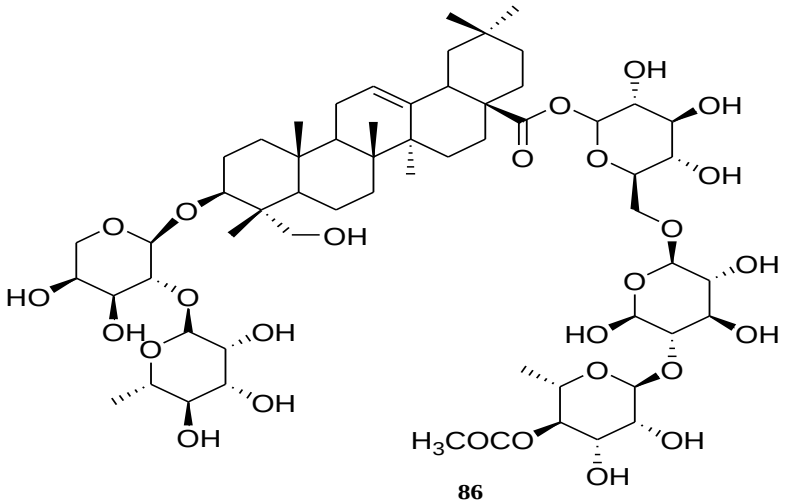

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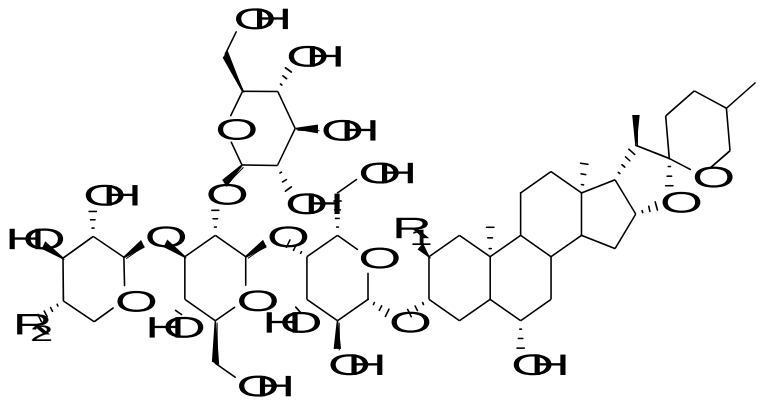
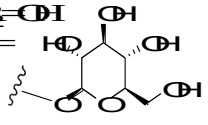
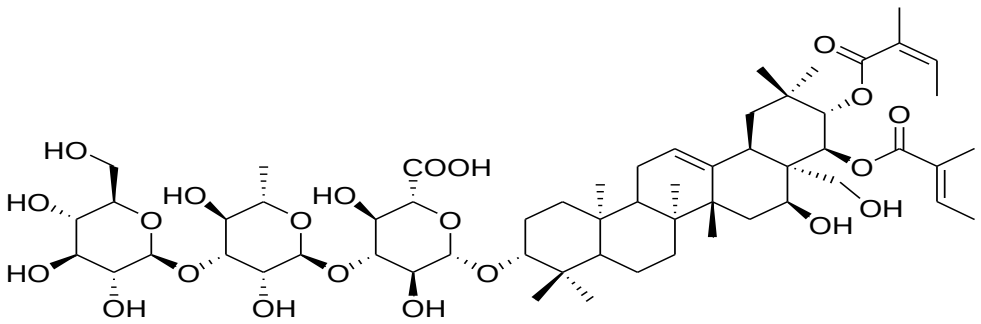


88 R_1 = H, R_2 = OH

89 R_1 = OH, R_2 = OH

90 R_1 = H, R_2 =





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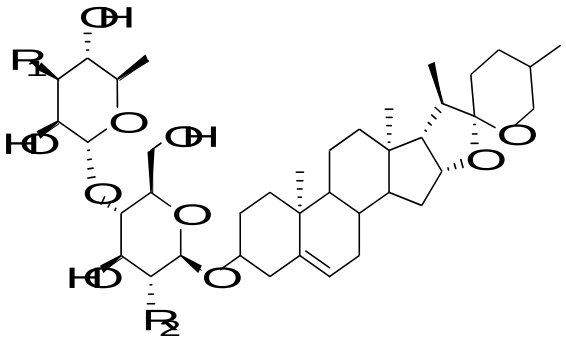
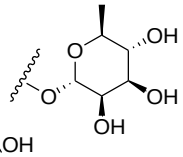
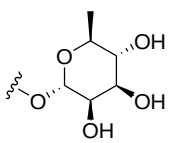


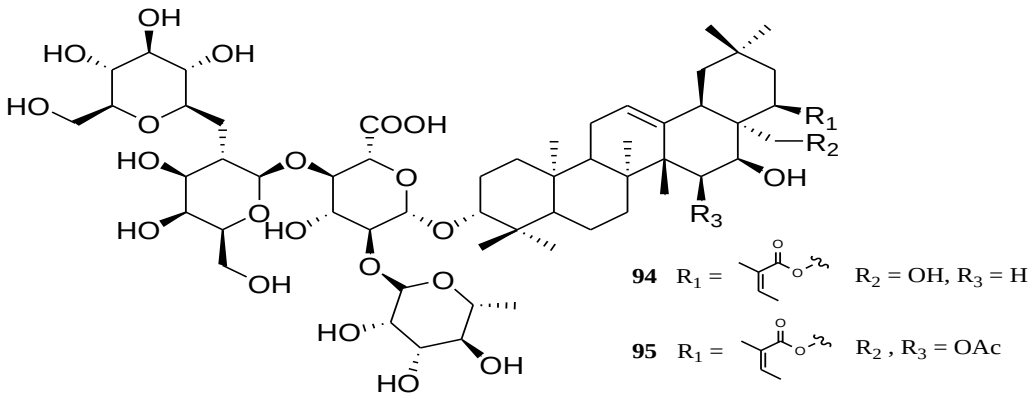
91 R_1 = OH, R_2 =

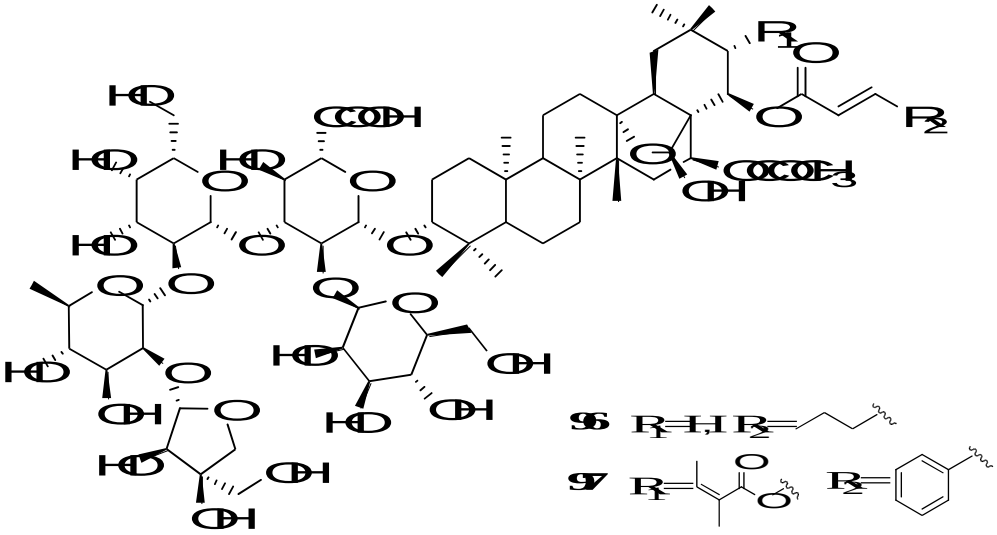


92 R_1 =



R_2 = OH





Terpenoids

Terpenes are major compounds of essential oils, and are produced to avoid injuries promoted by external agents, thus possessing antimicrobial activity and insecticide. It has a wide distribution, being found in plants, animals and microorganisms. Chemically they are formed by blocks of five carbons - the isoprene units - that are linked together by head-to-tail order, and may also exhibit tail-to-tail structural variations (Buck and Vall, 2009).

Three abietane diterpenoids isolated from the roots of a small tree *Clerodendrum eriophyllum* (Verbenaceae) showed antifungal activity (Machumi et al., 2010). Taxodione (**98**) was active against *C. glabrata* ATCC 90030 (MIC 10 µg mL^{-1}) and *C. neoformans* ATCC 90113 (MIC 1.25 µg mL^{-1}). This compound has the ability to form bonds with DNA, interfering with cell replication (Zaghloul et al., 2008). Compound 6-hydroxysalvinolone (**99**) showed strong activity against *C. neoformans* ATCC 30113 (MIC 2.5 µg mL^{-1}), while 6,11,12,16-tetrahydroxy-5,8,11,13-

abietatetra-en-7-one (**100**) was active against *C. glabrata*, *C. krusei* and *C. neoformans* (MIC 20 μg mL^{-1}). Compound **98** is also found in *Taxodium distichum* (Cupressaceae) and in *Salvia* sp. (Lamiaceae) as well as **99**, which may also be isolated from the roots of *Premna obtusifolia* (Lamiaceae) (Tayarani-Najaran, 2013; Moujir et al., 1996).

The pimarane diterpenes isopimara-7,15-dien-19-ol 19-*O*-*α*-L-arabinofuranoside (**101**) and its aglycone **102,** isolated from *Sagittaria latifolia* (Alismataceae) exhibited antifungal activity against *C. gattii* ATCC 32609 with an MIC of 20.0 μg mL^{-1}. The cytotoxicity of both compounds was evaluated against mammalian cells and it was observed that they are not cytotoxic at MIC concentration (Ravu et al., 2015).

Of branches of *Pseudolarix kaempferi* (Pinaceae), two new triterpenes 25-epi-pseudolarolide Q (**103**) and pseudolarolide P (**104**) were isolated and showed activity against *C. albicans*, with an MIC_{90} 20.40 μM (10.5 μg mL^{-1}) and 21.96 μM (10.3 μg mL^{-1}), respectively (He et al., 2011). Another triterpene, oleanane 3-(3'*R*-hydroxy)-hexadecanoate (**105**), isolated from *Rhynchospora corymbosa* (Cyperaceae), showed anti-cryptococcal activity against *C. neoformans* IP 90526 and *C. albicans* ATCC 9002, with an MIC of 16 μg mL^{-1} for both organisms (Pagning et al., 2016). Cassane diterpenes (5*S*,10*S*)-11,15(*S*)-dihydroxy-12-methoxyswartziarboreol G (**106**) and simplexene D (**107**) isolated from *Swartzia simplex* (Fabaceae) tree exhibited activity against *C. albicans* CAF2 -1 with an MIC of 32 μg mL^{-1} (Favre-Godal et al., 2015).

16α-hydroxycleroda-3,13(14)-*Z*-dien-15,16-olide (**108**), isolated from *Polyalthia longifolia* var. *pendula* (Annonaceae) showed activity against *C. albicans* NCIM3557 with an MIC_{90} of 50.3 μM (15.9 μg mL^{-1}). SAR studies showed that the double bond at C-3-C4 and the free hydroxyl group at C-16 are crucial for observed activity, probably mediated by intracellular production of reactive oxygen species, which compromises the integrity of celular membrane (Bhattacharya et al., 2015). The cytotoxicity of **108** was evaluated in the study of Misra et al. (2010), where was found that this compound was devoid of any cytotoxic effect against macrophages J774A.1 at the maximum concentration tested (200 mg mL^{-1}).

The common oleanane triperperne oleanolic acid (**109**) demonstrated activity against *C. albicans* ATCC 26555 with an MIC of 15 μg mL^{-1} (Yessoufou et al., 2015). In another antifungal study, **109** did not demonstrate activity against *C. albicans* ATCC 1663, but showed activity against *C. glabrata* IP 35 and *C. guilliermondii* (clinical isolate) with an MIC of 12.5 μg mL^{-1} for both microorganisms (Njateng et al., 2015). The antifungal activity of epifriedelanol (**110**) and epilupeol acetate (**111**) was demonstrated against *C. albicans* ATCC 26555 with MICs on 9 e 15 μg mL^{-1}, respectively. Compounds **109** - **111** were isolated from stem bark and leaves of *Ficus drupacea* (Moraceae) (Yessoufou et al., 2015) and can also be found in *Pseuderanthemum palatiferum* (Acanthaceae) (Mai et al., 2011), *Heteropappus altaicus* (Asteraceae) (Huang et al., 2013),

Euphorbia maddeni (Euphorbiaceae) (Sahai et al., 1981), *Vicoa indica* (Asteraceae) (Chowdhury et al., 1990), *Cirsium nipponicum* (Asteraceae) (Lee et al., 2005) and *Bursera copallifera* (Burseraceae) (Romero-Estrada et al., 2016).

In the study of Mollataghi et al. (2012), the common triterpene β-amyrone (**112**) isolated from *Beilschmiedia alloiophylla* (Lauraceae) showed activity against *C. albicans* with an MIC of 32 μg mL^{-1}. Ata et al. (2011) described for **112** an MIC of 8 μg mL^{-1} against the same microorganism. Compound **112** can also be found in *Stillingia oppositifolia* (Euphorbiaceae) (Cota et al., 2011) and *Drypetes gossweileri* (Putranjivaceae) (Ata et al., 2011).

The prenylated *p*-xylene caulerprenylol B (**113**) isolated from the marine alga *Caulerpa racemosa* (Caulerpaceae) showed an MIC_{80} of 4 μg mL^{-1} for both *C. neoformans* 32609 and *C. glabrata* 537, equal to the positive control amphotericin B (Liu et al., 2013). The sesquiterpene hydroquinone avarol (**114**), isolated from the marine sponge *Dysidea avara* (Dysideidae) showed strong anti-candida activity against *C. albicans* MH2, 4/07, 4/16, 2/24, ATCC 10231, *C. glabrata*, *C. krusei*, and *C. tropicalis* ATCC 750, with a range MIC of 0.8-6.0 μg mL^{-1} (Pejin et al., 2016).

The cembrane diterpenoid nephthenol (**115**) and the triterpene gorgost-5-ene-3β-ol (**116**) isolated from the marine sponge *Lobophytum pauciflorum* (Alcyoniidae) both exhibited an MIC of 50 μg mL^{-1} against *C. albicans* (Hassan et al., 2016). Compound **115** has already been isolated from the corals *Nephthea sp*. (Nephtheidae) (Tani et al., 2018), *Eunicea sp*. (Plexauridae) (Shi et al., 2001), *Sclerophytum sp*. (Rao et al., 1990), *Lobophytum catalai* (Alcyoniidae) (Anjaneyulu et al., 1998), *Sarcophyton glaucum* (Alcyoniidae) (Kobayashi and Osabe, 1989), and from the plants *Croton laui* (Euphorbiaceae) (Yang et al., 2017) and *Bursera multijuga* (Burseraceae) (Hernandez et al., 2014). Compound **116** can also be found in *Isis hippuris* (Isididae) (Tanaka et al., 1982), *Sarcophyton trocheliophorum* (Alcyoniidae) (Wang et al., 2004) and *Heteroxenia fuscescens* (Xeniidae) (Mohammed et al., 2012).

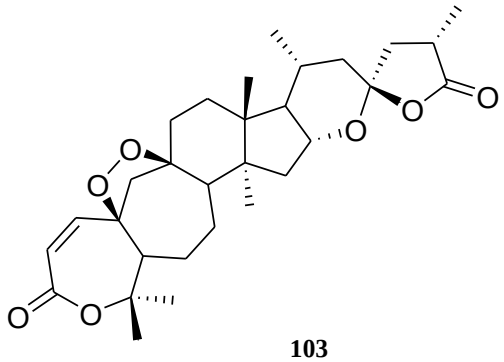
The aminosesquiterpene aminobisabolene (**117**) exhibited activity against *C. glabrata* and *C. krusei* with a range MIC_{90} of 36 to 38 μM (8.46 to 8.93 μg mL^{-1}) (Jamison et al., 2016). Compound **117** has already been isolated from the sponges of the genus *Halichondria sp*. (Halichondriidae) and *Theonella sp.* (Theonellidae) (Kitagawa et al., 1987).

Laurepoxyene (**118**), 3β-hydroperoxyaplysin (**119**), 3α-hydroperoxy-3-epiaplysin (**120**), 10-Bromoisoaplysin (**121**), Laurokamurene A (**122**) and Laurokamurene C (**123**) were isolated from the red alga *Laurencia okamurai* (Rhodomelaceae). Against *C. glabrata* 537, **118** exhibited an MIC_{80} of 2 μg mL^{-1}, **119** presented an MIC_{80} of 4 μg mL^{-1}, **121** showed an MIC_{80} of 32 μg mL^{-1} and **123** exhibited potent activity with an MIC_{80} of 1 μg mL^{-1}. Towards *C. neoformans* 32609, **119** presented an MIC_{80} of 4 μg mL^{-1}, **120** exhibited an MIC_{80} of 8 μg mL^{-1} and **122** exhibited an MIC_{80} of 32 μg mL^{-1} (Yu et al., 2014).

The indolditerpene drechmerin B (**124**), isolated from the fungus *Drechmeria* sp. (Clavicipitaceae), showed activity against *C. albicans* with an MIC of 12.5 μg mL^{-1} (Zhao et al., 2018).

The sesquiterpene (1*β*,4*β*,4a*β*,8a*α*)-4,8a-dimethyl-octahydro-naphthalene-1,4a(2H)-diol (**125**) was isolated from a culture of *Streptomyces albolongus* (Streptomycetaceae) and showed strong antifungal activity against *C. parapsilosis* ATCC 22019 and *C. albicans* ATCC MYA-2876 with an MIC of 3.13 μg mL^{-1} and 12.5 μg mL^{-1}, respectively. The 7-OH analogue of **125**, showed no activity against the fungi tested (MIC ≥ 100 μg mL^{-1}), indicating that substitution at this carbon may modify pharmacodynamic properties, thereby interfering in the activity (Ding et al., 2016). Isolation of compound **125** has also been described from a culture of *Nocardiopsis chromatogenes* (Nocardiopsaceae) (Sun et al., 2017).

Mitochondria is a major source of ROS generation in eukaryotic cells. Is known that terpenoids can play a role in diminishing the mitochondrial content (Lenaz, 2001). The excessive production of ROS, such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH^-) plays an important role as early signal mediators of apoptosis. Several pathogenic fungi, such as *Candida albicans* and *Cryptococcus neoformans*, are known as "petite-negative" yeasts because they cannot survive upon damage of mitochondrial genome (Haque et al., 2016).



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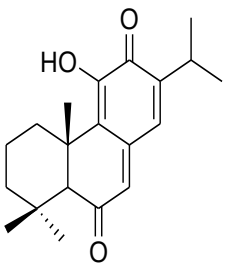

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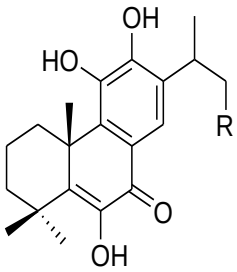
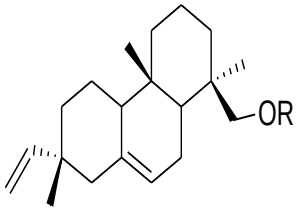


99 R = H
100 R = OH



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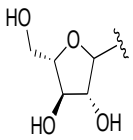
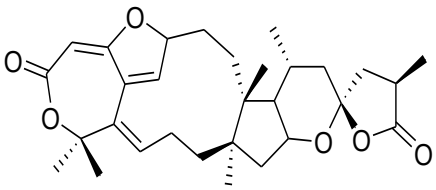


102 R = H



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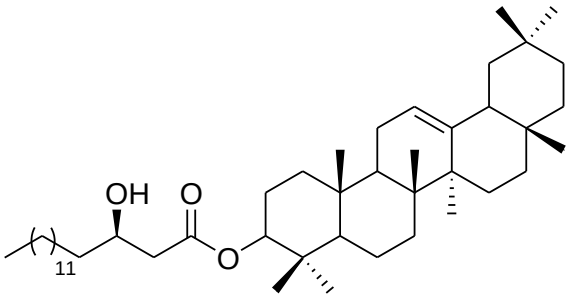

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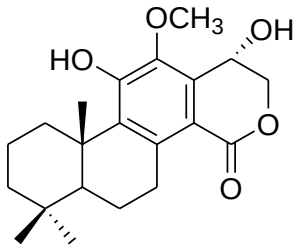

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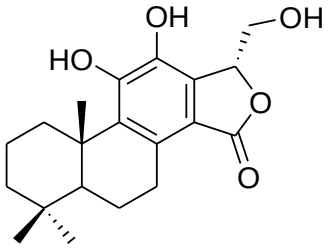

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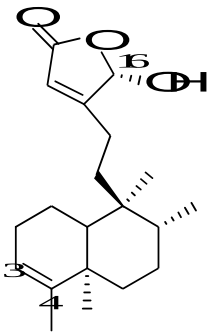

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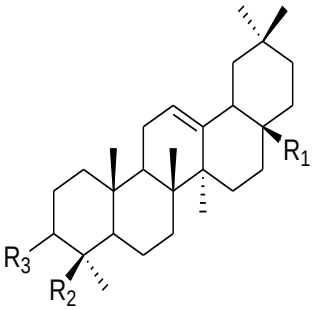
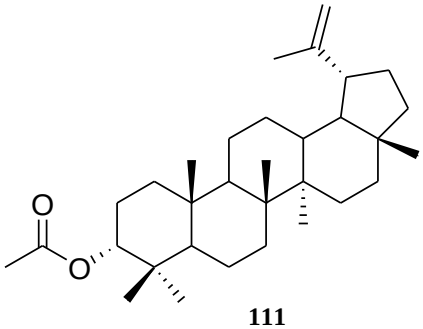


109 R_1 = COOH, R_2 = CH_3, R_3 = OH
110 R_1 = CH_3, R_2 = H, R_3 = H



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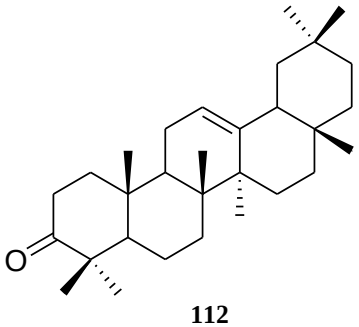

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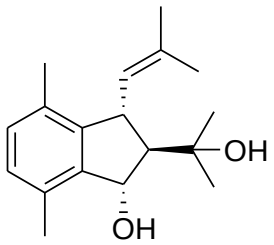

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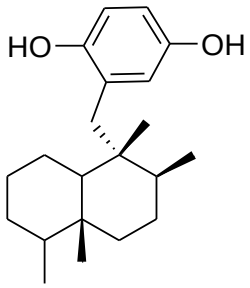

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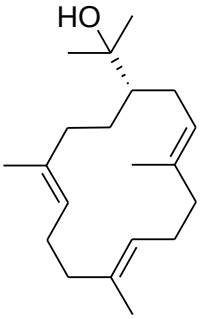

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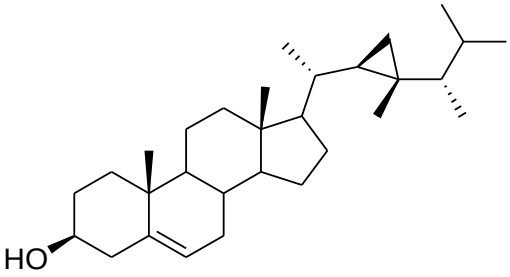

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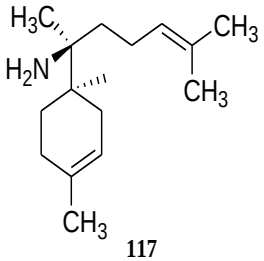

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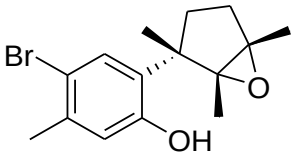

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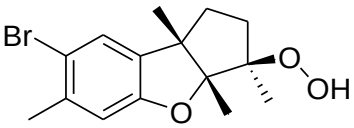

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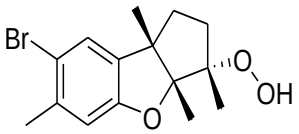

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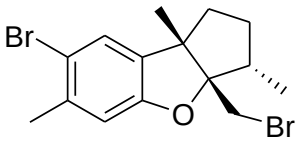

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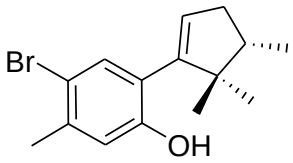

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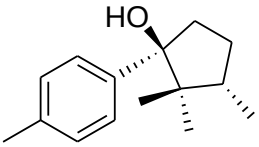

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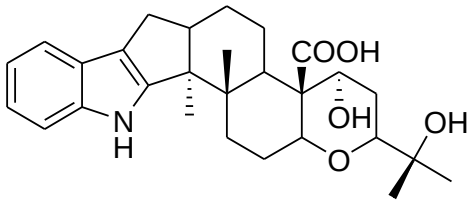

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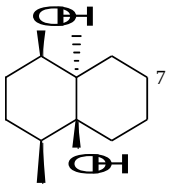

125

Conclusions

We described here more than a hundred compounds, with range MICs of 0.63 to 50 μg mL^{-1} that may be potential candidates for development of new anti-candida and anti-cryptococcal drugs.

The most potent compound against *Candida* sp. was the phenolic compound verbascoside which present an MIC range of 0.7 to 1.5 μg mL^{-1}. The most potent compound agains *Cryptoccosu* sp. was the alkaloid juliprosine (MIC 0.63 μg mL^{-1}). 88% of these molecules were active against fungal species of the genus *Candida* sp. and 35.2% were active against fungi of the genus *Cryptococcus* sp. Of all the isolated metabolites, 77.6% were molecules from plants, 8% from microorganisms and 13.6% from marine sources. The decrease in the proportion of molecules active against *Cryptococcus* in relation to the number of molecules active against *Candida* can be explained by the lower number of studies that test the secondary metabolites isolated from *Cryptococcus* species, that disadvantages the process of discovering new chemical entities with potentials of clinically significant activity against this pathogen in particular. It is important to note that many of the studies analyzed here had some methodological flaws when it comes to the determination of antifungal activity. For example, the non-comparison with drug control, few strains of fungi from clinical origin. Several of the molecules analyzed have previously been isolated from different plant species, and some of these molecules already have their complete published synthesis, which is an advantage in the production of these new drugs aimed at infection control, since the stage of mass production by synthesis becomes a possibility. Faced with so many promising in vitro chemical entities, further preclinical studies are required to gather information about these promising drug candidates, like pharmacodynamics and pharmacokinetics properties, besides toxicologic informations.

Authors' contributions

AAS performed the bibliographic research and wrote the manuscript; KLL realized the critical review of the manuscript.

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ANEXOS

Anexo 1.Guia para autores da Revista Brasileira de Farmacognosia

Revista Brasileira de Farmacognosia

Instructions for Authors

Introduction

The Revista Brasileira de Farmacognosia-Brazilian Journal of Pharmacognosy is a periodical dedicated to the publication of original scientific work, reviews and communications in the field of Pharmacognosy (the study of crude drugs and substances derived from natural sources used as medicines).

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The Brazilian Journal of Pharmacognosy accepts for publication original scientific work, reviews and communication articles written **only** in English.

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Reference to a website: Cancer Research UK, 1975. Cancer statistics reports for the UK. http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/ (accessed 13 March 2003).

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