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In silico search of *Myrcia tomentosa* (Myrtaceae) antineoplastic potential

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Abstract

Myrcia tomentosa, popularly known as “guava-brava”, belongs to the Myrtaceae family, widely used in folk medicine to treat various diseases. There already are studies proving the effectiveness of several of its components. However, there are few specific articles on the biological potential of *M. tomentosa* compounds. The aim of this study was to evaluate the potential antineoplastic activity from *M. tomentosa*. For these, we performed *in silico* analysis to evaluate pharmacological and toxicological activities, besides the interaction between *M. tomentosa* molecules with the human targets from *redocking* analysis. Our results showed that α-cadinol was the highest score molecule between the 11 compounds present in screening analysis. Among its possible actions, antineoplastic activity and interaction with cytochrome P450 19 A1 were found. This cytochrome was related to breast cancer and is the main target of the antineoplastic drugs used in this cancer’s treatment. Therefore, we believe that α-cadinol should be considered in future *in vitro* and *in vivo* assays against breast cancer.

Keywords: Breast cancer. Medicinal plants. α-cadinol. Molecular docking.

Introduction

Myrcia tomentosa, popularly known as “guava-brava”, is a deciduous, heliophobia, pioneer, and native tree of Brazilian cerrado. It inhibits other plants’ growth through the production of aleochemicals[1]. It can be found in an extensive area: from Panama and Venezuela to southeastern Brazil[2,3].

FIGURE 1: General aspect of *Myrcia tomentosa* specimen.

M. tomentosa (**FIGURE 1**) belongs to the Myrtaceae family, which has about 400 species only in Brazil[4,5]. The Myrtaceae family is widely used in folk medicine to treat diabetes, diarrhea, hemorrhage, ulcers and dyspepsia[4]; and there already are studies proving its components' effectiveness as antimicrobials and antioxidants[6]; anti-inflammatory and antinociceptive[7]; antiobesity and hypolipidemic[8]; thyroid peroxidase inhibitors[9] and anticancer drugs[10].

Drugs from natural products with important biological activities can treat 87% of categorized human diseases[11]. In the oncology area, 85 of the 175 drugs discovered between 1940 and 2010 were natural products or derived directly from them[12].

However, there are few specific studies about the biological potential of *M. tomentosa* molecules, even though its known compounds have already been tested *in vivo* and *in vitro*, proving their antifungal, antimicrobial[2,4,13], and antioxidant effect[14]. The aim of this study was to evaluate the potential antineoplastic activity from *M. tomentosa*.

Material and Methods

A bibliographic review was carried out to identify *M. tomentosa* chemical markers in the databases Medical Literature, Analysis, and Retrieval System Online (MEDLINE); Scientific Electronic Library Online (SciELO); Science Direct and Periódicos Capes.

All molecules found in the literature search were analyzed on the PASS Prediction server[15,16] to assess their respective biological activities. The identified molecules were evaluated in software to predict their biological and pharmacodynamic activity. In PASS Prediction[15], the values of Pa > 0.7 (probability of the molecule to present the investigated activity) and Pi < 0.05 (probability of the molecule not showing the investigated activity) were evaluated.

Toxicity prediction was performed using the ProTox Prediction program[17,18] which evaluates parameters that indicate toxicity in all human organs and tissues.

Oral absorption prediction was performed by the SwissADME server[19] in association with Molispiration[20], observing the parameters of Lipinski[21].

The prediction of interaction with human receptors was performed using SwissTargetPrediction server[22] that appraises the *in silico* possibility of interaction between the compound and human receptors.

The Hermes program in GOLD Suite 5.7.0[23] was used to prepare the selected target. The binding site used for docking was defined as all protein residues within the 10 Å of the reference ligand that accompanied the protein complex. The default values of all other parameters were used, and the complexes were subjected to 10 executions of genetic algorithms using the CHEMPLP suitability function, choosing the best graphical interfaces. Subsequently, *redocking* was used to validate the interaction model between the ligand and the selected target.

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Results and Discussion

We found in the literature review, several *M. tomentosa* molecules: sesquiterpenes (α-bisabol, bisabol β-oxide and α-cadinol), hydrocarbons (n-pentacosane and n-tetracosane), steroids (β-sitosterol), flavonoids (quercetin, kaempferol, and guaijaverin), avicularin and juglanin[2]. Almost all of these compounds showed *in vivo* and *in vitro* tests antifungical activity, mainly against the *Candida* sp. and *Criptococccus* sp.; antimicrobial, with moderate activity against most Gram-positive bacteria, in addition to *Pseudomonas aeruginosa*, *Micrococcus* sp., *Bacillus* sp. and *Staphylococcus aureus*[2,4,13], antioxidant[14], anti-inflammatory, antinociceptive, antiobesity, hypolipemic and thyroid peroxidase inhibitor effect[6,8].

The *in silico* analysis in the PASS Prediction revealed α-cadinol (**FIGURE 2**) as the main compound of this study **(TABLE 1)** and also this compound was the only one that presents antineoplastic activity.

FIGURE 2: α-cadinol structure.

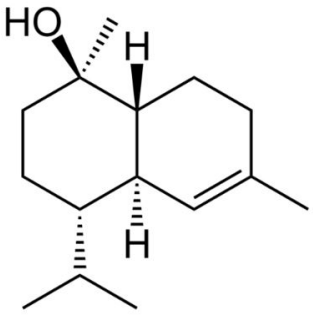


TABLE 1: compounds of *M. tomentosa* and their characteristics.

Compound	Lipinski's rule	TGI absorption	LD50 (mg/kg) and toxicity class	Activity	Target
α-bisabolol	5	High	1190 (4)	Apoptosis agonist,	Androgen receptor,
				Antieczematic,	Cytochrome P450 19A1,
				Antiulcerative	Sodium-dependent noradrenaline transporter
α-bisabolol oxide B	5	High	1190 (4)	Antiparasitic,	Androgen receptor,
				CYP2C12 substrate,	Platelet-activating factor receptor,
				Antieczematic	3-hydroxy-3-methylglutaryl-coenzyme A reductase
α-cadinol*	5	High	2830 (5)	Antieczematic,	Cytochrome P450 19A1,
				CYP2C12 substrate,	Steroid 17-alpha-hydroxylase/17,20 lyase,
				Antineoplastic	Estrogen receptor

β-sitosterol	4	Low	890 (4)	Antihypercholesterolemic,	Androgen receptor, 3-hydroxy-3-methylglutaryl-coenzyme A reductase,
				Cholesterol antagonista,	Tyrosyl-DNA phosphodiesterase 1
				Hypolipemic	
n-tetracosane	4	Low	1190 (4)	Sugar-phosphatase inhibitor, Acrocylindropepsin inhibitor, Chymosin inhibitor	Dynamin-1,
					M-phase inducer phosphatase 2,
					Sterol O-acyltransferase 1
n-pentacosane	4	Low	1190 (4)	Sugar-phosphatase inhibitor, Acrocylindropepsin inhibitor, Chymosin inhibitor	Dynamin-1,
					Sigma non-opioid intracellular receptor 1,
					Dual specificity protein phosphatase 3
Quercetin	5	High	1190 (4)	Chlordecone reductase inhibitor, Membrane integrity agonist, 2-Dehydropantoate 2-reductase inhibitor	Carbonic anhydrase 12, Epidermal growth factor receptor, Phospholipase A2
Kaempferol	5	High	1190 (4)	Chlordecone reductase inhibitor, Membrane integrity agonist, 2-Dehydropantoate 2-reductase inhibitor	Cytochrome P450 1A2, Multidrug resistance protein 1,
					Arachidonate 5-lipoxygenase
Avicularin	3	Low	1190 (4)	Membrane integrity agonist, Hemostatic,	Aldose reductase,
				Cardioprotectant	Aldo-keto reductase family 1 member B15, Tyrosyl-DNA phosphodiesterase 1
Juglanin	4	Low	5000 (5)	Membrane integrity	Aldose reductase,
				agonist,	Aldo-keto reductase family 1 member B15, Alcohol dehydrogenase
				Hemostatic,	
				Cardioprotectant	
Guaijaverin	3	Low	1190 (4)	Monophenol monooxygenase inhibitor,	Aldose reductase,
				Membrane integrity agonist, Membrane permeability inhibitor	Aldo-keto reductase family 1 member B15, Alcohol dehydrogenase

Subsequently, the drug-likeness classification[21] was performed, representing the possibility of the molecule exhibiting descriptors compatible with a favorable absorption profile in the gastrointestinal tract. Molinspiration[20] and SwissADME[19] programs were used, and the main parameter adopted was Lipinski's rule. α-cadinol met the five criteria of the Lipinski rule, being considered with high intestinal absorption[21].

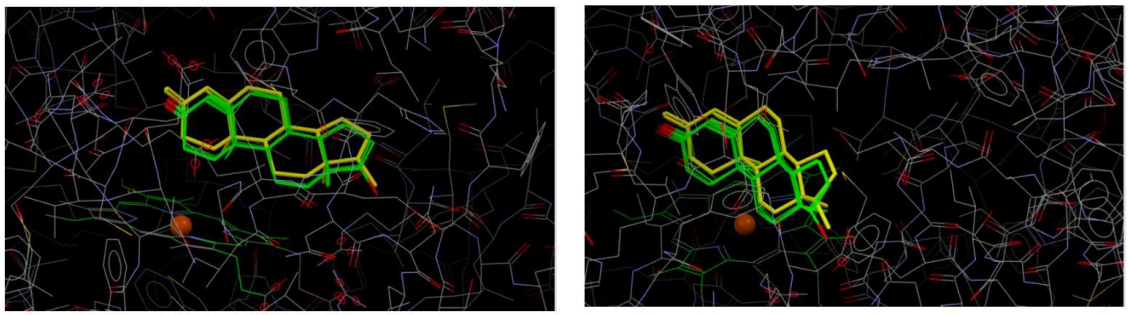
Research on ProTox Prediction[17] showed how α-cadinol (LD50: 2830 mg/Kg) has low toxicity, belonging to class 5 (with class 1 being the most toxic and class 6 being the least toxic). Furthermore, the toxicity targets of the compound were the immune system and the mitochondrial membrane.

In Swiss Target Prediction[22], an interaction was found between the compound α-cadinol and the cytochrome P450 19 A1 (PDB ID 5JKW). The cytochrome P450 19 A1 aromatase catalyzes with high specificity the synthesis of estrogens - estrone, 17β-estradiol, and 16α-estriol- from androgens - androstenedione, testosterone and 16α-hydroxyesterosterone[24]. Estrone is the predominant estrogen after menopause. During the pre-menopause period, it is mainly derived from the metabolism of estradiol secreted by the ovary. In the post-menopause period, estrone is almost exclusively produced by cytochrome P450 19 A1 in adipose tissue by aromatizing the androgens secreted by the adrenal[25].

To validate the molecular interaction model between the ligand and target, a *redocking* analysis was performed (**FIGURE 3**) between the co-crystallized ligand testosterone and the selected target, cytochrome P450 19 A1 (PDB ID 5JKW). In this analysis, the RMSD values of the 5 poses found were below 1A, revealing the reliability power of the generated model.

From the conditions established by molecular *redocking*, the anchorage analysis was performed with the selected ligand, α-cadinol, obtaining the configuration shown in **FIGURE 4.**

FIGURE 3: R*edocking* image of the co-crystallized ligand testosterone and the selected target, cytochrome P450 19 A1 (PDB ID 5JKW). The result from the best five poses (RMSD values below 1A).

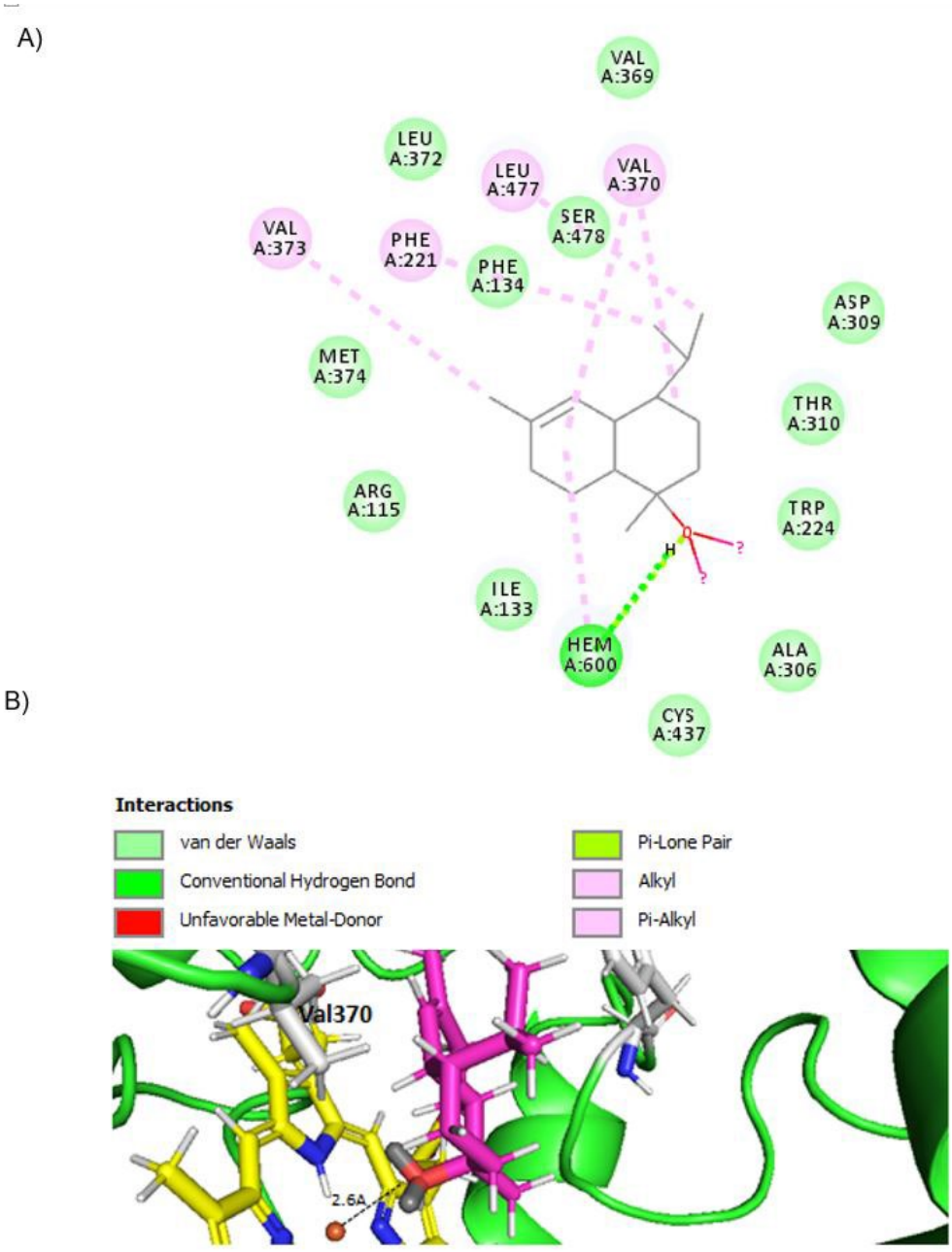


Understanding the production of estrogens, especially in the postmenopausal period, is essential to understand the pathophysiology of breast cancer and its possible therapeutic targets. Nowadays, for example, 60-80% of breast cancers have estrogen and progesterone receptors (molecular subtypes luminal A and luminal B)[26]. Thus, the inhibition of estrogen biosynthesis by third-generation aromatase inhibitors (AIs), such as letrozole, anastrozole and exemestane, constitute the front line of therapy for estrogen-dependent postmenopausal breast cancer. AIs have also been used effectively in the treatment of endometriosis, ovarian and lung cancer[27].

Similarly to AIs, α-cadinol should also act on cytochrome P450 19 A1 aromatase, inhibiting the conversion of androgens to estrogens and, therefore, being a possible new antineoplastic drug for the treatment of estrogen-dependent postmenopausal breast cancer.

When the amino acids necessary to link the aromatase of cytochrome P450 19 A1 and exemestane were compared, for example, with those present in the link between aromatase and α-cadinol, it was found that almost half of the amino acids were the same: PHE 134, PHE 221, ILE 133, ARG 115, LEU 372, VAL 370, SER 478, THR 310, ASP 309, ALA 306 and TRP 224[27]. In addition, like exemestane, α-cadinol had low toxicity, both with LD50 <3000 mg/kg[17]. These similarities with exemestane reaffirm α-cadinol antineoplastic potential.

FIGURE 4: (a) α-cadinol d*ocking* in the active site of CYP 450 19 A1 (PDB ID 5JKW). This figure was generated with Discovery Studio 3.5 Visualizer. (b) 2D interaction diagram between α-cadinol and the active site of CYP 450 19 A1 (PDB ID 5JKW). This figure was generated with Pymol 1.1r1 software.



Conclusion

Of all the 11 molecules present in *M. tomentosa*, α-cadinol was the one with the best *in silico* pharmacokinetic and biological properties, being the molecule chosen for the study. Among its possible actions, antineoplastic activity and interaction with cytochrome P450 19 A1, responsible for the synthesis of estrogens from androgens, were found. Therefore, this study suggests that α-cadinol should be considered for *in vitro* and *in vivo* antineoplastic assays to investigate its potential influence in estrogen-dependent postmenopausal breast cancer. The knowledge gained from this work should be useful for further exploitation of the resource.

References

1. Imatomi M, Novaes P, Matos AP, Gualtieri SCJ, Molinillo JMG, Lacret R et al. Phytotoxic effect of bioactive compounds isolated from *Myrcia tomentosa* (Myrtaceae) leaves. **Biochem Syst Ecol**. 2013; 46: 29-35. ISSN 0305-1978. [CrossRef] [Link].

2. Da Silva FAS, De Paula JAM, Dos Santos PA, Oliveira LDAR, Oliveira GDAR, Liao LM, et al. Phytochemical analysis and antimicrobial activity of *Myrcia tomentosa* (Aubl.) DC. leaves. **Molecules**. 2017; 22(7): 1-10. ISSN 1420-3049. [CrossRef] [PubMed].

3. Judd WS, Campbell CS, Kellogg EA, Stevens PF, Donoghue MJ. **Sistemática Vegetal - Um Enfoque Filogenético**. Taxon. 2009. ISBN-13: 978-8536317557.

4. Borges LL, Alves SF, Sampaio BL, Conceição EC, Bara MTF, Paula JR. Environmental factors affecting the concentration of phenolic compounds in *Myrcia tomentosa* leaves. **Braz J Pharmacogn.** 2013;23(2):230–8. ISSN 0102-695X. [CrossRef].

5. Flora do Brasil 2020. **Jardim Botânico do Rio Janeiro**. 2018. [Link].

6. Yadegarinia D, Gachkar L, Rezaei MB, Taghizadeh M, Astaneh SA, Rasooli I. Biochemical activities of Iranian *Mentha piperita* L. and *Myrtus communis* L. essential oils. **Phytochemistry**. 2006 June; 67(12): 1249-1255. ISSN 0031-9422. [CrossRef].

7. Andrade GS, Guimarães AG, Santana MT, Siqueira RS, Passos LO, Machado SMF et al. Phytochemical screening, antinociceptive and anti-inflammatory effects of the essential oil of *Myrcia pubiflora* in mice. **Braz J Pharmacogn**. 2012; 22(1): 181-188. ISSN 0102-69X. [CrossRef].

8. Ferreira EA, Gris EF, Rebello JM, Correia JFG, De Oliveira LFS, Filho DW et al. The 2′,4′,6′-trihydroxyacetophenone isolated from *Myrcia multiflora* has antiobesity and mixed hypolipidemic effects with the reduction of lipid intestinal absorption. **Pl Med**. 2011 Sep; 77(14): 1569-74. ISSN 0032-0943. [CrossRef] [PubMed].

9. Ferreira ACF, Neto JC, Da Silva ACM, Kuster RM, Carvalho DP. Inhibition of thyroid peroxidase by *Myrcia uniflora* flavonoids. **Chem Res Toxicol**. 2006 Mar; 19(3): 351-5. ISSN 1520-5010. [CrossRef] [PubMed].

10. Dexheimer G, Pozzobon A. Atividade biológica de plantas da família Myrtaceae*:* revisão sistemática de artigos entre 1989 e 2015. **Rev Cuba Pl Med**. 2017; 22(2). ISSN 1028-4796. [Link].

11. Newman D, Cragg G, Snader K. The influence of natural products upon drug discovery. **Nat Prod Rep**. 2000; 17(3): 215-34. ISSN 1460-4752. [CrossRef].

12. Newman D, Cragg G. Natural products as sources of new drugs over 30 years from 1981 to 2010. **J Nat Prod**. 2012; 75(3): 311-35. ISSN 1520-6025. [CrossRef].

13. Sá FAS. **Morfoanatomia, composição química do óleo essencial e atividade antimicrobiana das folhas e casca do caule de *Myrcia tomentosa* (Aubl.) DC**. Goiânia, 2010. 117f. Dissertação de Mestrado [Programa de Pós-graduação em Ciências Farmacêuticas] - Universidade Federal de Goiás, UFG, Goiânia, 2010.

14. Takao LK, Imatomi M, Gualtieri SCJ. Antioxidant activity and phenolic content of leaf infusions of *Myrtaceae* species from Cerrado (Brazilian Savanna). **Brazilian J Biol**. 2015; 75(4): 948-52. ISSN 1678-4375. [CrossRef] [Link].

15. Lagunin A, Stepanchikova A, Filimonov D, Poroikov V. PASS: Prediction of activity spectra for biologically active substances. **Bioinformatics**. 2000; 16(8): 747-8. ISSN 1754-7431. [CrossRef].

16. Sadym A, Lagunin A, Filimonov D, Poroikov V. Prediction of biological activity spectra via the Internet. **SAR QSAR Environm Res**. 2003. ISSN 1029-046X. [CrossRef].

17. Banerjee P, Eckert AO, Schrey AK, Preissner R. ProTox-II: A webserver for the prediction of toxicity of chemicals. **Nucleic Acids Res**. 2018; 46(W1): W257-63. ISSN 1362-4962. [CrossRef] [PubMed].

18. Drwal MN, Banerjee P, Dunkel M, Wettig MR, Preissner R. ProTox: A web server for the in silico prediction of rodent oral toxicity. **Nucleic Acids Res**. 2014. Jul;42(W1): W53-8. ISSN 1362-4962. [CrossRef] [PubMed].

19. Daina A, Michielin O, Zoete V. SwissADME : a free web tool to evaluate pharmacokinetics, drug- likeness and medicinal chemistry friendliness of small molecules. **Nat Publ Gr.** 2017 March 3; 7: 1-13. ISSN 2045-2322. [CrossRef] [PubMed].

20. Jarrahpour A, Fathi J, Mimouni M, Hadda T Ben, Sheikh J, Chohan Z et al. Petra, Osiris and Molinspiration (POM) together as a successful support in drug design: Antibacterial activity and biopharmaceutical characterization of some azo Schiff bases. **Med Chem Res**. 2012; 21(8): 1984-90. ISSN 1554-8120. [CrossRef].

21. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. **J Pharmacol Toxicol Methods**. 2000 Jul-Aug; 44(1): 235-249. ISSN 1056-8719. [CrossRef] [PubMed].

22. Gfeller D, Grosdidier A, Wirth M, Daina A, Michielin O, Zoete V. SwissTargetPrediction: A web server for target prediction of bioactive small molecules. **Nucleic Acids Res**. 2014 Jul 1; 42(W1): W32–W38. ISSN 1362-4962. [CrossRef] [PubMed].

23. Verdonk M, Cole J, Hartshorn M, Murray C, Taylor R. Improved protein-ligand docking using GOLD. **Proteins Struct Funct Genet**. 2003 Sep 1; 52(4): 609-23. ISSN 1097-0134. [CrossRef] [PubMed].

24. Ghosh D, Egbuta C, Lo J. Testosterone complex and non-steroidal ligands of human aromatase. **J Steroid Biochem Mol Biol**. 2018. ISSN 0960-0760. [CrossRef].

25. Wajchenberg BL. Tecido Adiposo como Glândula Endócrina. **Arq Bras Endocrinol Metab**. 2000; 44(1): 13-20. ISSN 1677-9487. [CrossRef].

26. Barros ACSD de, Leite KRM. Classificação molecular dos carcinomas de mama: uma visão contemporânea. **Rev Bras Mastol**. 2015. ISSN 0104-8058. [CrossRef].

27. Ghosh D, Lo J, Morton D, Valette D, Xi J, Griswold J et al. Novel aromatase inhibitors by structure-guided design. **J Med Chem**. 2012. ISSN 1520-4804. [CrossRef].

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