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"JÚLIO DE MESQUITA FILHO"
Câmpus de São José do Rio Preto

Reinaldo dos Santos Theodoro

Síntese e Avaliação Antibacteriana e Antimicobacteriana de 4-hidroxiderricina e seus análogos

São José do Rio Preto
2022

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Financiadora: FAPESP – Proc. 2019/11979-4

Orientador: Prof. Dr. Luis Octávio Regasini
Coorientador: Dr. Miguel Divino da Rocha

São José do Rio Preto
2022

T388s

Theodoro, Reinaldo dos Santos

Síntese e Avaliação Antibacteriana e Antimicobacteriana de 4-hidroxiderricina e seus análogos / Reinaldo dos Santos Theodoro. -- São José do Rio Preto, 2024

315 p.: il., tabs., fotos, mapas

Dissertação (mestrado) - Universidade Estadual Paulista (Unesp), Instituto de Biociências Letras e Ciências Exatas, São José do Rio Preto

1. Química. 2. Química medicinal. 3. Química orgânica. I. Título.

Sistema de geração automática de fichas catalográficas da Unesp. Biblioteca do Instituto de Biociências Letras e Ciências Exatas, São José do Rio Preto. Dados fornecidos pelo autor(a).

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Financiadora: FAPESP: Proc. 2019/11979-4

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São José do Rio Preto
27 de janeiro de 2022

"Fazer o teu melhor, na condição que você tem, enquanto você não tem condições melhores, para fazer melhor ainda"

Mario Sergio Cortella

Dedico este trabalho à minha família, especialmente, aos meus pais, ***Cidalina Rodrigues dos Santos Theodoro*** *e* ***Antonio Theodoro Filho*** *(in memoria), aos meus irmãos e irmãs, especialmente à* ***Ione dos Santos Theodoro de Carvalho*** *(in memoria).*

AGRADECIMENTOS

À **Deus**, por me guiar durante todos os momentos ao longo dos momentos bons e nas tempestades da vida.

Aos meus pais, **Cidalina Rodrigues dos Santos Theodoro** e **Antonio Theodoro Filho** (*in memoria*), que sempre me apoiaram nas minhas escolhas e lutas. Os senhores sempre foram minha inspiração e meus heróis, principalmente por serem guerreiros e conseguirem cuidar e educar uma família com 7 filhos mais agregados e nunca desistirem. Aos meus irmãos **Ione dos Santos Theodoro de Carvalho** (*in memoria*), **Celso dos Santos Theodoro**, **Marcelo dos Santos Theodoro**, **Cesar dos Santos Theodoro**, **José Antonio dos Santos Theodoro** e **Iara dos Santos Theodoro** e suas famílias que foram mais do que irmãos, foram meus amigos e pilares na minha vida. Agradeço as minhas sobrinhas **Isabela Theodoro** e **Isabele Carvalho** e suas famílias por todo apoio e parceiria. Além dos meus pequenos e lindos sobrinhos e sobrinhas **Gustavinho**, **Alice**, **Samuelzinho**, **Laurinha**, **Leticia**, **Leonardo**, **Davi**, **Heitor** e **Valentina** que mantém a minha esperança viva em um futuro melhor. Aos meus cunhados e cunhadas que são como irmãos para mim, principalmente, ao **Cabo PM Celso Luiz de Carvalho** (*in memoria*) pelas resenhas e conversas sobre a vida, que papai do céu o guarde.

Aos meus segundos pais nessa vida, minha madrinha **Vicenta Garcia de Paula** e meu padrinho **Udson Antonio de Paula "*Nenza*"** (*in memoria*) e sua família, que sempre nos ajudou, principalmente nos momentos mais difíceis quando morávamos em um barraquinho de pau e lona de plástico e nos ajudou a construir a nossa primeira casinha na Vila Baumam em Novo Horizonte, SP. A minha gratidão e da minha família pelo o que vocês fizeram por nós será eterna e levarei até nos meus últimos dias de vida.

À minha namorada **Leticia Ribeiro de Assis** por ser minha parceira de vida, pelo seu amor e carinho por mim e minha família, além de me apoiar em todas as minhas decisões, principalmente nas minhas estratégias sintéticas. Sou grato também pela sua família, a dona **Ivonete** e seu **Samuel** que sempre foram muito receptivos comigo e me trataram como um filho. Obrigado por tudo, principalmente pelas diversões e os churrascos.

A Me. **Julyanna Andrade** e **André Nascentes** pela a amizade e os momentos de confraternização que dividimos juntos. Vocês são incríveis e seres de luz nesse mundo tão cruel e massacrante. Gratidão eterna.

Aos meus brotheres de outras mães, **Nilson Lima**, **Guilherme Queiroz**, **Gustavo Queiroz**, **Otávio Queiroz**, **Jean Clanse** e **Fernando Silva** que sempre me apoiaram e foram a minha válvula de escape durante toda a minha vida. Agradeço aos meus amigos **Felipe Mazatti**, **Josué Alexsander**, **Victor Augusto**, **Ivan**, **RH** que foram meus parças de graduação e que me ajudaram nessa jornada da minha vida.

Ao meu orientador, Prof. Dr. **Luis Regasini**, por todos os ensinamentos. Todas as experiências vividas no decorrer desses 4 anos ficaram como aprendizado. Pela sua história de vida e por tudo o que você conquistou, saiba que eu te admiro.

Ao meu Coorientador Dr. **Miguel D. da Rocha** por toda a paciência e ensinamentos. Aprendi muito com o tempo compartilhado contigo, principalmente sobre a importância de ser criterioso e analista. Admiro sua história de vida e sua luta. Você é um exemplo.

Às agências de fomento, **CAPES**, **CNPq** e **FAPESP (2019/11979-4)** pela bolsa de mestrado e auxílio financeiro que foi o sálario mais alto que consegui em todos os trabalhos que fiz em minha vida, e sem os quais a realização desse trabalho seria impossível para o filho de um cortado de cana e empregada doméstica que sempre lutaram por mim e pelos meus irmãos.

Aos amigos que passaram pelo Labotoratório de Antibióticos e Quimioterápicos – LAQ. Agradeço, em especial, à Me. **Leticia Ribeiro**, Dr. **Miguel D. da Rocha**, Me. **Julyanna Andrade**, Me. **Veridianna Pattini**, Me. **Julio Sanches**, Me. **Dinis Caina**, Me. **Maria Beatriz**, Me. **Rodrigo Lemos** pela amizade, apoio emocional, discussões científicas, auxílio na execução dos experimentos e, principalmente, por tornarem esses 4 anos (desde IC) tão especiais. Vocês são amigos que levarei para sempre

Aos alunos que tive o prazer de coorientar em seus trabalhos de Iniciação Científica durante meu mestrado, **Ana Luiza**, **Amabila Luiza** e **Ruan Felipe**. Acreditem, quem mais aprendeu nessa caminhada fui eu porque pude dividir meu conhecimento com vocês. Foi uma troca mútua. Obrigado por tudo.

Ao Prof. Dr. **Carlos Henrique Gomes Martins** e as suas alunas **Meliza Arantes de Souza Bessa** e **Ralciane de Paula Menezes**, Universidade Federal de Uberlândia, Laboratório de Ensaios Antimicrobianos – LEA, pelos ensaios antimicrobianos contra as bactérias Gram-positivas e Gram-negativas e Micobactérias.

Ao Prof. Dr. **André Tempone** e seus alunos, Centro de Parasitologia e Micologia, Instituto Adolfo Lutz, pelos ensaios antibacterianos contra os isolados clínicos resistentes aos fármacos.

À Me. **Veridinna Pattini**, Me. **Julyanna Andrade**, Me. **Thiago Lemes** e a Profa. Dra. **Margarete Almeida**, Faculdade de Medicina de São José do Rio Preto, FAMERP/São José do Rio Preto, pelo auxílio nos estudos contra isolados clínicos de *Tricophyton* e *Candida*.

Ao Me. **Guilherme Dilarri** e Prof. Dr. **Henrique Ferreira**, membros do Laboratório de Genética de Bactérias, Instituto de Biociências, UNESP/Rio Claro, pelo auxílio nos experimentos de ensaio em Membrana de *B. subtilis*.

Ao Centro Multiusuário de Inovação Biomolecular, Instituto de Biociências, Letras e Ciências Exatas, UNESP/São José do Rio Preto (FAPESP – Processo nº 2009/53989-4), especialmente, ao Dr. **Fábio Moraes**, pela realização dos experimentos de Ressonância Magnética Nuclear. À Me. **Dani C Oliveira Lisboa**, Laboratório de Bioenergia (UNESP), pelas análises de HPLC. Aos pesquisadores **Lucas Monteiro Santa Cruz** e **Alan Roberto Costa**, Centro de Contaminantes Orgânicos, Instituto Adolfo Lutz, pelos experimentos de Massas dos compostos.

"Naquela mesa ele sentava sempre
E me dizia sempre o que é viver melhor
Naquela mesa ele contava histórias
Que hoje na memória eu guardo e sei de cor
Naquela mesa ele juntava gente
E contava contente o que fez de manhã
E nos seus olhos era tanto brilho
Que mais que seu filho
Eu fiquei seu fã..."

Naquela mesa – Nelson Gonçalves

"Look, if you had one shot
Or one opportunity
To seize everything you ever wanted
One moment
Would you capture it, or just let it slip? Yo...

...You better lose yourself in the music
The moment that you own it
you better never let it go
You only get one shot
Do not miss your chance to blow
Cause opportunity comes once in a lifetime go"

Lose Yourself – Eminem

RESUMO

As infecções microbianas e a resistência aos antibióticos têm sido os desafios mais significativos que ameaçam a saúde pública atualmente. A 4-hidroxiderricina (4HD) é uma chalcona prenilada de ocorrência natural que foi isolada da *Angelica keiskei* (Ashitaba) e demonstra múltiplas atividades farmacológicas, principalmente antibacteriana. Neste contexto, 4HD e três séries de análogos foram planejados, sintetizados e investigados contra bactérias, micobactérias e fungos clinicamente importantes. Este trabalho utilizou a 4-hidroxiderricina como protótipo para o planejamento de análogos, os quais foram concebidos pela permutação da subunidade *p*-hidroxila por grupos eletrodoadores e eletro-atratores (Série I), além das modificações nas subunidades 2'-hidroxila, 3'-prenila e 4'-metoxila (Série II) e reduções da cetona α,β-insaturadas (Série III). Foram descritas a síntese de 111 substâncias, incluindo intermediários (68) e substâncias-alvo (45), sendo 26 novas e 8 produtos naturais. As substâncias-alvo (1 - 45) foram preparadas através de reações de Iodações Regiosseletivas, O-Metilações, Proteções, Condensações Aldólicas entre aldeídos e cetonas via catálise básica, Acoplamentos de Suzuki, Rearrajnos [1,3]-Sigmatrópicos, Desproteções e reações de Redução. Primeiramente, 4HD se mostrou fortemente ativo contra bactérias e micobactérias com valores de CIM de 1,56 - 400 $\mu g.mL^{-1}$, principalmente contra bactérias gram-positivas. 4HD apresentou potente atividade inibitória contra biofilme de MSSA e MRSA com valores de $CIMB_{50}$ de 1,56 e 0,78 $\mu g.mL^{-1}$, respectivamente. Verificamos também que 4HD tem ação bactericida, por lesar a membrana citoplasmática de *B. subtilis*, com baixa citotoxicidade contra as células HaCaT. 4HD mostrou ser um potente agente antifúngico contra cepas de *T. rubrum* e *T. mentagrophytes* com valores de CIM de 0,9 - 31,2 $\mu g.mL^{-1}$, e atividade moderada contra *C. auris* com valores de CIM de 31,2 $\mu g.mL^{-1}$. 4HD agiu sinergicamente e potencializou a atividade da terbinafina em 5 a 10 vezes e do itraconazol em 2 a 4 vezes. Além disso, a membrana celular dos fungos dermatófitos foi o alvo do 4HD, pois o ergosterol exógeno diminuiu consideravelmente sua atividade antifúngica (CIM> 31,2 $\mu g.mL^{-1}$). As atividades antibacterianas e antimicobacterianas dos derivados chalcônicos **2** - **38** foram de 1,56 a 400 $\mu g.mL^{-1}$. Estudos de REA sugeriram que 3'-prenila, 2'-hidroxila e 4-hidroxila são pontos farmacofóricos fundamentais de 4HD para a atividade antibacteriana e antimicobacteriana. Além disso, a troca do grupo prenila em 4HD por um grupo benzila não alterou significativamente a atividade antibacteriana, proporcionando uma relação bioisostérica não-clássica entre essas duas subunidades. Derivados de chalconas reduzidas foram as classes de compostos mais ativos neste trabalho. A estratégia de redução da cetona α, β-insaturada causou aumento na atividade antibacteriana de algumas chalconas inicialmente inativas, como a 4'-O-metilbavachalcona (**16**). Além disso, a redução de 4HD formou as dihidrocalconas **29** e **30** e o 1,3-diarilpropano **35**, que foram mais promissores que seu substrato, principalmente contra MSSA e MRSA. Portanto, a redução da cetona α, β-insaturada de 4HD não levou à perda da atividade antibacteriana. Os compostos **13**, **29**, **30** e **37** mostraram potente atividade na inibição do biofilme de MSSA e MRSA. O composto **29** (4-hidroxidihidroderricina) mostrou baixa citotoxicidade contra células HaCaT. Portanto, a 4-hidroxiderricina e seus análogos são promissores agentes antibacterianos e antifúngicos, podendo ser uma alternativa no tratamento e combate às diversas infecções causadas por essas bactérias, micobactérias e fungos. Assim, **4HD** e **29** podem ser considerados compostos líderes promissores para a descoberta de novos fármacos.

Palavras-chave: 4-hidroxiderricina, chalconas preniladas, acoplamento de Suzuki, rearranjo sigmatrópico, redução, bactérias, micobactérias, fungos, bioisosterismo, biofilme.

ABSTRACT

Microbial infections and antibiotic resistance have been the most significant challenges threatening the health of society today. 4-hydroxyderricin (4HD) is a naturally occurring prenylated chalcone that has been isolated from *Angelica keiskei* (Ashitaba) and demonstrates multiple pharmacological activities, mainly antibacterial. In this context, 4HD and three series of analogs were designed, synthesized, and investigated against clinically important bacteria, mycobacteria, and fungi. This work used 4-hydroxyderricin as a prototype for the planning of analogs, which were designed by the permutation of the *p*-hydroxyl subunit by electron donor and electro-attracting groups (Series I), changing the 2'-hydroxyl, 3'-prenyl and 4'-methoxyl subunits (Series II) and α,β-unsaturated ketone reductions (Series III). The synthesized 111 substances were described, including intermediates (68) and target substances (45), 26 of which were new and 8 were natural products. The target substances (**1** – **45**) were prepared through Regioselective Iodations, O-Methylations, Protections, Aldol Condensations between aldehydes and ketones on basic catalysis, Suzuki couplings, [1,3]-Sigmatropic Rearrangements, Deprotections, and reactions of Reduction. First, 4HD showed to be strongly active against bacteria and mycobacteria with MIC values of 1.56 – 400 $\mu g.mL^{-1}$, mainly against gram-positive bacteria. 4HD showed potent inhibitory activity against *S. aureus* MSSA and MRSA biofilm with $MICB_{50}$ values of 1.56 and 0.78 $\mu g.mL^{-1}$, respectively. We also found that 4HD has a bactericidal action by damaging the cytoplasmatic membrane of *B. subtilis*, with low cytotoxicity against HaCaT cells. 4HD was shown to be a potent antifungal agent against *T. rubrum*, and *T. mentagrophytes* strains with MIC values of 0.9 – 31.2 $\mu g.mL^{-1}$ and moderate activity against *C. auris* with MIC values of 31.2 $\mu g.mL^{-1}$. 4HD acted synergistically and potentiated the activity of terbinafine 5- to 10-fold and itraconazole 2- to 4-fold. The cell membrane of dermatophyte fungi was the target of 4HD since exogenous ergosterol considerably decreased the antifungal activity (MIC>31.2 $\mu g.mL^{-1}$). The antibacterial and antimycobacterial activities of the chalcones derivatives **2** – **38** ranged from 1.56 to 400 $\mu g.mL^{-1}$. SAR studies have suggested that 3'-prenyl, 2'-hydroxyl, and 4-hydroxyl are fundamental pharmacophoric points of 4HD for antibacterial and antimycobacterial activity. Furthermore, exchanging the prenyl group in 4HD for a benzyl group did not significantly alter the antibacterial activity, providing a non-classical bioisosteric relationship between these two subunits. Reduced chalcones derivatives were the most active compounds classes in this work. The α,β-unsaturated ketone reduction strategy caused an increase in the antibacterial activity of some chalcones that were initially not active, such as 4'-O-methylbavachalcone (**16**). Furthermore, 4HD reduction formed dihydrochalcones **29** and **30** and 1,3-diarylpropane **35**, which were more promising than their substrate, mainly against MSSA and MRSA. Therefore, reduction of α,β-unsaturated ketone from 4HD did not lead to loss of antibacterial activity. Compounds **13**, **29**, **30**, and **37** showed potent activity in inhibiting the biofilm of MSSA and MRSA. Compound **29** (4-hydroxydihydroderricin) showed low cytotoxicity against HaCaT cells. Therefore, 4-hydroxyderricin and its analogs are promising antibacterial and antifungal agents and may be an alternative in treating and combating various infections caused by these bacteria, mycobacteria, and fungi. Thus, 4HD and 29 can be considered promising lead compounds to discover new drugs.

Keywords: 4-hydroxyderricin, Prenylated chalcones, Suzuki coupling, Sigmatropic rearrangement, Reduction, Bacteria, Mycobacteria, Fungi, Bioisosterism, Biofilm.

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LIST OF ABBREVIATIONS AND SYMBOLS

δ: chemical shift

4HD: 4-hydroxyderricin

ATCC: American Type Culture Collection

Bs: *Bacillus subtilis*

Ca: *Candida albicans*

Cau: *Candida auris*

CFU: colony-forming unit

CHX: chlorhexidine

d: doublet

dd: double doublet

ddd: double double doublet

dt: double triplet

Ec: *Escherichia coli*

Ef: *Enterococcus faecalis*

FCZ: fluconazole

FDA: Food and Drug Administration

FIC: fractional inhibitory concentration

FICI: fractional inhibitory concentration index

Hp: *Helicobacter pylori*

Hz: Hertz

IC_{50}: concentration required in order to reduce cell viability at 50%

IP: propidium iodide

ITRA: itraconazole

J: coupling constant

Kp: *Klebsiella pneumoniae*

Log *P*: lipophilicity

Log *S*: water solubility

m: multiplet

Ma: *Mycobacterium avium*

MBC: Minimum Bactericidal Concentration

MDR: multidrug resistant

MFC: Minimum Fungicidal Concentration

MIC: Minimum Inhibitory Concentration

$MICB_{50}$: Minimum Inhibitory Concentration of Biofilm that inhibited 50% or more

Mk: *Mycobacterium kansasii*

MOM: methoxymethyl protecting group

MRSA: Methicillin-Resistant *Staphylococcus aureus*

MSSA: Methicillin-Sensitive *Staphylococcus aureus*

Mt: *Mycobacterium tuberculosis*

MW: molecular weight

NC: negative control

NMR: Nuclear Magnetic Resonance

NTM: nontuberculous mycobacteria

OP: optical density

Pa: *Pseudomonas aeruginosa*

PC: positive control

ppm: part per million

q: quartet

REMA: resazurin microtiter assay plate

r.t.: room temperature

s: singlet

SAR: structure-activity relationship

Sa: *Staphylococcus aureus*

Se: *Staphylococcus epidermidis*

Sm: *Streptococcus mutans*

Sp: *Streptococcus pneumoniae*

Ss: *Streptococcus sanguinis*

Sso: *Streptococcus sobrinus*

t: triplet

TERB: terbinafine

Tm:*Trichophyton mentagrophytes*

Tr: *Trichophyton rubrum*

VAN: vancomycin

VC: vehicle control

SUMMARY

CHAPTER I

INITIAL CONSIDERATIONS AND OBJECTIVES

1. INITIAL CONSIDERATIONS

Natural products are sources of prototypes for researching and developing new drugs and bioactive substances. In this context, the Laboratório de Antibióticos e Quimioterápicos (LAQ) of the Instituto de Biociências, Letras e Ciênicas Exatas – UNESP/São José do Rio Preto-SP, uses the structure of natural products derived from plants for the development of new bioactive substances. 4-hydroxyderricin (4HD) is a substance with an α,β-unsaturated ketone, and the isoprenyl, hydroxyl, and methoxyl subunits in its core used in this work as a prototype for planning new antimicrobial agents. It was first isolated from the *Angelica Keiskei* plant, a hardy perennial belonging to Umbelliferae. The herb is called 'Myeong-Il Yeob' in Korea and 'Ashitaba' in Japan, both meaning 'Tomorrow's Leaf' and called by the Korean name "Shinsuncho" meaning "elixir of life". The first reported 4HD synthesis was by [1,3]-Sigmatropic Rearrangement; however, this methodology was not selective for 4HD synthesis. 4HD has a broad spectrum of biological activities, emphasizing its antibacterial effects. However, 4HD has not been evaluated against resistant multi-drug bacteria such as *M. tuberculosis* and Staphylococcus, Enterococcus, and Streptococcus species. Furthermore, there are no in-depth studies on the pharmacophoric contributions of the 4HD subunits and their primary target on bacteria that demonstrate their antibacterial potential. Moreover, 4HD has not been selectively synthesized in the literature.

In this perspective, 4HD and its analogs were designed, synthesized, and evaluated against bacteria of clinical interest, including *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Helicobacter pylori*, *Staphylococcus aureus*, *S. epidermidis*, *Enterococcus faecalis*, *Streptococcus pneumoniae*, *Streptococcus sanguinis*, *Streptococcus sobrinus,* and *Streptococcus mutans*. In addition, 4HD was evaluated against fungi of genus Trichophyton, including the species of *T. rubrum* and *T. mentagrophytes,* and fungi of the genus Candida, including the species *C. albicans* and *C. auris*.

The dissertation was organized into seven Chapters (I−VII). In chapter I, the initial considerations of work were presented, and at the end of that chapter, the general objective of the dissertation and the specific objectives of Chapters II−VI. Chapter II contains a literature review article to contextualize the importance of 4-hydroxyderricin, including its broad pharmacological activity spectrum. Chapters III and IV contain the manuscripts obtained from the studies of 4-hydroxyderricin against bacteria and fungi of clinical interest, respectively. While Chapters V and VI cover investigations of synthetic analogs of 4HD against gram-positive and gram-negative bacteria. Chapter V shows the potent activity of a reduced derivative of 4HD against clinical isolates multi-drug resistant. In contrast, Chapter VI shows the selective

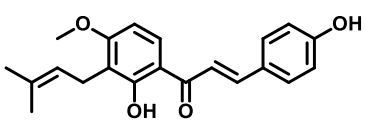
synthesis of 4HD and evaluation of the pharmacophoric contributions of 4HD by the antibacterial activity of its analogs against Gram-positive and Gram-negative bacteria. Finally, Chapter VII presents the general conclusions of studies with 4HD and its analogs against bacteria and fungi, in addition to the references and appendices of Chapters III, V, and VI.

General Conclusions

This work used 4-hydroxyderricin as a prototype for the planning of analogs, which were designed by the permutation of the *p*-hydroxyl subunit by electron donor and electro-attracting groups (Series I), changing the 2'-hydroxyl, 3'-prenyl and 4'-methoxyl subunits (Series II) and α,β-unsaturated ketone reductions (Series III). The synthesized 111 substances were described, including intermediates (68) and target substances (45), 26 of which were new and 8 were natural products. The target substances (**1** – **45**) were prepared through Regioselective Iodations, O-Methylations, Protections, Aldol Condensations between aldehydes and ketones on basic catalysis, Suzuki couplings, [1,3]-Sigmatropic Rearrangements, Deprotections, and reactions of Reduction.

4HD demonstrated strongly antibacterial activity against mycobacteria and bacteria species; in addition, it was able to inhibit the MSSA and MRSA biofilm formation at low concentrations. We also found that 4HD has a bactericidal action by damaging the cytoplasmatic membrane of *B. subtilis*. Low cytotoxicity activity was observed for 4HD against HaCat cells. Thus, 4HD is a promising antibacterial compound, which could be an alternative to combat several infections caused by many mycobacteria and bacteria species.

4HD has demonstrated antibacterial activity against gram-positive bacteria, being inactive or weakly active against gram-negative:



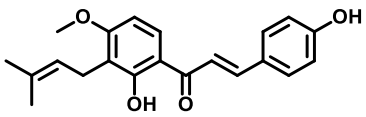
4-hydroxyderricin

- ✓MIC against MSSA and MRSA = 3.12 µg.mL^{-1};
- ✓It showed antibacterial activity against other gram-positive species (*S. epidermidis, E. faecalis, S. mutans, S. sanguinis, S. sobrinus*) with a MIC of 1.56 to 12.5 µg.mL^{-1};
- ✓MIC against *M. tuberculosis*, *M. avium*, and *M. kansassi* of 15,56 to 31,25 µg.mL^{-1};
- ✓It inhibited MSSA and MRSA biofilm formation at $MICB_{50}$ of 1.56 to 0.78 µg.mL^{-1}, respectively;
- ✓Caused damage to the plasma membrane of *B. subtilis*;
- ✓It was not against human keratinocytes;

Furthermore, 4HD was a potent antifungal agent against *T. rubrum* and *T. mentagrophytes* strains and moderate activity against *C. auris*. In addition, 4HD acted synergistically and potentiated the activity of the antifungal drugs terbinafine and itraconazole. The cell membrane of

dermatophyte fungi was the main target of 4HD. Thus, our results showed that 4-hydroxyderricin is a promising antifungal agent with low toxicity.

4HD demonstrated antifungal activity against Trichophyton species, being reactive or weakly active against Candida species:

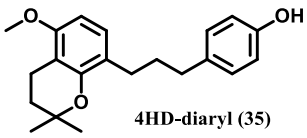


4-hydroxyderricin

- ✓MIC against *T. mentagrophytes* = 0,9 – 3,9 µg.mL^{-1};
- ✓MIC against *T. rubrum* = 0,9 – 31,2 µg/mL;
- ✓4HD showed synergism when combined with terbinafine and itraconazole against *T. mentagrophytes* and *T. rubrum*;
- ✓4HD acts on the cell membrane by inhibiting Ergosterol;

4HD was used as a substrate to obtain a novel diarylpropane (4HD-diaryl, **35**), which demonstrated strongly antibacterial activity against gram-positive bacteria, including ATCC and multidrug-resistant clinical isolates of *Enterococcus, Staphylococcus,* and *Bacillus* spp. In addition, 4HD-diaryl was able to inhibit the MSSA and MRSA biofilm formation at low concentrations. We also found that 4HD-diaryl has a bactericidal action by damaging the cytoplasmatic membrane of *B. subtilis*. No cytotoxicity activity was observed for 4HD-diaryl against BALB/c mice erythrocytes. Thus, 4HD-diaryl is a novel promising antibacterial compound, which could be an alternative to combat several infections caused by MDR strains of gram-positive bacteria.

4HD-diaryl has demonstrated antibacterial activity against gram-positive bacteria multi-drug resistant (MDR), being inactive or weakly active against gram-negative:

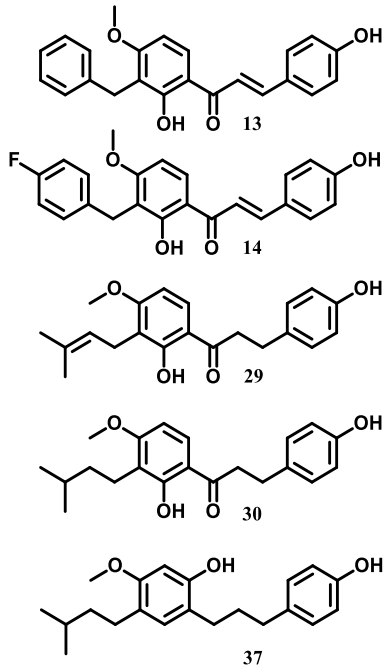


4HD-diaryl (35)

- ✓ 4HD-diaryl was active against Clinical Isolates of drug-resistant Enterococcus and Staphylococcus species with MIC of 5 to 20 µM (1.6 to 6.5 µg.mL^{-1});
- ✓It showed antibacterial activity against other gram-positive species (*S. epidermidis, E. faecalis, S. mutans, S. sanguinis, S. sobrinus*) with a MIC of 3.12 to 6.25 µg.mL^{-1};
- ✓MIC against *M. tuberculosis*, *M. avium*, and *M. kansassi* of 31,25 µg.mL^{-1};
- ✓It inhibited MSSA and MRSA biofilm formation at $MICB_{50}$ of 1.56 to 0.78 µg.mL^{-1}, respectively;
- ✓Caused damage to the plasma membrane of *B. subtilis*;
- ✓It was not toxic against erythrocytes collected from BALB/c mice;

Compounds **13**, **29**, **30**, and **37** showed antibacterial and antimycobacterial activity equal to 4HD. Compound **13** showed that the benzyl subunit has a non-classical bioisosterism with isoprenyl in 4-hydroxyderricin. Compounds **13** and **14** are classic bioisosteres as they both had approximately the same antibacterial potency. Furthermore, analog **29** showed that the α,β-unsaturated ketone in 4HD is not a pharmacophoric group for antibacterial and antimycobacterial activities since the reduced analog 29 was as potent as 4HD. Moreover, compounds 13, 29, 30, and 37 showed potent inhibitory activity against *S. aureus* Biofilms (MSSA and MRSA). Compound 29 was chosen as HIT from the series of compounds evaluated, and its cytotoxic activity was determined against HaCat cells. Low cytotoxicity activity was observed for 29.

The other analogs also showed antibacterial activity against gram-positive bacteria, being inactive or weakly active against gram-negative bacteria:



- ✓ 14 synthesized substances showed antibacterial activity against gram-positive species (MSSA, MRSA, *S. epidermidis*, *E. faecalis*, *S. mutans*, *S. sanguinis*, *S. sobrinus*) with a MIC of 1.56 to 12.5 µg.mL^{-1};
- ✓ 11 substances showed anti-*H. pylori* activity with MIC from 15.62 to 62.50 µg.mL^{-1};
- ✓ 19 substances showed antimycobacterial activity against *M. tuberculosis*, *M. kansasii* and *M. avium* with a MIC of 15.62 to 62.50 µg.mL^{-1};
- ✓ Compounds **13**, **29**, **30** and **37** inhibited MSSA and MRSA biofilm formation at concentrations from 0.78 to 3.12 µg.mL^{-1};
- ✓ Compound **29** was not toxic against human keratinocytes;

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