WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 18, 21-33. Research Article ISSN 2277– 7105

ANTIBACTERIAL ACTIVITY OF IMIDAZO [1,2-α] PYRIDINYL-CHALCONES DERIVATIVES AGAINST ENTEROCOCCUS FAECALIS

Déto U. Jean – Paul N'guessan[1], Mahama Ouattara[1]*, Songuigama Coulibaly[1], Mamidou W. Kone[3], Drissa Sissouma[2]

[1]Département de Chimie Thérapeutique et Chimie Organique, UFR Sciences Pharmaceutiques, Université Félix Houphouët-Boigny, 01 BP V34 Abidjan, Côte d'Ivoire.

[2]Laboratoire de Chimie Organique Structurale, UFR SSMT, Université Félix Houphouët Boigny, 22 BP 582 Abidjan, Côte d'Ivoire.

[3]Centre Suisse de Recherches Scientifiques en Côte d'Ivoire, 01 BP 1303 Abidjan, Côte d'Ivoire.

Article Received on
22 August 2018,

Revised on 12 Sept. 2018,
Accepted on 02 Oct. 2018,

DOI: 10.20959/wjpr201818-13501

***Corresponding Author**
Mahama Ouattara
Département de Chimie organique et Chimie Thérapeutique, UFR Sciences Pharmaceutiques, Université Félix Houphouët-Boigny, 01 BP V34 Abidjan, Côte d'Ivoire.

ABSTRACT

The emergence of nosocomial strains of *Enterococcus faecalis* and drug resistance that antibiotics faces in the treatment of enterococcal infections, prompted us searching for new more efficient bioactive molecules For this purpose, 10 chalcones based imidazo[1,2-*a*]pyridine (5a-5d) were synthesized and assessed for their antibacterial activity against susceptible and resistant strains of *Enterococcus faecalis*. The screening was fulfilled using the agar diffusion method to select best molecule, then by the method of dilution in liquid medium compared to Amoxicillin and Gentamicin. The compounds 5h and 5d, with respective MIC 44.6 µM and 9.9 µM, exhibited the best antibacterial profiles. It appears from the structure activity relationship studies that the presence of fluorine on the benzene homocycle or replacement of this homocycle by a furan ring lead to significant antibacterial activities. Paradoxically, all activities were more effective against resistant strains than on sensitive ones. Compounds 5h and 5d may constitute seeds of a new class of antibacterial effective against resistant *Enterococcus faecalis*.

KEYWORDS: imidazo[1,2-a]pyridine, Chalcone, Antibacterial activity, *Enterococcus faecalis*.

INTRODUCTION

Enterococcus faecalis is the most common enterococcal species and is responsible for 80 to 90% of human enterococci infections.[1] These bacteria are a major cause of nosocomial infections and opportunistic infections especially in patients debilitated by chronic diseases (renal failure, diabetes).[2] Furthermore, enterococci have been reported as being involved in periodontal infection.[3] The adhesion and the production of a biofilm by E. faecalis on various medical devices have been demonstrated,[4] including the ureteral stents,[5] intravascular catheters[6] and biliary stents.[7] Biofilms are difficult to eradicate and are a source of many chronic infections. Their presence and their nature limited the therapeutic armory of infections caused by these germs (Fig. 1).

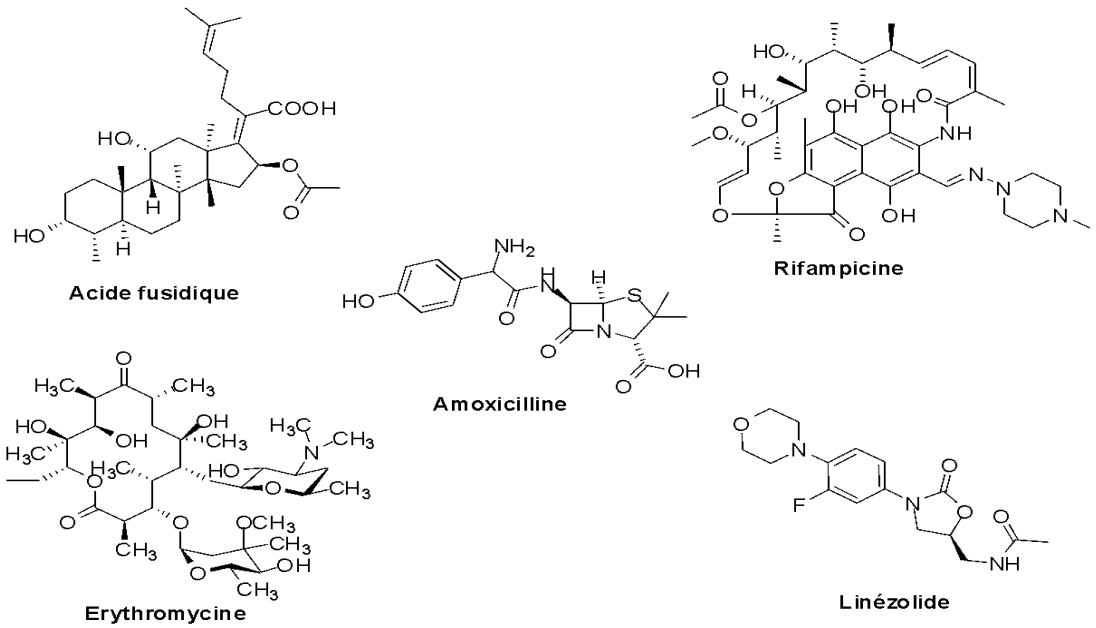


Figure 1: Some current anti-enterococcal drugs.

In front of the proliferation of nosocomial enterococci infections multiresistant to antibiotics, it is urgent to develop new and more effective anti-enterococcal. Heterocycles play a fundamental role in the design and development of new classes of compounds exploitable for medicinal applications. In particular, imidazole and its derivatives occupy a key place in medicinal chemistry due to their diverse biological activities and their presence in several biologically active natural products.[10] Synthetic imidazole-based scaffolds like imidazo[1,2-a]pyridine have shown to be endowed with a wide spectrum of antiinfectious activities.[11,12]

On the basis of these considerations, we have synthesized a series of imidazo[1,2-a]pyridine derivatives with different substitutions on the phenyl ring in order to evaluate their antimicrobial activity. Precisely, the aim of the herewith work was to determine the minimum concentration able to inhibit the proliferation of drug-resistant *Enterococcus faecalis*. Besides, structural elements favorable to the appearance, maintenance and improvement of antibacterial activities in this series were established.

MATERIAL AND METHODS

1. Chemistry

1.1. Characterization

For all compounds, the spectra of nuclear magnetic resonance (NMR) ^{1}H proton (300 MHz) and carbon-^{13}C (75 MHz) were recorded on a Brucker Avance 300. The tetramethylsilane (TMS) is used as reference shifts expressed in ppm. The description of the NMR spectra uses the following symbols: S = singlet; d = doublet; dd = doublet of doublets; t = triplet; q = quadruplet; quint = quintet; m = multiplet. Mass spectra were recorded on a JEOL JMS DX300 spectrometer in ESI (electrospray ionization / quadrupole). Melting points (mp) were determined using a Kofler bench and are not corrected. The thin layer chromatographies (TLC) were performed on silica plates Macherey-Nagel Sil G/UV254 or alumina Macherey-Nagel ALOX N/UV254. The products are then revealed under the UV lamp. The solvents and reagents including benzaldehydes used, purchased from Acros Organics (France) or Aldrich (France). Melting point were determined on a Köfler bench.

1.2. Chemical material

Two drugs, Amoxicillin and Gentamicin, were used as references because of their antibacterial efficiencies against the enterococci. In addition, an alternative treatment of endocarditis infections caused by Vancomycine-resistant *Enterococcus faecalis* employs the synergistic aminopenicillin / aminoglycoside combination.[13] These drugs were bought from SIGMA Chimical Co. (USA).

Ten chalcones containing imidazo[1,2-*a*]pyridine nucleus, synthesized as described previously[14] were used. Furthermore, 1,3-diphénylpropénone or chalcone used as a molecular model, was synthesized and characterized by our research laboratory.

1.3. General method for synthesis of 3-acetyl-2-methylimidazo [1,2-*a*] pyridine (3)

To a solution of 2-aminopyridine (4.8 g; 42 mmol) in 50 mL of ethanol are added 1.05 equivalents of 3-chloro pentan-2,4-dione (107.09 mmol, 14.4 g). The mixture is refluxed for 6 hours. After evaporating the solvent, 125 mL of water are added and the reaction medium is neutralized with a saturated solution of sodium bicarbonate. The resulting solution was stored in a refrigerator for 5 hours. The precipitate obtained is filtered and recrystallized from water.

1.4. General method for accessing imidazo [1,2-*a*] pyridinyl-phénylpropénones (5a-j)

To 1.5 g (8.62 mmol) of 3-acetyl-2-methyl imidazo[1,2-a]pyridine (**3**) dissolved in an ethanolic solution of sodium hydroxide (64.6 mmol of NaOH in 40 mL of ethanol), was added 8.62 mmol of benzaldehyde derivatives. The reaction mixture is left at room temperature and stirred for 5 h. After neutralization with a 30% acetic acid solution, the resulting precipitate was dried and recrystallized to give **5a-5d**.

2. Biology

2.1. Microbiological material

To evaluate the antibacterial activity, particularly anti-*Enterococcus faecalis* of chalcones containing imidazo[1,2-*a*]pyridine, we used 2 strains of Enterococcus faecalis provided by the Swiss Center of Scientific Research (SCSR) of Ivory Coast, one chemoresistant and another sensitive.

2.2. Microbiological method

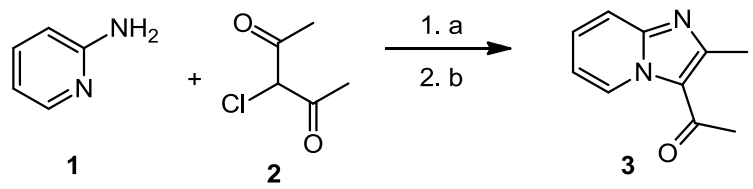
The screening was performed using the agar diffusion method.[15] Subsequently, we determined in liquid medium, the minimum inhibitory concentrations (MIC) of imidazo[1,2-*a*]pyridinyl-chalcones by the method of dilution in liquid medium.[15] Both methods were conducted according to the standards recommended by the 'National Commitee for Clinical Laboratory Standards".[16]

RESULTS

1. Chemistry

1.1. Synthesis of 3-acetyl-2-methylimidazo [1,2-*a*] pyridine (3)

3-Acetyl-2-methylimidazo [1,2-*a*] pyridine was prepared according to the method described by Starrett,[17] from 2-aminopyridine (1) and 3-chloro-pentan-2,4-dione (2) (Fig. 2) with a yield of 53%.



reagents and media : a) EtOH reflux ; b) NH_4OH dilué

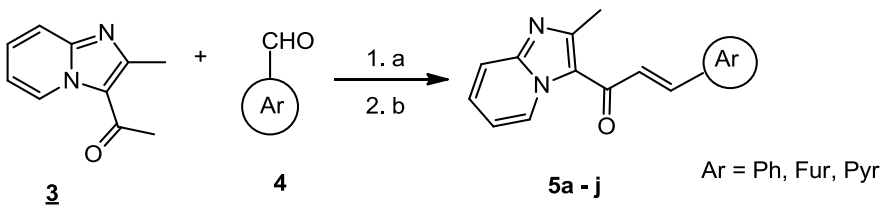
Figure 2: Synthesis of 3-acetyl-2-methylimidazo [1,2-*a*]pyridine (3).

1- (2-methylimidazo [1,2-*a*] pyridin-3-yl) ethanone (3)

White solid, 53%. ^{1}H NMR (300MHz, DMSO-d6) δ: 9.53 (d, 1H, *J* = 5.8 Hz, H_5); 7.63 (m, 1H, H_8); 7.54 (m, 3H, H_7); 7.12 (m, 1H, H_6); 2.65 (s, 3H, C$\underline{H}_3$); 2.51 (s, 3H, CO-C$\underline{H}_3$). ^{13}C NMR (75MHz, DMSO-d6) δ: 187.5 ($\underline{C}$=O), 152.6 (C_2), 146.1 (C_{8a}), 129.3 (C_2), 126.2 (C_7), 121.1 (C_6), 116.2 (C_5), 114.8 (C_3), 30.13 (CO-$\underline{C}H_3$), 17.9 ($\underline{C}H_3$). Mp : 155-159°C. ES + MS: 263 [M + H +]. Recrystallization from MeCN / H_2O (1: 1).

1.2. Synthesis of imidazo[1,2-*a*]pyridinyl-chalcones (5a-f)

Ten imidazo[1,2-*a*]pyridinyl-chalcones were synthesized by a Claisen-Schmidt like condensation[14] between the 3-acetyl-2-méthylimidazo[1,2-*a*]pyridine (**3**) and various substituted benzaldehydes (**4**) with a yield of 30 to 85% (Fig. 3).



reagents and media : a) NaOH \ EtOH, ambient temperature; b) AcOH 30 %

Figure 3: Synthesis of imidazo[1,2-*a*]pyridinyl-chalcones.

1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)-3-phenylprop-2-en-1-one (5a)

Pale yellow solid, 80%. ^{1}H NMR (300MHz, DMSO-d6) δ: 9.78 (d, 1H, *J* = 5.8 Hz, H_5); 7.80 (d, 1H, *J* = 15.6 Hz, CH=C$\underline{H}$); 7.60 to 7.68 (m, 3H, Ph-2,6 and H_8); 7.50 (d, 1H, *J* = 15.6 Hz, C$\underline{H}$=CH); 7.46 (m, 1H, H_7); 7.15 to 7.44 (m, 3H, Ph-3,5 and H_6); 7.06 (m, 1H, Ph-4); 2.89 (s, 3H, C$\underline{H}_3$). ^{13}C NMR (75MHz, DMSO-d6) δ: 179.5 ($\underline{C}$=O), 152.0 (C_{8a}), 146.5 (C_2), 141.6 (CH=$\underline{C}$H), 132.0 (C_5), 128.4 (Ph-1), 125.4 (C_7), 124.2 (Ph-2,6), 122.5 (Ph-3,5), 121.7 ($\underline{C}$H=CH), 120.1 (C_8), 117.0 (C_6), 114.7 (C_3), 18.4 ($\underline{C}H_3$). Mp: 155-159°C. ES + MS: 263 [M + H +]. Recrystallization from MeCN / H_2O (1: 1).

1- (2-methylimidazo[1,2-*a*]pyridin-3-yl)-3-o-tolylprop-2-en-1-one (5b)

Solid yellow brown, 70%. ^{1}H NMR (300MHz, DMSO-d6) δ: 9.66 (d, 1H, *J* = 4.5 Hz, H_5); 7.75 (d, 1H, *J* = 16 Hz, CH=C<u>H</u>); 7.55 - 7.68 (m, 3H, CH_3-Ph-6, H_7 and H_8); 7.48 (d, 1H, *J* = 16 Hz, C<u>H</u>=CH); 7.15 - 7.44 (m, 4H, CH_3-Ph-3,4,5 and H_6); 2.89 (s, 3H, C<u>H</u>$_3$), 2.33 (s, 3H, C<u>H</u>$_3$-Ph). ^{13}C NMR (75MHz, DMSO-d6) δ: 179.4 (<u>C</u>=O), 152.0 (C_{8a}), 146.5 (C_2), 141.5 (CH=<u>C</u>H), 140.9 (CH_3-Ph-2), 132.0 (C_5), 128.4 (CH_3-Ph-1), 125.40 (C_8), 124.9 (CH_3-Ph-3), 124.5 (CH_3-Ph-6), 122.5 (CH_3-Ph-5), 121.7 (<u>C</u>H=CH), 120.3 (CH_3-Ph-4), 120.2 (C_6), 117.1 (C_7), 114.7 (C_3) 21.1 (<u>C</u>H$_3$-Ph), 18.1 (<u>C</u>H$_3$). Mp: 154-158°C. ES + MS: 277 [M + H +]. Recrystallization from hexane.

3- (2-hydroxyphenyl)-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl) prop-2-en-1-one (5c)

Yellow solid, 56%. ^{1}H NMR (300MHz, DMSO-d6) δ: 9.78 (d, 1H, *J* = 5.8 Hz, H_5); 7.80 (d, 1H, *J* = 15.6 Hz, CH=C<u>H</u>); 7.60 (m, 1H, H_8); 7.53 (m, 1H, H_7); 7.38 (d, 1H, *J* = 15.6 Hz, C<u>H</u>=CH); 7.29-7.33 (m, 3H, OH-Ph-4,5,6); 7.13 (1H, m, H_6), 6.86 (d, 1H, *J* = 8.4 Hz, OH-Ph-3); 2.78 (s, 3H, C<u>H</u>$_3$), ^{13}C NMR (75MHz, DMSO-d6) δ: 179.5 (<u>C</u>=O), 162.1 (OH-Ph-2), 152.0 (C_{8a}), 146.7 (C_2), 141.6 (CH=<u>C</u>H), 131.1 (C_5), 129.2 (OH-Ph-1), 125.4 (C_7), 124.2 (OH-Ph-6), 121,8 (OH-Ph-4), 121.5 (OH-Ph-5), 120.9 (<u>C</u>H=CH), 120.0 (C_8), 118.4 (OH-Ph-3), 117.0 (C_6), 114.7 (C_3), 18.3 (<u>C</u>H$_3$). Mp>260°C. ES + MS: 279 [M + H +]. Recrystallization from ethanol.

3- (2-methoxyphenyl)-1-(2-methylimidazo [1,2-*a*] pyridin-3-yl) prop-2-en-1-one (5d)

Pale yellow solid, 71%. ^{1}H NMR (300MHz, DMSO-d_6) δ: 9.68 (d, 1H, *J* = 6.9 Hz, H_5); 7.72 (d, 1H, *J* = 15.6 Hz, CH=C<u>H</u>); 7.66 (m, 1H, H_8); 7.58 (m, 1H, H_7); 7.50 (d, 1H, *J* = 15.6 Hz, C<u>H</u>=CH); 7.30-7.40 (m, 3H, OCH_3-Ph-4,5,6); 7.20 (1H, m, H_6), 7.00 (d, 1H, *J* = 8.4 Hz, OCH_3-Ph-3); 3.93 (s, 3H, O<u>C</u>H$_3$-Ph), 2.80 (s, 3H, C<u>H</u>$_3$). ^{13}C NMR (75MHz, DMSO-d_6) δ: 179.3 (<u>C</u>=O), 159.5 (OCH_3-Ph-2), 152.1 (C_{8a}), 146.6 (C_2), 141.2 (CH=<u>C</u>H) , 132.0 (C_5), 128.9 (OCH_3-Ph-1), 125.4 (C_7), 124.2 (OCH_3-Ph-6), 121.5 (OCH_3-Ph-5), 121,3 (OCH_3-Ph-3), 120.9 (<u>C</u>H=CH), 120.0 (C_8), 116.4 (C_6), 114.8 (C_3), 55.3 (O<u>C</u>H$_3$-Ph), 18,2 (<u>C</u>H$_3$). Mp: 195 - 199°C. ES + MS: 279 [M + H +]. Recrystallization from hexane / DCM (3: 1).

3- (4-dimethylaminophenyl)-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl) prop-2-en-1-one (5e)

Orange solid, 30%. ^{1}H NMR (300MHz, DMSO-d_6) δ: 9.66 (d, 1H, *J* = 4.5 Hz, H_5); 7.78 (d, 1H, *J* = 16 Hz, CH=C<u>H</u>); 7.52-7.69 (m, 4H, $N(CH_3)_2$-Ph-2,6, H_6 and H_8); 7.45 (d, 1H, *J* = 16 Hz, C<u>H</u>=CH); 7.08-7.32 (m, 3H, $N(CH_3)_2$-Ph-3,5 and H_7); 2.85 (s, 3H, C<u>H</u>$_3$); 2.26 (s, 6H,

N($C\underline{H}_3$)$_2$-Ph). ^{13}C NMR (75MHz, DMSO-d_6) δ: 179.4 ($\underline{C}$=O), 152.0 (C_{8a}), 146.5 (N(CH_3)$_2$-Ph-4), 143.6 (C_2), 141.5 (CH=$\underline{C}$H), 132.0 (C_5), 129.5 (N(CH_3)$_2$-Ph-1), 125.4 (C_7), 125.3 (N(CH_3)$_2$-Ph-3,5), 122.9 (N(CH_3)$_2$-Ph-2,6), 121.7 ($\underline{C}$H=CH), 120.3 (C_6), 114.7 (C_8), 40.2 (N($\underline{C}H_3$)$_2$-Ph), 33.4 (C_3), 18.1 ($\underline{C}H_3$). Mp: 196 - 200 °C. ES + MS: 306 [M + H +]. Precipitation in water.

3- (2-chlorophenyl)-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl) prop-2-en-1-one (5f)

Yellow solid, 65%. ^{1}H NMR (300MHz, DMSO-d_6) δ: 9.82 (d, 1H, *J* = 5.8 Hz, H_5); 7.80 (d, 1H, *J* = 15.6 Hz, CH=C$\underline{H}$); 7.68 (m, 1H, H_8); 7.53 (m, 1H, H_7); 7.43 (d, 1H, J = 15.9 Hz, C$\underline{H}$=CH); 7.33-7.39 (m, 4H, Cl-Ph-3,4,5,6); 7.23 (m, 1H, H_6); 2.83 (s, 3H, C$\underline{H}_3$). ^{13}C NMR (75MHz, DMSO-d_6) δ: 179.2 ($\underline{C}$=O), 152.7 (C_{8a}), 146.6 (C_2), 139.9 (CH=$\underline{C}$H), 137.2 (Cl-Ph-2), 133.9 (C_5), 130.8 (Cl-Ph-1), 128.4 (C_7), 128.0 (Cl-Ph-3), 127.2 (Cl-Ph-6), 126.8 (Cl-Ph-4), 121.5 (Cl-Ph-5), 120.9 ($\underline{C}$H=CH), 120.0 (C_8), 116.4 (C_6), 115.2 (C_3), 18.2 (CH_3). Mp: 169-173°C. ES + MS: 297.75 [M + H +]. Recrystallization from hexane / DCM (3: 1).

3- (2-bromophenyl)-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)prop-2-en-1-one (5g)

Pale yellow solid, 85%. ^{1}H NMR (300MHz, DMSO-d_6) δ: 9.90 (d, 1H, *J* =6.9 Hz, H5); 8.24 (d, 1H, *J* = 1.5 Hz, Ph-Br-3); 8.15 (d, 1H, *J* = 15.3 Hz, CH=C$\underline{H}$); 7.92 - 7.96 (m, 3H, Ph-Br-4,5,6); 7.90 (d, 1H, *J* = 15.9 Hz, C$\underline{H}$=CH); 7.84 (m, 1H, H_8); 7.70 (m, 1H, H_7); 7.45 (m, 1H, H_6); 2.83 (s, 3H, C$\underline{H}_3$). ^{13}C NMR (75MHz, DMSO-d_6) δ: 178.53 ($\underline{C}$=O), 152.7 (C_{8a}), 146.7 (C_2), 138.8 (CH=$\underline{C}$H), 134.0 (Br-Ph-2), 133.3 (C_5), 131.8 (Br-Ph-1), 130.0 (Br-Ph-3), 128.4 (C_7), 127.8 (Br-Ph-6), 125.0 (Br-Ph-4), 121.8 (Br-Ph-5), 120.9 ($\underline{C}$H=CH), 120.0 (C_8), 116.4 (C_6), 115.1 (C_3), 18.2 ($\underline{C}H_3$). Mp : 176-180°C. ES + MS: 342 [M + H +]. Recrystallization from hexane / DCM (3:1).

3- (4-fluorophenyl)-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl) prop-2-en-1-one (5h)

Pale yellow solid, 75%. ^{1}H NMR (300MHz, DMSO-d_6) δ: 9.7 (d, 1H, *J* = 6.9 Hz, H_5); 7.70 (d, 2H, *J* = 6.5 Hz, F-Ph-3,5); 7.68 (d, 1H, *J* = 15.3 Hz, CH=C$\underline{H}$); 7.64 (d, 2H, *J* = 6.5 Hz, F-Ph-2,6); 7.58 (d, 1H, *J* = 15.3 Hz, C$\underline{H}$=CH); 7.42 (m, 1H, H_8); 7.28 (m, 1H, H_7); 7.22 (m, 1H, H_6); 2.73 (s, 3H, C$\underline{H}_3$). ^{13}C NMR (75MHz, DMSO-d_6) δ: 180.0 ($\underline{C}$=O), 157.4 (F-Ph-4), 152.6 (C_{8a}), 146.7 (C_2), 139.9 (CH=$\underline{C}$H), 132.8 (C_5), 131.1 (F-Ph-1), 128.4 (C_7), 128.3 (F-Ph-2,6), 121.9 ($\underline{C}$H=CH), 120.6 (F-Ph-3,5), 120.1 (C_8), 116.5 (C_6), 115.1 (C_3), 18.1 ($\underline{C}H_3$). Mp : 191-195°C. ES + MS: 281 [M + H +]. Recrystallization from hexane / DCM (3: 1).

1- (2-methylimidazo[1,2-*a*] pyridin-3-yl)-3-(pyridin-3-yl)prop-2-en-1-one (5i)

Brown solid, 44%. ^{1}H NMR (300MHz, DMSO-d_6) δ: 9.7 (d, 1H, *J* = 6.9 Hz, H_5); 8.68 (s, 1H, Pyr-2); 8.43 (m, 1H, Pyr-4); 7.68 (d, 1H, *J* = 15.3 Hz, CH=C<u>H</u>); 7.55 (m, 2H, Pyr-5,6); 7.50 (d, 2H, *J* = 15.3 Hz, C<u>H</u>=CH); 7.36 (m, 1H, H_8); 7.31 (m, 1H, H_7); 7.29 (m, 1H, H_6); 2.85 (s, 3H, C<u>H</u>$_3$). ^{13}C NMR (75MHz, DMSO-d_6) δ: 178.06 (<u>C</u>=O), 153.0 (C_{8a}), 139.1 (C_2), 136.1 (C_5), 135.5 (Pyr-2); 134.3 (CH=<u>C</u>H), 132.4 (Pyr-4), 130.03 (Pyr-1), 128.5 (Pyr-5), 127.9 (C_7), 123.1 (Pyr-6), 121.0 (<u>C</u>H=CH), 120.2 (C_8), 116.6 (C_6), 115.2 (C_3), 18.0 (<u>C</u>H$_3$). PF: 209-213°C. ES + MS: 264 [M + H +]. Recrystallization from acetone / water (1: 1).

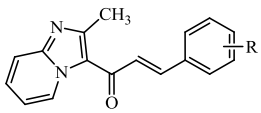
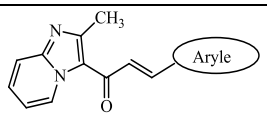
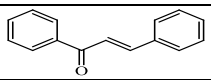
(E) -3-(furan-2-yl)-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)prop-2-en-1-one (5j)

Solid orange-yellow, 38%. 1H NMR (300MHz, DMSO-d_6) δ: 9.7 (d, 1H, *J* = 6.9 Hz, H_5); 8.43 (m, 1H, Fur-4); 7.59 (d, 1H, *J* = 15.3 Hz, CH=C<u>H</u>); 7.46 (m, 1H, H_8); 7.34 (d, 2H, *J* = 15.3 Hz, C<u>H</u>=CH); 7.29 (m, 2H, Fur-3,5), 7.29 (m, 1H, H_7); 7.06 (m, 1H, H_6); 2.39 (s, 3H, C<u>H</u>$_3$). ^{13}C NMR (75MHz, DMSO-d_6) δ: 171.06 (<u>C</u>=O), 142.8 (C_{8a}), 139.1(C_2), 136.1(C_5), 134.5 (CH=<u>C</u>H), 128,6 (Fur-4), 127.3 (Fur-3), 123.4 (C_7), 126.8 (Fur-5), 121.0 (<u>C</u>H=CH), 118.1 (C_8), 116.6 (C_6), 114.4 (C_3), 18.0 (<u>C</u>H$_3$). Mp: 196 - 200°C. ES + MS: 252 [M + H +]. Recrystallization from acetone / water (1: 1).

2. Antibacterial Activities

The result of antibacterial screening with imidazo[1,2-*a*]pyridinyl-chalcones, amoxicillin, gentamicin and 1,3-diphénylpropénone against resistant clinical isolates of *Enterococcus faecalis* are summarized in **Table 1**. These results show that 3 chalcones namely compounds **5g**, **5h** and **5j** have presented higher inhibition diameter, beyond 12 mm. The molecular model showed no activity against resistant strain of *Enterococcus faecalis*. The reference drugs, for their part, were active on *Enterococcus faecalis* resistant at threshold diameter of 12 mm.

Table 1: Activity of tested compounds against the clinical isolate of *Enterococcus faecalis.*

Compounds	Structures	R	Inhibition diameter (ID in mm) *Enterococcus faecalis* clinical isolate
5a		H	6
5b		2-CH_3	6
5c		2-OH	7
5d		2-OCH_3	6
5e		4-$N(CH_3)_2$	0
5f		2-Cl	8
5g		2-Br	13.5
5h		4-F	13
5i			0
5j			13
			0
amoxicillin			12
gentamicin			12

1,3-diphénylpropénone as well as dimethylamine and pyridine derivatives of imidazo[1,2-*a*]pyridinyl-chalcones (**5e** and **5i**) were activeless against *Enterococcus faecalis.* With inhibition diameters between 0 and 8, the unsubstituted, methyl, methoxy, hydroxy and chlorinated derivatives experienced moderate antibacterial activities. The brominated, fluorinated and furan derivatives (**5g, 5h** and **5j**) have exhibited the best activity (ID > 12mm).

The second step was to determine the MIC of these 3 best molecules, having presented inhibition diameter superior than 12 mm. The results obtained in liquid medium on sensitive and resistant strains of *Enterococcus faecalis* are given in Table 2.

Table 2: MIC of selected compounds on resistant and sensitive strains of *Enterococcus faecalis.*

Compounds	*Enterococcus faecalis* ATCC 29212 (sensitive)		*Enterococcus faecalis* clinical (resistant)	
	Minimum Inhibitory Concentration (MIC)			
	(µg/mL)	(µM)	(µg/mL)	(µM)
5g	50	146.54	50	146.5
5h	50	178.4	12.5	44.6
5d	50	198.4	2.5	9.9
amoxicillin	50	136.8	12.5	34.2
gentamicin	25	52.3	25	52.4

DISCUSSION

The replacement of benzene at position 1 of the 1,3-diphénylpropénone, by heterocycle imidazo [1,2-*a*] pyridine, led to imidazo [1,2-*a*] pyridinyl-chalcone **5a**. This compound presented an inhibition diameter of 6 mm, greater than the molecular model which was non-existent. So we went from an inactive chalcone to imidazo[1,2-*a*]pyridinyl-chalcone active on *Enterococcus faecalis*. The induction of the anti-*Enterococcus faecalis* activity can be explained by the intrinsic antibacterial activities of imidazo[1,2-*a*]pyridine nucleus and chalcones.[11,17]

The structural variations made around the benzene homocycle of the imidazo[1,2-*a*] pyridinyl-chalcone as a result of the introduction of various alkyl type modulators, hydroxyl, alkyl, aminoalkyl, or halogen led to compounds **5b-5h**. These activity modulators are indeed known as entities able to improved anti-infective performance in chalcones series.[18] Thus, it appears that the presence of the methyl, hydroxyl, methoxyl, dimethylamine groups or chlorine (**5b** to **5f**) on the benzene ring didn't improved antibacterial activities expected. Indeed, they have given an ID against resistant *Enterococcus faecalis* lower than 9 mm, which is significantly less than the inhibiton diameter (ID) threshold of 12mm. However, the bromine derivative **5g** led to an improvement in antibacterial activity. In fact, this compound with a 13.5 mm diameter of inhibition showed a MIC 146,5µM. If this anti-*Enterococcus faecalis* resistant activity is markedly greater than that of the imidazo[1,2-*a*]pyridinyl-chalcone **5a**, it remains lower than that of amoxicillin (34.2 µM) and Gentamicin (52,4µM). In addition, with a 13mm ID and an MIC of 44.6 µM, the fluorinated derivative (**5h**) showed a performance three times higher than the brominated derivative and also superior than that of Gentamicin. Thus, the presence of a Fluor atom leading to the induction of a good antibacterial activity could be explained by the fact that this atom protects a metabolization site.[19]

The replacement of benzene ring by pyridine (**5i**) resulted annihilation of anti-*Enterococcus faecalis* activities. On the other side, replacement of the benzene homocycle by a furan has increased antibacterial activity against (ID = 12mm). This derivative furan (**5j**) with MIC of 9.9 µM presented the best performance of antibacterial-resistant *Enterococcus faecalis*. This is 5 times greater than that of gentamicin and 3 times that of Amoxicillin. However, it is clear that the effectiveness of fluorinated derivatives (**5h**) and furan (**5j**) is better on the drug-resistant strain compared to the susceptible strain. Indeed, the fluorinated derivative presented

a MIC of 44.6 µM on the drug-resistant strain, and a MIC of 178.4 µM on the susceptible strain. Similarly, the furan derivative is 20 times more effective on the drug-resistant strain than on the sensitive strain of *Enterococcus faecalis*. Several assumptions can be made, one is that the imidazo [1,2-*a*] pyridinyl-chalcones exert their antibacterial activity by a different mechanism of action including destruction of biofilm, one of protection and pathogenicity factors of this bacterium. Indeed, the presence of chalcone in their structures, could justify their mode of action by inhibiting the production of glycocalyx and biofilm formation thereby making the bacteria more vulnerable.[17] The other hypothesis is that changes in receptor-target conformation, acquired during resistance mechanisms, would be favorable to the activity of these imidazo [1,2-*a*] pyridinyl-chalcones.[20]

CONCLUSION

The evaluation of antibacterial activities against resistant *Enterococcus faecalis*, has shown that the imidazo[1,2-*a*]pyridinyl-chalcone **5a**, did not possess any anti-*Enterococcus faecalis* activitiy. The different structural variations undertaken established that improvement of antibacterial activities against resistant *Enterococcus faecalis*, requires the presence on the benzene ring, atoms of bromine or fluorine or the replacement of the homocycle by furan ring. This study showed that our imidazo [1,2-*a*] pyridinylchalcones paradoxically have better efficacy on resistant strain than on the sensitive strain of *Enterococcus faecalis*. Determining the mechanism of action of these compounds could highlight the value of this new antibacterials class in the treatment of infections caused by Vancomycine-resistant *Enterococcus faecalis*.

ACKNOWLEDGMENTS

The authors express their gratitude to the Swiss Center for Scientific Research of Côte d'Ivoire (for antibacterial tests); the Laboratory of the University of Nantes 'CEISAM' (for NMR and MS spectra).

REFERENCES

1. Jones ME, Draghi DC, Thornsberry C, Karlowsky JA, Sahm DF and Wenzel RP. Emerging resistance among bacterial pathogens in the intensive care unit. a European and North American Surveillance study (2000–2002). *Ann Clin Microbiol Antimicrob*., 2004; 3: 14.
2. Lammers M. Physiology of *Enterococcus faecalis* and *faecium*. *Master Immunity and Infection University of Utrecht*, 2009; 26.

3. Peciuliene V, Balciuniene I, Eriksen HM, Haapasalo M. Isolation of *Enterococcus faecalis* in previously root-filled canals in a Lithuanian population. *J Endod*, 2000; 26(10): 593-5.
4. Joyanes P, Pascual A, Martínez-Martínez L, Hevia A, Perea EJ. In vitro adherence of *Enterococcus faecalis* and *Enterococcus faecium* to urinary catheters. *Eur J Clin Microbiol Infect Dis*., 2000; 19(2): 124-7.
5. Keane PF, Bonner MC, Johnston SR, Zafar A, Gorman SP. Characterization of biofilm and encrustation on ureteric stents in vivo. *Br J Urol*., 1994; 73: 687–91.
6. Sandoe JA, Witherden IR, Cove JH, Heritage J, Wilcox MH. Correlation between enterococcal biofilm formation in vitro and medical-device-related infection potential. *J Med Microbiol*, 2003; 52(Pt 7): 547-50.
7. Dowidar N, Moesgaard F, Matzen P. Clogging and other complications of endoscopic biliary endoprostheses. *Scand J Gastroenterol*, 1991; 26(11): 1132-6.
8. Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS). Diagnostic et antibiothérapie des infections urinaires bactériennes communautaires du nourrisson et de l'enfant. AFSSAPS, 2007; 8-10.
9. Ling Zhang, Xin-Mei Peng, Guri L. V. Damu, Rong-Xia Geng, and Cheng-He Zhou. Comprehensive Review in Current Developments of Imidazole-Based Medicinal Chemistry. *Med. Res. Rev.*, 2013; 00(0): 1–98.
10. N'Guessan DUJ-P, Delaye P-O, Pénichon M, Charvet CL, Neveu C, Ouattara M, Enguehard-Gueiffier C, Gueiffier A, Allouchi H. Discovery of imidazo[1,2-*a*]pyridine-based anthelmintic targeting cholinergic receptors of *Haemonchus contortus*. *Bioorg. Med. Chem.*, 2017; 25(24): 6695-6706.
11. Enguehard-Gueiffier C and Gueiffier A. Recent Progress in the Pharmacology of Imidazo[1,2-*a*]pyridines. *Mini-Rev. Med. Chem.*, 2007; 7: 888-99.
12. Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, Volume 1. 8th ed. Elsevier Health Sciences, 2014; 3904.
13. Sissouma D, Ouattara M, Koné M, Menan H, Adjou A, Ouattara L. Synthesis and *in vitro* nematicidal activity of new chalcones vectorised by imidazopyridine. *Afr. J. Pharm. Pharmacol.*, 2011; 5(18): 2086 – 93.
14. Dosso M, Kette F. Antibiotiques. Documents techniques de l'Université Nationale de Côte d'Ivoire, Faculté de Médecine d'Abidjan, Département de Microbiologie, Abidjan; Laboratoire de Bactériologie-Virologie, 1995; 178.

15. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial susceptibility testing. NCCLS, eighth informational supplement, 1998; M100-S8.
16. Starrett JE, Montzka TA, Crosswell AR, Cavanagh RL. Synthesis and biological activity of 3-substituted imidazo[1,2-a]pyridines as antiulcer agents. *J. Med. Chem*., 1989; 32: 2204-10.
17. Mahapatra DK, Bharti SK, Asati V. Chalcone scaffolds as anti-infective agents: Structural and molecular target perspectives. *Eur. J. Med. Chem.*, 2015; 101: 496-524.
18. Nielsen S, Larsen M, Boesen T, Shonning K, Kromann H. Cationic chalcone antibiotics: design, synthesis and mecanisme of action. . *J Med Chem*., 2005; 48(7): 2667-77.
19. Bégué JP, Bonnet-Delpon D. Chimie bioorganique et medicinale du Fluor. Paris ; CNRS Edition and EDP sciences, 2005; 22.
20. World Health Organization (WHO). antibiotic resistance. Checklist N194, September 2016. http://origin.who.int/mediacentre/factsheets/fs194/fr/. Accessed August 5, 2018.