The Pharmaceutical and Chemical Journal, 2022, 9(4):44-51

Available online www.tpcj.org

Research Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

Synthesis and Evaluation of the Antibacterial Activity of New Imidazo[1,2-a]pyridine- Chalcones Derivatives

Kouassi Francesco Adingra[1], Souleymane Coulibaly[1], Camara Tchambaga Etienne[1], Coulibali Sioménan[1], Adjou Ané[1], Drissa Sissouma[1]*

Laboratoire de Constitution et Réaction de la Matière, UFR Sciences des Structures de la Matière et Technologie, Université Félix Houphouët Boigny, 22 BP 582 Abidjan 22, Côte d'Ivoire.
*Corresponding authors: Souleymane Coulibaly souleydestras@yahoo.fr, +2250759544673, Drissa Sissouma dsissouma@gmail.com, +2250778793230
Received the 26/07/2022, Accepted the 26/08/2022, Published the 29/08/2022

Abstract Numerous studies have shown that conjugated imidazo[1,2-a]pyridine derivatives possess various kinds of biological activities, including antibacterial properties. In this work, we designed and synthesized fifteen (15) imidazo[1,2-a]pyridine-chalcone derivatives (**4a-o**) and studied their antibacterial activity. These compounds were obtained by Claisen-Schmidt condensation between imidazo[1,2-a]pyridine-3-carbaldehyde derivatives (**2a-b** and **3**) and acetophenone derivatives in the presence of sodium hydroxide (NaOH). The synthesized compounds were characterized by NMR spectroscopic analyses (^{1}H, ^{13}C NMR). The antibacterial activity of these 15 derivatives was determined against *Escherichia Coli* strain by disc diffusion method. The results showed that three (3) of these 3-imidazo[1,2-a]pyridinyl-1-arylpropenone (**4e**, **4n** and **4o**) derivatives were active with inhibition diameters between 8 and 15 mm. The **4e** compound was the most potent with a diameter of 15 mm.

Keywords imidazo[1,2-a]pyridine, arylpropenone, NMR spectroscopic analyses antibacterial, inhibition diameter

Introduction

Infectious diseases are the leading causes of death worldwide and especially in Africa [1,2]. Germs that are responsible for these diseases include bacteria, parasites, viruses and fungi [3–8]. It continues to be a challenge that most drugs used in the treatment of these diseases face drug resistance developed by infectious germs. This phenomenon of resistance makes the fight against infections a public health issue. The imidazopyridine scaffold and chalcones have been the focus of several research projects. Imidazopyridine, an aromatic N-containing heterocycle derived from type a conflation between pyridine and imidazole, is known for its good antinfectious activities including antibacterial[9,10], antifungal[11,12], anthelminthic[13], antimalarial[14], and antituberculosis[15]. Chalcones are naturally occurring α,β-ethylene carbonylated organic compounds that are precursors to flavonoids and isoflavonoids[16]. These compounds have been described for their antibacterial[17], antiviral[18], anticancer[19], and antimalarial activities [3].

To make our contribution to the research of new effective molecules to fight against infections, we have synthesized derivatives of 3-imidazo [1,2-a]pyridinylchalcone and studied their antibacterial activities.

Material and Methods

Chemistry Material

All reagents and solvents were purchased at the highest commercial quality and used without further purification unless otherwise noted. All anhydrous solvents, reagent grade solvents for chromatography and starting materials were purchased at the highest commercial quality from either Aldrich Chemical or Fisher Scientific. The reactions were monitored by TLC on precoated Merck 60 F_{254} silica gel plates and visualized using UV-Lamp (6 W, 254 nm and/or 365 nm) or $KMnO_4$ solution followed by heating. Unless otherwise indicated, ^1H and ^{13}C NMR spectra were recorded either on a *Bruker Advance* at 300 and 75 MHz. The spectra were internally referenced to the residual proton solvent signal. Residual solvent peaks were taken as reference ($CDCl_3$: 7.26 ppm, (DMSO-*d6*: 2.50 ppm) at room temperature. For ^1H NMR assignments, the chemical shifts are given in ppm on the ***δ*** scale. Multiplicities are described as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet) and coupling constants, *J* are reported in Hz. Solid compound melting points were measured using a Köfler bench.

General synthetic methods of compounds 2a, b

A round bottom flask was charged with 1.5 mL of DMF at 0°C, 2.3 mmol (2.3eq) of $POCl_3$. The mixture was stirred at room temperature for 15 minutes. After the color disappears in the solution, 1mmol (1eq) of imidazo[1,2-a]pyridine derivatives (**1a** or **1b**) was added. The mixture was warmed up and held at 80°C for 5 hours. Then the reaction medium was neutralized by a saturated solution of hydrogenocarbonate sodium ($NaHCO_3$). The mixture was extracted with DCM. The organic layer was dried over Na_2SO_4, filtered and purified by silica chromatographic column (Hexane/AcOEt: 80/20).

2-phenyl-H-imidazo[1,2-a]pyridine-3-carbaldehyde (2a)

White crystals, yield = 71%, m.p = 159-161°C. ^1H NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1H, CH=O), 9.70 (dt, *J* = 6.8, 1.1 Hz, 1H, H_{Ar}), 7.86 (dd, *J* = 7.4, 5.4, 2.1 Hz, 3H, H_{Ar}), 7.65 – 7.52 (m, 4H, H_{Ar}), 7.16 (td, *J* = 6.9, 1.1 Hz, 1H, H_{Ar}) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.64, 158.37, 147.78, 132.39, 130.44, 129.86, 128.92, 128.85, 120.78, 117.48, 115.32 .

6-chloro-2-phenyl-H-imidazo[1,2-a]pyridine-3-carbaldehyde (2b)

Yellow crystals, yield = 80%, m.p = 150-152°C. ^1H NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1H, CH=O), 9.80 – 9.76 (m, 1H, H_{Ar}), 7.86 (d, *J* = 4.2 Hz, 1H, H_{Ar}), 7.84 (d, *J* = 2.2 Hz, 1H, H_{Ar}), 7.78 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 7.60 (d, *J* = 2.1 Hz, 1H, H_{Ar}), 7.59 – 7.54 (m, 3H, H_{Ar}) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.75, 158.40, 146.02, 131.97, 131.58, 130.09, 129.77, 129.01, 126.78, 123.54, 120.84, 117.67.

Synthetic method of 2-chloro-H-imidazo[1,2-a]pyridine-3-carbaldehyde (3)

White crystals, yield = 85%, m.p = 120-122°C. ^1H NMR (300 MHz, $CDCl_3$) δ 9.99 (s, 1H, CH=O), 9.49 (dt, *J* = 6.8, 1.1 Hz, 1H, H_{Ar}), 7.71 (dd, *J* = 9.0, 1.0 Hz, 1H, H_{Ar}), 7.65 – 7.57 (m, 1H, H_{Ar}), 7.18 (td, *J* = 6.9, 1.2 Hz, 1H, H_{Ar}) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.21, 147.51, 146.25, 130.92, 128.09, 118.79, 117.07, 116.03.

General synthesis method of compounds 4a-o

In a round bottom flask containing 1.5 mL of DMF, 2.3 mmol (2.3eq) of $POCl_3$ were added dropwise at 5°C. The mixture was left at room temperature under magnetic agitation for 15 minutes. After discoloration of the solution, 1mmol (1eq) of 2-chloroimidazo[1,2-a]pyridine (**2**) was added. The mixture was kept at room temperature for 2 hours. The reaction medium was dumped into ice water and the formed precipitate was filtered. The residue formed was dissolved in DCM and extracted with the same solvent. The organic layer was dried with Na_2SO_4 and filtered. The obtained residue was purified by silica gel chromatography (Hexane/ethyl acetate: 70/30).

3-(2-chloro-H-imidazo[1,2-a]pyridin-3-yl)-1-phenylprop-2-en-1-one (4a)

Yellow crystals, yield = 94%, m.p = 189-192°C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, *J* = 6.9 Hz, 1H, H_{Ar}), 8.28 (d, *J* = 15.5 Hz, 1H, H_3), 7.84 – 7.74 (m, 3H, H_{Ar} and H_2), 7.62 (dd, *J* = 8.1, 1.5 Hz, 1H, H_{Ar}), 7.59 – 7.37 (m, 6H, H_{Ar}), 7.09 (td, *J* = 6.9, 1.2 Hz, 1H, H_{Ar}), 7.00 (dd, *J* = 8.4, 1.0 Hz, 1H, H_{Ar}), 6.93 – 6.82 (m, 1H, H_{Ar}) ; ^{13}C NMR (75

MHz, $CDCl_3$) δ 193.06, 163.64, 152.70, 147.79, 136.25, 133.99, 130.41, 129.66, 129.35, 129.20, 129.00, 127.55, 125.39, 120.21, 118.92, 118.77, 118.53, 115.33, 114.56.

3-(2-chloro-H-imidazo[1,2-a]pyridin-3-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one (4b)

Orange crystals, yield = 81%, m.p = 236-238°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, *J* = 7.0 Hz, 1H, H_{Ar}), 8.16 (d, *J* = 15.4 Hz, 1H, H_3), 8.01 (d, *J* = 15.4 Hz, 1H, H_2), 7.93 (dd, *J* = 8.1, 1.5 Hz, 1H, H_{Ar}), 7.66 (d, *J* = 9.0 Hz, 1H, H_{Ar}), 7.56 – 7.40 (m, 2H, H_{Ar}), 7.16 – 6.94 (m, 3H, H_{Ar}) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.03, 163.64, 136.47, 129.46, 127.82, 126.49, 123.90, 119.03, 118.68, 117.85, 117.14, 114.78.

3-(2-chloro-H-imidazo[1,2-a]pyridin-3-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (4c)

Yellow crystals, yield = 95%, m.p = 202-204°C. ^{1}H NMR (300 MHz, $CDCl_3$) 8.36 (d, *J* = 6.6 Hz, 1H, H_{Ar}), 8.14 – 8.00 (m, 3H, H_{Ar} and H_3), 7.92 (d, *J* = 15.6 Hz, 1H, H_2), 7.63 (d, *J* = 8.8 Hz, 1H, H_{Ar}), 7.45 – 7.34 (m, 1H, H_{Ar}), 7.07 (d, *J* = 6.5 Hz, 1H, H_{Ar}), 7.00 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 3.90 (s, 3H, OCH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.82, 163.59, 144.89, 131.04, 130.78, 127.23, 125.27, 123.85, 119.17, 117.68, 116.95, 114.43, 113.97, 55.55.

3-(2-chloro-H-imidazo[1,2-a]pyridin-3-yl)-1-(4-fluorophenyl)prop-2-en-1-one (4d)

Yellow crystals, yield = 90%, m.p = 208-210°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, *J* = 6.9 Hz, 1H, H_{Ar}), 8.15 – 8.04 (m, 3H, H_{Ar} and H_3), 7.89 (d, *J* = 15.5 Hz, 1H, H_2), 7.68 – 7.62 (m, 1H, H_{Ar}), 7.24 (dd, *J* = 7.0, 4.2 Hz, 1H, H_{Ar}), 7.18 (dd, *J* = 6.8, 4.8 Hz, 1H, H_{Ar}), 7.09 (td, *J* = 6.9, 1.2 Hz, 1H, H_{Ar}) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.88, 145.11, 139.79, 131.10, 130.98, 127.52, 126.18, 123.86, 118.44, 117.78, 116.02, 115.73, 114.61.

3-(2-chloro-H-imidazo[1,2-a]pyridin-3-yl)-1-(4-aminophenyl)prop-2-en-1-one (4e)

Yellow crystals, yield = 88%, m.p = 262-264°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (d, *J* = 6.9 Hz, 1H, H_{Ar}), 7.98 – 7.88 (m, 3H, H_{Ar} and H_3), 7.84 (d, *J* = 15.8 Hz, 1H, H_2), 7.71 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 7.62 – 7.51 (m, 1H, H_{Ar}), 7.23 (td, *J* = 6.9, 1.1 Hz, 1H, H_{Ar}), 6.65 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 6.19 (s, 2H, NH2) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.67, 154.40, 144.92, 139.04, 131.46, 128.57, 127.17, 125.70, 124.70, 118.79, 117.11, 116.99, 115.26, 113.27.

3-(2-chloro-H-imidazo[1,2-a]pyridin-3-yl)-1-(3-hydroxyphenyl)prop-2-en-1-one (4f)

Yellow crystals, yield = 75%, m.p = 216-218°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H, OH), 9.03 (d, *J* = 6.8 Hz, $1H_{Ar}$), 8.05 (d, *J* = 15.7 Hz, 1H, H_3), 7.83 (d, *J* = 15.7 Hz, 1H, H_2), 7.74 (d, *J* = 8.9 Hz, $1H_{Ar}$), 7.60 (t, *J* = 7.2 Hz, $2H_{Ar}$), 7.47 (s, $1H_{Ar}$), 7.40 (t, *J* = 7.8 Hz, $1H_{Ar}$), 7.26 (t, *J* = 6.8 Hz, $1H_{Ar}$), 7.07 (d, *J* = 6.5 Hz, $1H_{Ar}$) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.77, 158.22, 145.31, 139.97, 139.58, 130.41, 129.14, 127.37, 126.81, 120.72, 119.77, 117.94, 117.18, 116.86, 115.48, 114.93.

3-(2-chloro-H-imidazo[1,2-a]pyridin-3-yl)-1-(4-methylphenyl)prop-2-en-1-one (4g)

Yellow crystals, yield = 50%, m.p = 206-208°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, *J* = 6.9 Hz, 1H, H_{Ar}), 8.07 (d, *J* = 15.6 Hz, 1H, H_3), 7.98 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 7.92 (d, *J* = 15.6 Hz, 1H, H_2), 7.64 (d, *J* = 9.0 Hz, 1H, H_{Ar}), 7.46 – 7.36 (m, 1H, H_{Ar}), 7.33 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 7.07 (td, *J* = 6.9, 1.1 Hz, 1H, H_{Ar}), 2.44 (d, *J* = 7.0 Hz, 3H, CH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.07, 143.89, 135.60, 129.46, 128.60, 127.31, 125.64, 123.89, 119.19, 117.72, 114.49, 21.74.

3-(2-chloro-H-imidazo[1,2-a]pyridin-3-yl)-1-(4-bromophenyl)prop-2-en-1-one (4h)

Yellow crystals, yield = 82%, m.p = 216-218°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, *J* = 6.9 Hz, 1H, H_{Ar}), 8.11 (d, *J* = 15.5 Hz, 1H, H_3), 7.99 – 7.92 (m, 2H, H_{Ar}), 7.88 (d, *J* = 15.5 Hz, 1H, H_2), 7.74 – 7.61 (m, 3H, H_{Ar}), 7.51 – 7.40 (m, 1H, H_{Ar}), 7.12 (td, *J* = 6.9, 1.2 Hz, 1H, H_{Ar}) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.40, 145.18, 139.99, 136.89, 132.05, 129.95, 128.11, 127.64, 126.46, 123.89, 118.14, 117.80, 116.81, 114.68.

1-(2-hydroxyphenyl)-3-(2-phenyl-H-imidazo[1,2-a]pyridin-3-yl)prop-2-en-1-one (4i)

Yellow crystals, yield = 65%, m.p = 100-102°C. ^{1}H NMR (300 MHz, $CDCl_3$) 8.54 (d, *J* = 6.9 Hz, 1H, H_{Ar}), 8.28 (d, *J* = 15.5 Hz, 1H, H_3), 7.84 – 7.74 (m, 3H, H_{Ar} and H_2), 7.62 (dd, *J* = 8.1, 1.5 Hz, 1H, H_{Ar}), 7.59 – 7.37 (m, 6H, H_{Ar}), 7.09 (td, *J* = 6.9, 1.2 Hz, 1H, H_{Ar}), 7.00 (dd, *J* = 8.4, 1.0 Hz, 1H, H_{Ar}), 6.93 – 6.82 (m, 1H, H_{Ar}) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.06, 163.64, 152.70, 147.79, 136.25, 133.99, 130.41, 129.66, 129.35, 129.20, 129.00, 127.55, 125.39, 120.21, 118.92, 118.77, 118.53, 115.33, 114.56.

1-(4-methoxyphenyl)-3-(2-phenyl-H-imidazo[1,2-a]pyridin-3-yl)prop-2-en-1-one (4j)

Yellow crystals, yield = 60%, m.p = 112-114°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, *J* = 6.9 Hz, 1H, H_{Ar}), 8.20 (d, *J* = 15.7 Hz, 1H, H_3), 7.95 (t, *J* = 10.2 Hz, 2H, H_{Ar}), 7.87 – 7.73 (m, 3H, H_{Ar} and H_2), 7.59 – 7.45 (m, 4H, H_{Ar}),

7.40 (dd, *J* = 8.3 Hz, 1H, H_{Ar}), 7.06 (dd, *J* = 6.9, 5.9 Hz, 1H, H_{Ar}), 6.95 (dd, *J* = 9.2, 2.3 Hz, 2H, H_{Ar}), 3.88 (s, 3H, OCH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.96, 163.39, 134.11, 131.17, 130.59, 129.51, 129.14, 128.95, 128.80, 126.78, 125.15, 118.32, 117.80, 114.04, 113.88, 55.52.

3-(6-chloro-2-phenyl-H-imidazo[1,2-a]pyridin-3-yl)-1-phenylprop-2-en-1-one (4k)

Yellow crystals, yield = 73%, m.p = 150-152°C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, *J* = 1.2 Hz, 1H, H_{Ar}), 8.14 (d, *J* = 15.8 Hz, 1H, H_3), 7.91 (dd, *J* = 5.2, 3.3 Hz, 2H, H_{Ar}), 7.78 (dd, *J* = 4.9, 2.9 Hz, 1H, H_{Ar}), 7.74 (d, *J* = 15.8 Hz, 1H, H_2), 7.72 – 7.66 (m, 1H, H_{Ar}), 7.60 – 7.44 (m, 7H, H_{Ar}), 7.35 (dd, *J* = 9.5, 2.0 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.51, 151.88, 145.54, 138.05, 133.60, 132.92, 129.42, 129.29, 129.24, 128.89, 128.73, 128.35, 128.07, 125.79, 123.10, 122.41, 118.84, 118.57.

3-(6-chloro-2-phenyl-H-imidazo[1,2-a]pyridin-3-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one (4l)

Orange crystals, yield = 75%, m.p = 196-198°C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, *J* = 1.2 Hz, 1H, H_{Ar}), 8.21 (d, *J* = 15.6 Hz, 1H, H_3), 7.81 – 7.68 (m, 3H, H_{Ar} and H_2), 7.63 – 7.45 (m, 6H, H_{Ar}), 7.39 (dd, *J* = 9.5, 1.9 Hz, 1H, H_{Ar}), 7.05 – 6.99 (m, 1H, H_{Ar}), 6.94 – 6.86 (m, 1H, H_{Ar}) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.82, 163.59, 152.46, 145.74, 136.36, 133.57, 129.51, 129.42, 129.14, 128.96, 128.41, 122.99, 122.64, 119.98, 118.91, 118.71, 118.66, 116.80.

3-(6-chloro-2-phenyl-H-imidazo[1,2-a]pyridin-3-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (4m)

Yellow crystals, yield = 60%, m.p = 184-186°C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 1.2 Hz, 1H, H_{Ar}), 8.14 (d, *J* = 15.8 Hz, 1H, H_3), 7.94 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.81 (dd, *J* = 7.9, 1.5 Hz, 2H, H_{Ar} and H_2), 7.70 (t, *J* = 8.1 Hz, 1H, H_{Ar}), 7.59 – 7.45 (m, 4H, H_{Ar}), 7.41 – 7.32 (m, 1H, H_{Ar}), 6.99 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 3.91 (s, 3H, OCH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.72, 163.54, 151.33, 145.36, 133.73, 130.93, 130.67, 129.39, 129.14, 128.87, 128.45, 127.84, 122.96, 122.27, 119.14, 118.70, 118.54, 113.95, 55.54.

1-(4-aminophenyl)-3-(6-chloro-2-phenyl-H-imidazo[1,2-a]pyridin-3-yl)prop-2-en-1-one (4n)

Yellow crystals, yield = 75%, m.p = 210-212°C. ^1H NMR (300 MHz, DMSO-*d6*) δ 9.10 (d, *J* = 1.2 Hz, 1H, H_{Ar}), 7.94 (d, *J* = 15.8 Hz, 1H, H_3), 7.88 – 7.79 (m, 3H, H_{Ar}), 7.78 – 7.69 (m, 3H, $2H_{Ar}$ and H_2), 7.64 – 7.48 (m, 4H, H_{Ar}), 6.62 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 6.16 (s, 2H, NH_2) ; ^{13}C NMR (75 MHz, DMSO-*d6*) δ 186.02, 154.32, 150.51, 145.20, 134.18, 131.55, 129.67, 129.24, 128.43, 127.08, 125.74, 125.42, 121.52, 120.42, 119.25, 118.42, 113.15.

3-(6-chloro-2-phenyl-H-imidazo[1,2-a]pyridin-3-yl)-1-(3-nitrophenyl)prop-2-en-1-one (4o)

Yellow crystals, yield= 55%, m.p = 188-190°C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.70 (t, *J* = 1.9 Hz, 1H, H_{Ar}), 8.57 (d, *J* = 1.2 Hz, 1H, H_{Ar}), 8.45 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H, H_{Ar}), 8.28 – 8.25 (m, 1H, H_{Ar}), 8.22 (d, *J* = 15.7 Hz, 1H, H_3), 7.82 – 7.68 (m, 4H, H_{Ar}), 7.62 – 7.55 (m, $3H_{Ar}$), 7.49 – 7.40 (m, 2H, H_{Ar} and H_2) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.18, 159.19, 156.09, 139.45, 138.54, 133.90, 130.48, 129.98, 129.64, 129.39, 129.06, 128.66, 127.08, 123.54, 123.16, 123.03, 122.80, 118.71, 118.49, 116.90.

Materials of Biology

The antibacterial activity assessment of imidazo[1,2-a]pyridinechalcone derivatives was conducted on an *E. coli* 1289 strain. That strain was provided by the Microbiology Laboratory of the National Center of Floristics (CNF) of Université Felix Houphouët Boigny de Cocody. The disk diffusion method [20] was used to evaluate this activity.

Preparation of chemical compounds

A 1000 µg/mL stock solution was prepared by dissolving 1 mg of substance in 1 mL of a 50/50 DMSO/distilled water mixture. Then, this solution was put in a water bath for 10 minutes at 45°C. After warming, the solution was homogenized by a vortex mixer and it was left for 24 hours at room temperature. The stock solution was then diluted to a concentration of 500 µg/mL.

Preparation of bacterial inoculum

The bacteria to be tested were transplanted to chromogenic *E. coli* agar for *E. coli* strains and then incubated at 37°C for 24 hours to obtain young and well-isolated colonies. After incubation, one or two (1-2) well-isolated and perfectly identical bacterial colonies were collected using a platinum loop and then emulsified in a tube containing 2

mL of physiological water and stirred in the vortex mixer. The inoculum density was adjusted to 0.5 Mac Farland using DENSIMAT.

Seeding and deposition of disks

0.1 mL of the bacterial inoculum was inoculated on a Muller Hinton agar surface and homogenously spread. A disk of 6 mm diameter from sterile blotting paper was impregnated with a volume of 20 µL of the chemical compound added with 10% DMSO of varying concentrations. Two controls were performed, negative control with 20 µL of sterile distilled water in the presence of 10% DMSO and an antibiotic disc as a positive control. These discs were then deposited on the surface of the Muller Hinton agar.

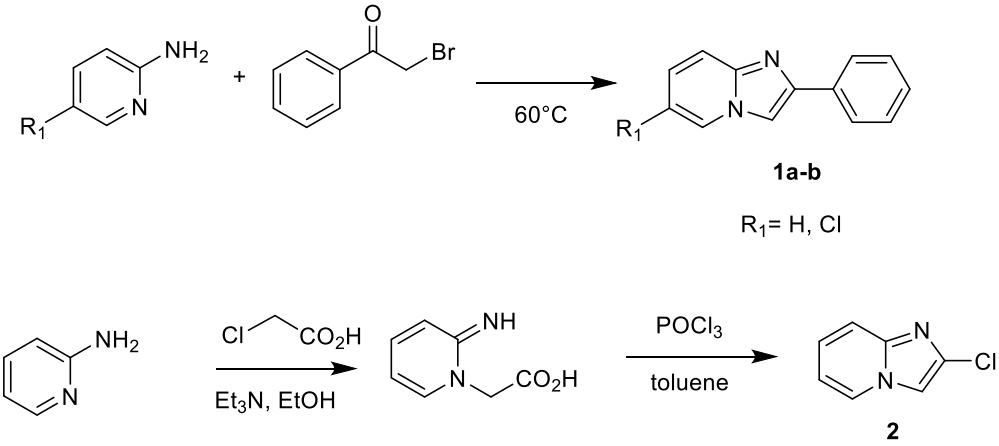
Incubation

The boxes were left for one hour at room temperature and incubated at 37°C for 18 to 24 hours. After incubation, the inhibition diameter was measured in millimeters (disc included) using a caliper.

Result and Discussions

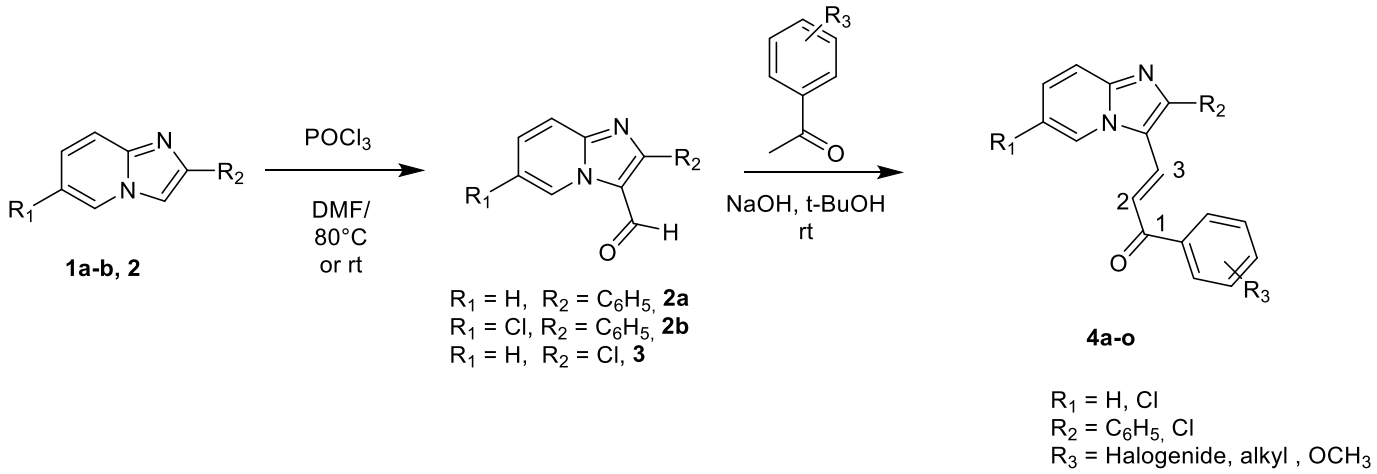
Chemistry

The synthesis of compounds **1a-b** and **2** was carried out following the method shown in **Scheme 1**. The synthesis of compounds **2a-b** was carried out in two steps starting with phenacyl (**1**). First, phenacyl reacts in a solvent-free system *via* substitution reaction and intramolecular cyclization with 2-aminopyridine or 2-amino-5-chloropyridine at 60°C to form 2-phenylimidazo[1,2-a]pyridine (**1a-b**) as described by Zhu et *al.* [21]. Then, we synthesized 2-chloroimidazo[1,2-a]pyridine (**2**) in two steps inspired by the work done by Maxwell et *al.* [22].



Scheme 1: Synthesis of 2-phenyl-*H*-imidazo[1,2-a]pyridine (**1a-b**) and 2-chloro-*H*-imidazo[1,2-a]pyridine (**2**)

Compounds **1a-b** and **2** underwent a Vilsmeier-Haack formylation reaction to give compounds **2a-b** and **3**. Finally, compounds **2a-b** and **3** were reacted with methyl ketone following a Claisen-Schmidt condensation reaction in basic medium to yield 3-imidazo[1,2-a]pyridinylchalcones derivatives **4a-o** (**Scheme 2**). After silica gel chromatography, **4a-o** were isolated with yields ranging from 60% to 95%. Interestingly, we observed that conversion yields of **4a-h** compounds were higher than those of the **4f-o** compounds. This could be due to the chlorine in position -2 of compound **2** would create a smaller steric hindrance compared to the phenyl in the same position -2 of compounds **2a-b.**



Scheme 2: Synthesis of imidazo[1,2-a]pyridine-chalcone derivatives

The ^{1}H and ^{13}C NMR spectra of compounds **2a-b** and **3** are consistent and agreed with the proposed structures. Indeed, on the ^{1}H NMR spectra, the presence of the proton peak signals of the group CH=O was observed in the zone of 10.10 ppm and 9.99 ppm for the compounds **2a-b** and **3** respectively. In the ^{13}C NMR spectra, the carbon peak of the CH=O group for compounds **2a** and **2b** was observed at 179 ppm, while for compound **3**, it resonated at 177.21 ppm. The coupling constants of the ethylene protons around 15 Hz show that the **4a-o** compounds are in *trans* configuration [19].

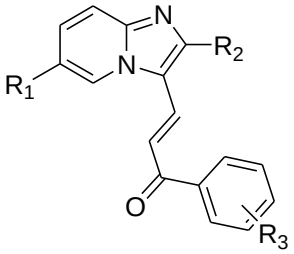
Biology

Agar Diffusion Test

Sensitivity tests of the fifteen (15) imidazo [1,2-a]pyridinechalcone derivatives were performed to determine their antibacterial activity. The results are resumed below in table 1:

Table 1: antibacterial activity of 3-imidazo[1,2-a]pyridine-chalcone derivatives

- Means no sensibility on the *E. Coli* strain

Compounds	General structure	R_1	R_2	R_3	Inhibition diameter (mm)
4a		H	Cl	H	-
4b		H	Cl	2-OH	-
4c		H	Cl	4-OCH_3	-
4d		H	Cl	4-F	-
4e		H	Cl	4-NH_2	15
4f		H	Cl	3-OH	-
4g		H	Cl	4-CH_3	-
4h		H	Cl	4-Br	-
4i		H	C_6H_5	2-OH	-
4j		H	C_6H_5	4-OCH_3	-
4k		Cl	C_6H_5	H	-
4l		Cl	C_6H_5	2-OH	-
4m		Cl	C_6H_5	4-OCH_3	-
4n		Cl	C_6H_5	4-NH_2	11
4o		Cl	C_6H_5	3-NO_2	8

According to Ponce et *al*. [23], the compound is designated as non-sensitive when its inhibition diameter is less than 8 mm. When this diameter is between 9 and 14 mm, the compound is called sensitive, and when the diameter is between 15 and 19 mm, the compound is considered very sensitive. Beyond 20 mm, the compound is described as extremely sensitive. The determination of inhibition diameters allows an estimation of the sensitivity of the bacterial strain against the tested compounds. Thus, the results of this study showed that the majority of these imidazo[1,2-a]pyridinechalcone derivatives did not possess a diameter greater than or equal to 8 mm *vs*. *E. Coli*. Structural variations around the benzene scaffold of 3-imidazo[1,2-a]pyridinyl-1-arylpropenone consisted of the introduction of various alkyl, hydroxyl, amino, or halogenide modulators. These activity modulators are indeed known as entities capable to improve anti-infectious performance in the series of chalcones [24]. Thus, it appears that the presence of methyl, hydroxyl, methoxy or amino groups on the benzene ring did not improve the antibacterial activities as are expected in the majority of cases. However, the compounds **4e**, **4n** and **4o** were substituted by amino (NH_2) and nitro (NO_2) induced activity concerning *E. coli*. Compound **4e** is the most potent, of the compounds studied, exhibiting a 15 mm inhibition diameter when exposed to *E. coli*.

Conclusion

This work resulted in the development of fifteen (15) imidazo [1,2-a]pyridine-based chalcone derivatives. The structures of the synthesized compounds were characterized by (^{1}H and ^{13}C) NMR spectroscopy. The antibacterial activity of the compounds **4a-o** was determined by the method of disk diffusion on *E. coli*. The **4e**, **4n** and **4o** compounds exhibited antibacterial activity. The compound **4e** was the most potent with a diameter of 15 mm.

Acknowledgments

The authors express their gratitude to the Laboratory of Microbiology of the National Center of Floristics (CNF) of the University Felix Houphouët Boigny de Cocody Abidjan (Côte d'Ivoire) where antibacterial tests were carried out and at the Laboratoire de Méthodologie et Synthèse de Produits Naturels at the University of Quebec (Canada) for spectroscopic analyses.

References

[1]. Herrmann, M., Abdullah, S., Alabi, A., Alonso, P., Friedrich, A.W., Fuhr, G., Germann, A., and Kern, W. V (2013) Staphylococcal disease in Africa: another neglected 'tropical' disease. *disease*, 17–26.

[2]. Sileshi, G.W., and Gebeyehu, S. (2021) Emerging infectious diseases threatening food security and economies in Africa. *Glob. Food Sec.*, **28** (October 2020), 100479.

[3]. Ouattara, M., Sissouma, D., and Yavo, W. (2015) Synthèse et criblage antiplasmodial de quelques benzimidazolyl-chalcones. **9** (June), 1697–1710.

[4]. Sakagami, T., Kawano, T., Yamashita, K., Yamada, E., Fujino, N., Kaeriyama, M., Fukuda, Y., Nomura, N., Mitsuyama, J., Suematsu, H., Watanabe, H., Asai, N., Koizumi, Y., Yamagishi, Y., and Mikamo, H. (2019) Antifungal susceptibility trend and analysis of resistance mechanism for Candida species isolated from bloodstream at a Japanese university hospital. *J. Infect. Chemother.*, **25** (1), 34–40.

[5]. Flay, K.J., and Hill, F.I. (2022) A Review : Haemonchus contortus Infection in Pasture-Based Sheep Production Systems , with a Focus on the Pathogenesis of Anaemia and Changes in Haematological Parameters.

[6]. Holding, P.A., and Snow, R.W. (2001) Impact of Plasmodium falciparum malaria on performance and learning: Review of the evidence. *Am. J. Trop. Med. Hyg.*, **64** (1-2 SUPPL.), 68–75.

[7]. Cruz-Tamayo, A.A., López-Arellano, M.E., González-Garduño, R., Torres-Hernández, G., de la Mora-Valle, A., Becerril-Pérez, C., Hernández-Mendo, O., Ramírez-Bribiesca, E., and Huchin-Cab, M. (2021) Haemonchus contortus infection induces a variable immune response in resistant and susceptible Pelibuey sheep. *Vet. Immunol. Immunopathol.*, **234** (February).

[8]. Moser, D., Biere, K., Han, B., Hoerl, M., Schelling, G., Choukér, A., and Woehrle, T. (2021) COVID-19 Impairs Immune Response to Candida albicans. *Front. Immunol.*, **12** (February), 1–10.

[9]. N'guessan, D.U.J.– P., Ouattara, M., Coulibaly, S., Kone, M.W., and Sissouma, D. (2018) antibacterial activity of imidazo [1,2-α] pyridinyl- chalcones derivatives against enterococcus faecalis. *World J. Pharm. Res.*, **7** (18), 21–33.

[10]. Lal, K., Yadav, P., Kumar, A., Kumar, A., and Paul, A.K. (2018) Design, synthesis, characterization, antimicrobial evaluation and molecular modeling studies of some dehydroacetic acid-chalcone-1,2,3-triazole hybrids. *Bioorg. Chem.*, **77**, 236–244.

[11]. S, C., JP, N., MW, K., D, S., and M, O. (2014) Anticandidal Activities of new arylpropenones supported by imidazopyridine. *Afrique Biomed.*, **19** (4), 4–10.

[12]. Rival, Y., Grassy, G., Taudou, A., and Ecalle, R. (1991) Antifungal activity in vitro of some imidazo[1,2-a]pyrimidine derivatives. *Eur. J. Med. Chem.*, **26** (1), 13–18.

[13]. N'Guessan, J.P.D.U., Delaye, P.O., Pénichon, M., Charvet, C.L., Neveu, C., Ouattara, M., Enguehard-Gueiffier, C., Gueiffier, A., and Allouchi, H. (2017) Discovery of imidazo[1,2-a]pyridine-based anthelmintic targeting cholinergic receptors of Haemonchus contortus. *Bioorganic Med. Chem.*, **25** (24), 6695–6706.

[14]. Ouattara, M., Sissouma, D., Koné, M.W., and Yavo, W. (2016) Composés á structure imidazopyridinyl-arylpropénone, nouveaux agents anti-infectieux potentiels. *Comptes Rendus Chim.*, **19** (7), 850–856.

[15]. Nandikolla, A., Srinivasarao, S., Khetmalis, Y.M., Kumar, B.K., Murugesan, S., Shetye, G., Ma, R., Franzblau, S.G., and Sekhar, K.V.G.C. (2021) Design, synthesis and biological evaluation of novel 1,2,3-triazole analogues of Imidazo-[1,2-a]-pyridine-3-carboxamide against Mycobacterium tuberculosis. *Toxicol. Vitr.*, **74** (March), 105137.

[16]. Gomes, M.N., Muratov, E.N., Pereira, M., Peixoto, J.C., Rosseto, L.P., Cravo, P.V.L., Andrade, C.H., and Neves, B.J. (2017) Chalcone derivatives: Promising starting points for drug design. *Molecules*, **22** (8).

[17]. Benouda, H., Bouchal, B., Challioui, A., Oulmidi, A., Harit, T., Malek, F., Riahi, A., Bellaoui, M., and Bouammali, B. (2018) Synthesis of a Series of Chalcones and Related Flavones and Evaluation of their Antibacterial and Antifungal Activities. *Lett. Drug Des. Discov.*, **16** (1), 93–100.

[18]. Mahapatra, D.K., Bharti, S.K., and Asati, V. (2015) Chalcone scaffolds as anti-infective agents: Structural and molecular target perspectives. *Eur. J. Med. Chem.*, **101**, 496–524.

[19]. Rammohan, A., Reddy, J.S., Sravya, G., Rao, C.N., and Zyryanov, G. V. (2020) Chalcone synthesis, properties and medicinal applications: a review. *Environ. Chem. Lett.*, **18** (2), 433–458.

[20]. Hayes, A.J., and Markovic, B. (2002) Toxicity of Australian essential oil Backhousia citriodora (Lemon myrtle). Part 1. Antimicrobial activity and in vitro cytotoxicity. *Food Chem. Toxicol.*, **40** (4), 535–543.

[21]. Zhu, D., Chen, J., Liu, M., Ding, J., and Wu, H. (2009) Catalyst- and Solvent-free Synthesis of Imidazo[1,2-a]pyridine. **20** (3), 482–487.

[22]. Maxwell, B.D., Boyé, O.G., and Ohta, K. (2005) The 14C, 13C and 15N syntheses of MON 37500, a sulfonylurea wheat herbicide. *J. Label. Compd. Radiopharm.*, **48** (6), 397–406.

[23]. Ponce, A.G., Fritz, R., Del Valle, C., and Roura, S.I. (2003) Antimicrobial activity of essential oils on the native microflora of organic Swiss chard. *LWT - Food Sci. Technol.*, **36** (7), 679–684.

[24]. Nielsen, S.F., Larsen, M., Boesen, T., Schønning, K., and Kromann, H. (2005) Cationic chalcone antibiotics. Design, synthesis, and mechanism of action. *J. Med. Chem.*, **48** (7), 2667–2677.