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Synthesis and Potential Antibacterial Activity of Hydrazone Derivatives with Imidazo [1,2-a] pyridine support against *Escherichia Coli*

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Abstract

This work presents the synthesis and investigated the antibacterial activity of seventeen (17) hydrazone derivatives with imidazo[1,2-a] pyridine support (5a-q). These compounds were obtained by condensation between 2-hydrazino-3-nitroimidazo [1,2-a] pyridine and aldehyde derivatives. The synthesized compounds were characterized by spectroscopic analyses (^{1}H, ^{13}C NMR), and High-Resolution Mass Spectrometry (HRMS). A preliminary antibacterial activity of the 5a-q compounds was determined on an *E. coli* strain by the disc diffusion method. The results showed that among the seventeen (17), twelve (12) imidazo[1,2-a]pyridinehydrazone derivatives were potent with inhibition diameters between 8 mm and 11 mm. Compound 5a was more active with a diameter of 11 mm.

Keywords: Imidazo[1,2-a]pyridine, Hydrazone, Antibacterial activity, Inhibition diameter.

Introduction

Imidazopyridine drugs exhibit a wide range of biological activities as a result of changes in the groups on the core structure, as shown in **Figure 1** [1-3]. There's a lot of interest in that heterocycle, particularly in terms of pharmacology. It's a reference pharmacophore for its presence in the structures of many marketed drugs such as Zolimidine [4], a drug used in the treatment of duodenal gastroulcer while Zolpidem is used for insomnia [5]. Molecules such as Alpidem [6], Nicopidem, and Saripidem are used as an anti-anxiolytic agents [7]. Finally, GSK812397 is used in the treatment of HIV infections [8]. In addition to these commercial molecules, several research studies have largely revealed the different biological activities of imidazo[1,2-a]pyridine derivatives such as antibacterial, antifungal, anthelminthic, and antimalarial [8-11]. This heterocycle can be used in the research of new active drugs against infectious germs. Infectious diseases are indeed one of the leading causes of death in the world and especially in developing countries. As seen with the Covid-19 pandemic in 2019, more than 100 million people were infected with more than two million deaths [12]. One of the leading causes of death was bacterial infections in addition to the coronavirus [13–15]. However, antibiotics used in the treatment of these bacterial infections face resistance [16]. Antimicrobial resistance is one of the most pressing health hazards of our time. WHO estimates that drug-resistant infections contribute to nearly 5 million deaths every year in the world [17].

In this context, the emergence of multiresistant bacterial strains poses important public health problems. Germs such as *E. coli* are bacteria of the family *Enterobacteriaceae that* reside in the digestive tract of humans and animals [18]. The majority of *E. coli* strains are harmless, and only a few are pathogenic to humans. But in this context, all those kinds of pathogens became dangerous.

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This is the case with strains of Enterohemorrhagic *E. coli* (ECEH) responsible for urinary tract infections, diarrhea, and meningitis in newborns [19-23]. *E. coli* infections are generally transmitted through the consumption of undercooked or raw animal (meat or dairy) products [24]. Thus, the need for innovative molecules to circumvent drug resistance problems becomes paramount. The use of chemical grounds with anti-infective potentials, such as imidazo[1,2-a]pyridine derivatives, and hydrazone derivatives [25–27], may be of interest. The purpose of this study is to synthesize imidazo[1,2-a]arylhydrazone derivatives under the principle of the juxtaposition of biologically active entities and to evaluate the antibacterial activity of these compounds.

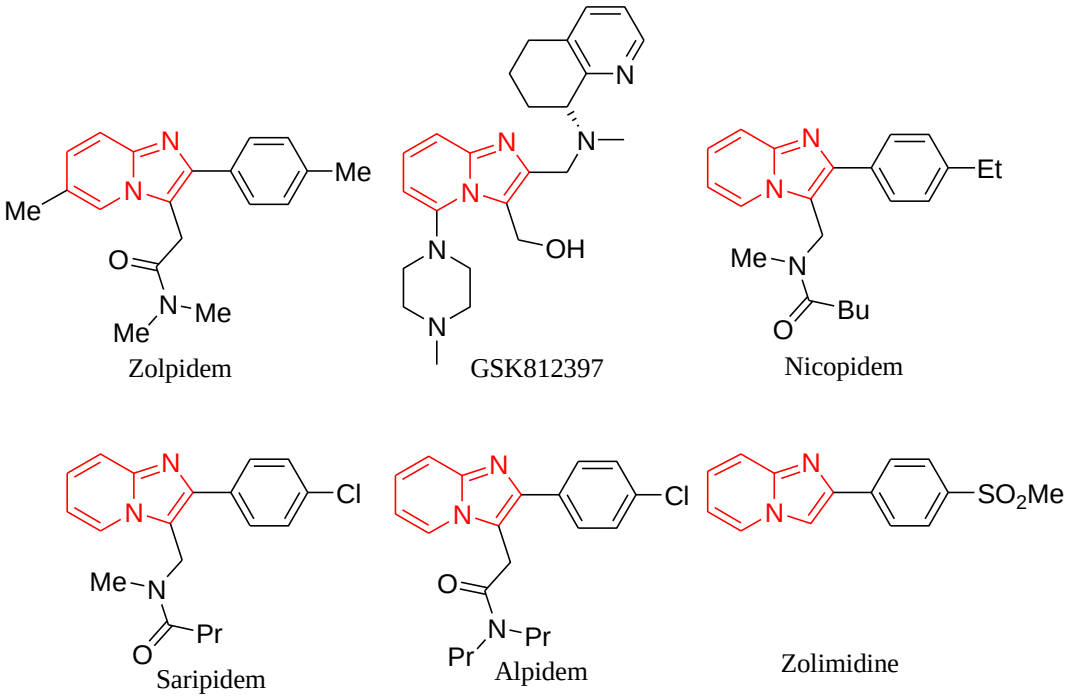


FIG.1. I**midazo[1,2-a]pyridine-containing drugs marketed.**

Materials and Methods

Chemical 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 F254 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, 400, 500, and 75, 101, or 126 MHz. The spectra were internally referenced to the residual proton solvent signal. Residual solvent peaks were taken as reference ($CDCl_3$: 7.26 ppm, Acetone-*d6:* 2.05 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 further qualified as app (apparent), BS (broad signal) coupling constants, *J* are reported in Hz. HRMS were measured in the Electrospray (ESI) mode on an LC-MSD TOF mass analyzer. Solid compound melting points were measured using a Köfler bench.

Biological material

The antibacterial activity assessment of imidazo[1,2-a]pyridinehydrazone derivatives was conducted on an *E. coli* 1289 strain.This strain was provided by the Laboratoire de Microbiologie du Centre National de Floristique (CNF) of the Université Felix Houphouët Boigny de Cocody. To evaluate this activity, the disk diffusion method was used [28].

Methods

Methods of synthesis

A round bottom flask immersed in an ice bath containing 15 mL of H_2SO_4, 1 eq (1.5 g, 9.83mmol) of 2-chloro-*H*-imidazo[1,2-a] pyridine **1**, and 3.5 eq (1.6 mL, 34.40 mmol) of HNO_3 was added. The reaction mixture was stirred at room temperature for 3 h and followed by TLC analysis. The reaction mixture was extracted with DCM and the organic layer was dried over Na_2SO_4. The organic phase was evaporated under *vacuum*, dried, and without any further purification to yield 1.76 g (91%) compound **5** as yellow crystals, m.p: 166°C-168°C**.** ^{1}H NMR (400 MHz, Acetone-*d6*) δ 9.42 (dt, *J*=7.0, 1.1 Hz, 1H; H_{Ar}), 7.92–7.79 (m, 2H; H_{Ar}), 7.52 (td, *J*=7.0, 1.5 Hz, 1H; H_{Ar}). ^{13}C NMR (400 MHz, Acetone-*d6*) δ 132.08, 117.33. HRMS (ESI): Calc for $C_7H_5ClN_3O_2$ $[M+H]^+$=198.8974 Found =198.8977

Synthesis methods of 2-hydrazino-3-nitroimidazo[1,2-a]pyridine 3: In a flask containing 5 mL of ethanol were added compound **2** (1 mmol), and hydrated hydrazide (20 eq, 20 mmol) were added dropwise. The mixture was stirred at 60°C -70°C and then monitored by TLC for 30 minutes. The precipitate formed was filtered, washed with 2 mL of ethanol, and recrystallized in ethanol yielded to 2-hydrazino-3-nitroimidazo[1,2-a]pyridine. Yellow powder, m.p=198°C-200°C, yield=78%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.42 (d, *J* =6.8 Hz, 1H, H_{Ar}), 8.23 (s, 1H, NH), 7.65 (dd, *J*=11.7, 4.4 Hz, 1H, H_{Ar}), 7.52 (d, *J*=8.8 Hz, 1H, H_{Ar}), 7.13 (t, *J*=6.5 Hz, 1H, H_{Ar}), 4.25 (s, 2H, NH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.48, 128.62, 117.29, 115.44, 114.39. HRMS (ESI): Calc for $C_7H_5ClN_2O_2$ $[M+H]^+$=194.0832 Found=194.0834

General procedure for the synthesis of 1-(3-nitroimidazo[1,2-a]pyridinyl)-3-phenylhydrazone derivatives 5a-q The compound **3** (1 mmol) and aromatic aldehydes **4** (1 eq, 1 mmol) were dissolved in 5 mL of methanol. Then two drops of acetic acid were added to the mixture medium. The reaction mixture was refluxed for 30 min to 1 h. After cooling to room temperature, the precipitate formed was filtered, dried, and then purified by recrystallization in ethanol to give compounds 5a-q with yields between 49 and 95%.

1-(3-nitroimidazo[1,2-a] pyridinyl)-3-phenylhydrazone 5a: Yellow powder, m.p=258°C-260°C; yield=80%. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 11.25 (s, 1H, NH), 9.34 (d, *J*=6.8 Hz, 1H, H_{Ar}), 8.67 (s, 1H, CH=N), 7.89–7.65 (m, 4H, H_{Ar}), 7.56–7.41 (m, 3H, H_{Ar}), 7.29 (td, *J*=7.0, 1.2 Hz, 1H, H_{Ar}). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 150.57, 148.37, 146.75, 134.85, 134.55, 130.40, 129.34, 129.03, 127.47, 116.01, 115.37. HRMS (ESI) Calc. for $C_{14}H_{12}N_5O_2$ $[M+H]^+$=282.1881 Found=282.1883

1-(3-nitroimidazo[1,2-a]pyridinyl)-3-(4-methoxyphenyl) hydrazone 5b: Yellow powder, m.p=251-253°C, yield=89%. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 11.12 (s, 1H, NH), 9.32 (d, *J*=6.8 Hz, 1H, H_{Ar}), 8.58 (s, 1H, CH=N), 7.87–7.74 (m, 1H, H_{Ar}), 7.67 (d, *J*=8.8 Hz, 3H, H_{Ar}), 7.27 (td, *J*=7.0, 1.0 Hz, 1H, H_{Ar}), 7.03 (d, *J*=8.8 Hz, 2H, H_{Ar}), 3.82 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, DMSO*d6*) δ 161.15, 150.60, 148.39, 146.90, 134.59, 129.11, 129.04, 127.37, 117.59, 115.83, 115.22, 114.83, 55.79. HRMS (ESI) $C_{15}H_{14}N_5O_3$ $[M+H]^+$=312.2571 Found=312.2573

1-(3-nitroimidazo[1,2-a]pyridinyl)-3-(4-fluorophenyl) hydrazone 5c: Yellow powder, m.p=260°C-262°C, yield=88%. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 11.27 (s, 1H, NH), 9.42–9.30 (m, 1H, H_{Ar}), 8.66 (s, 1H, CH=N), 7.85–7.76 (m, 3H, H_{Ar}), 7.70 (d, *J*=8.8 Hz, 1H, H_{Ar}), 7.37–7.25 (m, 3H, H_{Ar}). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 150.56, 147.18, 146.73, 134.54, 131.49, 131.45, 129.65, 129.53, 129.03, 116.58, 116.29, 116.00, 115.39. HRMS (ESI) Calc. for $C_{14}H_{11}FN_5O_2$ $[M+H]^+$=300.1752 Found=300.1756

1-(3-nitroimidazo[1,2-a]pyridinyl)-3-(2-methylphenyl) hydrazone 5d: Yellow powder, m.p=234-236°C, yield=94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.53 (s, 1H, NH), 9.41 (dt, *J*=6.8, 1.1 Hz, 1H, H_{Ar}), 8.44 (s, 1H, CH=N), 8.11 (dd, *J*=7.6, 1.5 Hz, 1H, H_{Ar}), 7.69–7.63 (m, 2H, H_{Ar}), 7.33–7.27 (m, 1H, H_{Ar}), 7.25–7.10 (m, 3H, H_{Ar}), 2.51 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.47, 147.11, 146.24, 137.09, 133.69, 131.41, 130.78, 130.37, 128.52, 127.09, 126.31, 116.32, 114.74, 19.45. HRMS (ESI) Calc. for $C_{15}H_{14}N_5O_2$ $[M+H]^+$=296.1147 Found=296.1150

1-(3-nitroimidazo[1,2-a]pyridinyl)-3-(2-hydroxyphenyl) hydrazone 5e: Yellow powder, m.p=n.d (>266°C), yield=95%. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 11.55 (s, 1H, OH), 11.29 (s, 1H, NH), 9.33 (d, *J*=6.8 Hz, 1H, H_{Ar}), 8.85 (s, 1H, CH=N), 7.81 (ddd, *J*=8.5, 7.1, 1.2 Hz, 1H, H_{Ar}), 7.68 (d, *J*=8.8 Hz, 1H, H_{Ar}), 7.47 (dd, *J*=8.0, 1.6 Hz, 1H, H_{Ar}), 7.36–7.23(m, 2H, H_{Ar}), 6.92 (dd, *J*=10.3, 4.5 Hz, 2H, H_{Ar}). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 157.80, 150.02, 148.89, 146.51, 134.48, 131.62, 130.05, 128.99, 119.82, 119.24, 116.92, 116.01, 115.47. HRMS (ESI) Calc. for $C_{14}H_{11}N_5O_3Na$ $[M+Na]^+$=320.0538 Found=320.0543

1-(3-nitroimidazo[1,2-a]pyridinyl)-3-(4-chlorophenyl) hydrazone 5f: Yellow powder, m.p=264-266°C, yield=90%. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 11.31 (s, 1H, NH), 9.34 (d, *J*=6.8 Hz, 1H, H_{Ar}), 8.65 (s, 1H, CH=N), 7.87–7.65 (m, 4H, H_{Ar}), 7.54 (d, *J*=8.5 Hz, 2H, H_{Ar}), 7.29 (td, *J*=7.0, 1.2 Hz, 1H, H_{Ar}). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 150.45, 146.87, 146.65, 134.75, 134.51, 133.80, 129.44, 129.02, 116.04, 115.44. HRMS (ESI) Calc. for $C_{14}H_{10}ClN_5O_2Na$ $[M+Na]^+$=338.0381 Found=338.0384

1-(3-nitroimidazo[1,2-a]pyridinyl)-3-(3-cyanophenyl) hydrazone 5g: Yellow powder, m.p=n.d (>266°C), yield=91%. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 11.44 (s, 1H, NH), 9.33 (d, *J*=6.7 Hz, 1H, H_{Ar}), 8.68 (s, 1H, CH=N), 8.13–8.02 (m, 2H, H_{Ar}), 7.92–7.77 (m, 2H, H_{Ar}), 7.69 (dd, *J*=15.1, 7.9 Hz, 2H, H_{Ar}), 7.30 (t, *J*=6.9 Hz, 1H, H_{Ar}). ^{13}C NMR (75 MHz, DMSO *d6*) δ 150.36, 146.52, 145.74, 136.22, 134.50, 133.45, 131.52, 130.70, 129.02, 116.12, 115.58, 112.52. HRMS (ESI) Calc. for $C_{15}H_{10}N_6O_2Na$ $[M+Na]^+$=329.0487 Found=329.0489

1-(3-nitroimidazo[1,2-a]pyridinyl)-3-(4-hydroxyphenyl) hydrazone 5h: Orange powder, m.p=n.d (>266°C), yield=90%, ^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.07 (s, 1H, NH), 9.93 (s, 1H, OH), 9.42–9.26 (m, 1H, H_{Ar}), 8.54 (s, 1H, CH=N), 7.80 (ddd, *J*=8.6, 7.1, 1.3 Hz, 1H, H_{Ar}), 7.67 (d, *J*=8.8 Hz, 1H, H_{Ar}), 7.60–7.56 (m, 2H, H_{Ar}), 7.27 (td, *J*=7.0, 1.2 Hz,

1H, H_{Ar}), 6.88(m, 2H, H_{Ar})–6.83 (m, 2H, H_{Ar}). ^{13}C NMR (126 MHz, DMSO-*d6*) δ 159.37, 150.16, 148.40, 146.49, 134.11, 128.81, 128.56, 125.33, 115.74, 115.37, 114.65. HRMS (ESI) Calc. for $C_{14}H_{12}N_5O_3$ $[M+H]^+$=298.0733 Found =298.0736

1-(3-nitroimidazo[1,2-a]pyridinyl)-3-(2-nitrophenyl) hydrazone 5i: Yellow powder, m.p=260°C-262°C, yield=73%. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 11.71 (s, 1H, NH), 9.37–9.31 (m, 1H, H_{Ar}), 9.09 (s, 1H, CH=N), 8.17 (dd, *J*=7.9, 1.2 Hz, 1H, H_{Ar}), 8.07 (dd, *J*=8.2, 1.1 Hz, 1H, H_{Ar}), 7.82 (ddd, *J*=8.4, 6.9, 2.7 Hz, 2H, H_{Ar}), 7.74 -7.62 (m, 2H, H_{Ar}), 7.31 (td, *J*=7.0, 1.3 Hz, 1H, H_{Ar}). ^{13}C

NMR (75 MHz, DMSO-*d6*) δ 150.27, 148.63, 146.35, 142.68, 134.35, 134.07, 130.88, 129.18, 128.98, 128.19, 125.08, 116.15, 115.60. HRMS (ESI) Calc. for $C_{14}H_{11}N_6O_4$ $[M+H]^+$=327.0664 Found =327.0668

1-(3-nitroimidazo[1,2-a]pyridinyl)-3-(4-methyl phenyl) hydrazone 5j: Yellow powder, m.p=n.d (>266°C), yield=71%. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 11.20 (s, 1H, NH), 9.34 (d, *J*=6.8 Hz, 1H, H_{Ar}), 8.63 (s, 1H, N=CH), 7.82 (dd, *J*=8.5, 7.1, 1.3 Hz, 1H, HAr), 7.67 (dd, *J*=18.0, 8.4 Hz, 3H, H_{Ar}), 7.28 (dd, *J*=9.8, 4.3 Hz, 3H, H_{Ar}), 2.36 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 150.61, 148.47, 146.82, 140.26, 134.59, 132.15, 129.96, 129.06, 127.49, 115.97, 115.32, 21.54. HRMS (ESI) Calc. for $C_{15}H_{13}N_5O_2Na$ $[M+Na]^+$=318.1835 Found=318.1837

1-(3-nitroimidazo[1,2-a]pyridinyl)-3-(2,4-chlorophenyl) hydrazone 5k: Yellow powder, m.p=n.d (>266°C), yield=66%. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 11.70 (s, 1H, NH), 9.34 (d, *J*=6.8 Hz, 1H, H_{Ar}), 9.06 (s, 1H, CH=N), 8.06 (d, *J*=8.6 Hz, 1H, H_{Ar}), 7.89–7.65 (m, 4H, H_{Ar}), 7.55 (dd, *J*=8.6, 2.0 Hz, 1H, H_{Ar}), 7.31 (td, *J*=7.0, 1.2 Hz, 1H, H_{Ar}). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 150.28, 146.42, 142.83, 135.19, 134.39, 134.15, 131.54, 129.86, 128.99, 128.44, 116.12, 115.56. HRMS (ESI) Calc. for $C_{14}H_{10}Cl_2N_5O_2$ $[M+H]^+$=351.1725 Found =351.1727

1-(3-nitroimidazo[1,2-a]pyridinyl)-3-(3-nitrophenyl) hydrazone 5l: Yellow powder, m.p=n.d (>266°C), yield=91%. ^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.45 (s, 1H, NH), 9.34 (dt, *J*=6.8, 1.1 Hz, 1H, H_{Ar}), 8.78 (s, 1H, CH=N), 8.55 – 8.51 (m, 1H, H_{Ar}), 8.26 (ddd, *J*=8.2, 2.4, 1.0 Hz, 1H, H_{Ar}), 8.14–8.09 (m, 1H, H_{Ar}), 7.85–7.81 (m, 1H, H_{Ar}), 7.79(m, 2H, H_{Ar})–7.74

(m, 2H, H_{Ar}), 7.31 (td, *J*=6.9, 1.3 Hz, 1H, H_{Ar}). ^{13}C NMR (126 MHz, DMSO-*d6*) δ 149.82, 148.25, 146.02, 145.20, 136.20, 133.99, 133.31, 130.52, 128.50, 123.99, 120.44, 115.69, 115.12. HRMS (ESI) Calc. for $C_{14}H_{11}N_6O_4$ $[M+H]^+$=327.0562 Found =327.0567

1-(3-nitroimidazo[1,2-a]pyridinyl)-3-(3-bromophenyl) hydrazone 5m: Yellow powder, m.p =260-262°C, yield=65%. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 11.37 (s, 1H, NH), 9.34 (d, *J*=6.8 Hz, 1H, H_{Ar}), 8.63 (s, 1H, CH=N), 7.93 (t, *J*=1.6 Hz, 1H, H_{Ar}), 7.88–7.79 (m, 1H, H_{Ar}), 7.71 (dd, *J*=8.2, 7.2 Hz, 2H, H_{Ar}), 7.63 (ddd, *J*=7.9, 1.9, 0.9 Hz, 1H, H_{Ar}), 7.44 (t, *J*=7.8 Hz, 1H, H_{Ar}), 7.31 (td, *J*=6.9, 1.3 Hz, 1H, H_{Ar}). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 150.43, 146.60, 146.36, 137.33, 134.54, 132.85, 131.58, 129.18, 129.03, 126.77, 122.68, 116.09, 115.53. HRMS (ESI) Calc. for $C_{14}H_{11}BrN_5O_2$ $[M+H]^+$=361.0991 Found =361.0995

1-(3-nitroimidazo[1,2-a]pyridinyl)-3-(4-nitrophenyl) hydrazone 5n: Yellow powder, m.p=264-266°C, yield=69%. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 11,54 (s, 1H, HAr), 9,35 (s, 1H, CH=N), 8.82 (d, *J*=6,3 Hz, 1H, H_{Ar}), 8,35 (d, *J*=7,3 Hz, 2H, H_{Ar}), 8,07 (d, *J*=7,2 Hz, 3H, H_{Ar}), 7,78 (dd, *J*=7,7, 7,9 Hz, 2H, H_{Ar}), 7,32 (td, *J*=6,8, 1,3 Hz, 1H, HAr). ^{13}C NMR (75 MHz, DMSO *d6*) δ 150.05, 148.44, 146.19, 143.94, 135.26, 134.03, 132.09, 129.85, 128.74, 126.09, 122.76, 115.92, 115.36. HRMS (ESI) Calc. for $C_{14}H_{11}N_6O_4$ $[M+H]^+$=327.0268 Found=327.0271

1-(3-nitroimidazo[1,2-a]pyridinyl)-3-(4-hydroxy-3-methoxyphenyl) hydrazone 5o: Orange powder, m.p=n.d (>266°C), yield=79%. ^{1}H NMR (300 MHz, DMSO-d6) δ 11.07 (s, 1H, NH), 9.59 (s, 1H, OH), 9.34 (d, *J*=6.7 Hz, 1H, H_{Ar}) , 8.53 (s, 1H, CH=N), 7.81 (ddd, *J*=8.5, 7.1, 1.2 Hz, 1H, H_{Ar}), 7.67 (d, *J*=8.8 Hz, 1H, H_{Ar}), 7.28 (ddd, *J*=13.9, 6.4, 1.4 Hz, 3H, H_{Ar}), 7.11 (dd, *J*=8.2, 1.8 Hz, 1H, H_{Ar}), 6.87 (d, *J*=8.1 Hz, 1H, H_{Ar}), 3.86 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 150.57, 149.50, 149.25, 148.52, 146.97, 134.66, 129.08, 126.17, 122.59, 117.55, 116.02, 115.87, 115.18, 109.62, 56.11. HRMS (ESI) Calc. for $C_{15}H_{14}N_5O_4$ $[M+H]^+$=328.1522 Found=328.1525

1-(3-nitroimidazo[1,2-a]pyridinyl)-3-(2,4-dimethoxyphenyl) hydrazone 5p: Orange powder, m.p=262-264°C, yield=76%. ^{1}H NMR (300 MHz, DMSO-*d6*) 11.23 (s, 1H, NH), 9.33 (d, *J*=6.8 Hz, 1H, H_{Ar}), 8.85 (s, 1H, CH=N), 7.93–7.78 (m, 2H, H_{Ar}), 7.66 (d, *J*=8.8 Hz, 1H, HA_r), 7.26 (td, *J*=7.0, 1.2 Hz, 1H, H_{Ar}), 6.74 –6.59 (m, 2H, H_{Ar}), 3.87 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 162.86, 159.57, 150.61, 146.90, 144.11, 134.52, 129.04, 127.25, 117.45, 115.83, 115.10, 106.89, 98.75, 56.28, 55.93. HRMS (ESI) Calc. for $C_{16}H_{16}N_5O$ $[M+H]^+$=342.2956 Found=342.2960

1-(3-nitroimidazo[1,2-a]pyridinyl)-3-pyridinylhydrazone 5q: Yellow powder, m.p=n.d (>266°C), yield=81%. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 11.52 (s, 1H, NH), 9.35 (d, *J*=6.8 Hz, 1H, H_{Ar}), 8.67 (s, 3H, H_{Ar}, CH=N), 7.88–7.78 (m, 1H, H_{Ar}), 7.74 (d, *J*=8.7 Hz, 1H, H_{Ar}), 7.66 (d, *J*=5.9 Hz, 2H, H_{Ar}), 7.33 (td, *J*=6.9, 1.3 Hz, 1H, H_{Ar}). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 150.66, 150.23, 146.41, 145.51, 141.99, 134.48, 129.02, 121.30, 117.89, 116.22, 115.70. HRMS (ESI) Calc. for $C_{13}H_{11}N_6O_2$ $[M+H]^+$=283.0745 Found=283.0747

Biological Methods

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 homogenization by a vortex, it was finally left for 24 hours at room temperature. From this solution, a concentration of 500 µg/mL has been prepared.

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, well-isolated colonies. After incubation, 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. 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 the surface of a Muller Hinton agar and spread evenly. Disks of 6 mm diameter sterile blotting paper were impregnated with a volume of 20 µL of the chemical substance supplemented with 10% DMSO of varying concentrations [29]. 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 hours to 24 hours [30]. After incubation, the inhibition diameter was measured in millimetres (disc included) using a caliper.

Results and Discussion

Chemistry

The synthesis of compounds **5a-r** was performed in three steps starting from the intermediate 2-chloroimidazo[1,2-a] pyridine **1**. This compound **1** was obtained in two steps following the work described by Brad et *al*. [29]. The 2-chloro-3-nitroimidazo[1,2-a]pyridine **2** was obtained by the nitration of the position-3 of compound **1**. Then, compound **3** was synthesized *via* a nucleophilic substitution reaction between 2-chloro-3-nitroimidazo[1,2-a]pyridine **2** and hydrazine-hydrate at around 60°C-70°C in ethanol for 20 minutes. Compound **3** was obtained as a yellow solid with a 78% yield. The new 1-(3-nitroimidazole[1,2-a] pyridinyl)-3phenylhydrazone derivatives (**5a-q**) synthesis was carried out by condensation of 2-hydrazino-3-nitroimidazo[1,2-a]pyridine 3 with **4a-q** aromatic aldehydes (**Figure 2**).

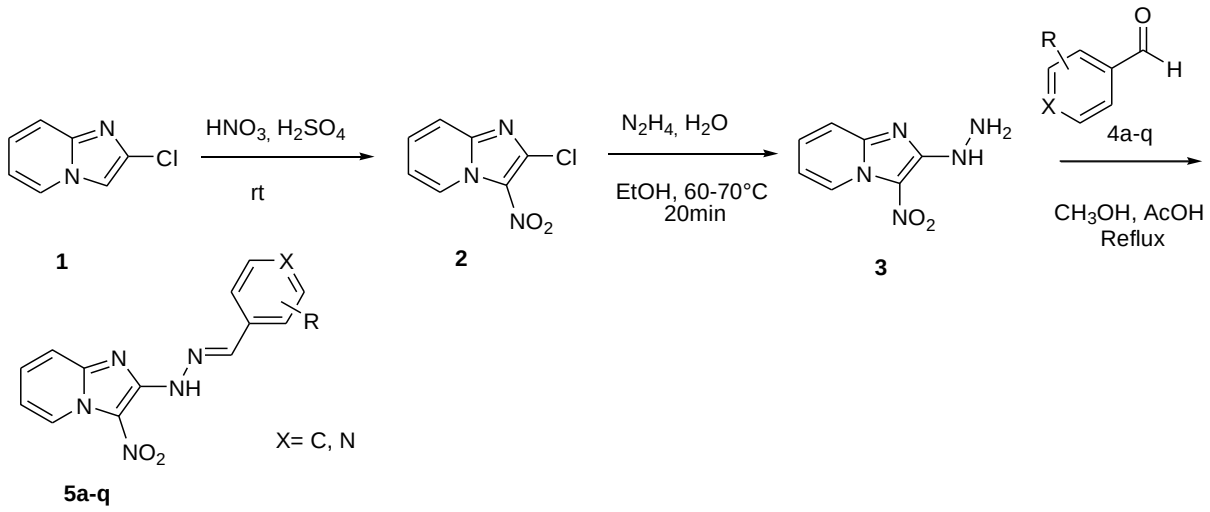


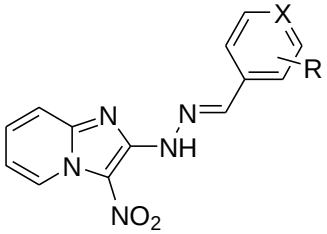
FIG.2. Synthesis route of compounds **5a-q**

These derivatives **5a-q** were obtained by heating the mixture of compound **3** and the aromatic aldehydes **4a-q** in the presence of two drops of acetic acid for one hour under reflux of methanol. A precipitate was formed, filtered off while hot, and then washed with methanol. The compounds **5a-q** were isolated and purified by recrystallization in ethanol. The ^{1}H NMR spectrum of compound **3** revealed the presence of peaks corresponding to the protons of the different nitrogen. We note the presence of two new singlets, one at 4.25 ppm integrating for two protons (NH_2 proton) and the other one at 8.23 ppm integrating for one proton (NH proton). The NMR spectra of compounds **5a-q** obtained show, besides the presence of new peaks in the aromatic zone, the disappearance of the singlet at 4.25 ppm corresponding to the protons of the NH_2 group of compound **3** and the appearance of a singlet in the zone of 8.4 ppm to 9 ppm characteristic of the imine function proton (N=CH). We also note a strong shielding of the NH proton from 8.23 ppm to around 11 ppm. This shielding can be explained by the fact that this proton is conjugated with the double bond of the imine function.

Biology

The antibacterial activity of the seventeen (17) imidazo[1,2-a]pyridinylhydrazone derivatives synthesized was achieved by the *E. coli* disk diffusion method. The inhibition diameters of the 5a-q compounds have been described in **Table 1**.

Table 1. **Antibacterial activity of imidazo[1,2-a]pyridinylhydrazone derivatives 5a-q.**

Compounds	General structure	R	X	Inhibition diameter (mm)
		E. coli		
5a		H	C	11
5b		4-OCH_3	C	10
5c		4-F	C	10
5d		2-CH_3	C	10
5e		2-OH	C	8
5f		4-Cl	C	10
5g		3-CN	C	10
5h		4-OH	C	-
5i		2-NO_2	C	-
5j		4-CH_3	C	10
5k		2,4- Cl	C	-
5l		3-NO_2	C	9
5m		3-Br	C	9
5n		4-NO_2	C	10
5o		3-OCH_3, 4-OH	C	-
5p		2,4-OCH_3	C	-
5q		H	N	10

According to Ponce et *al*. [30], the compound could be designed as non-sensitive when its inhibition diameter is less than 8 mm. When this diameter is between 9 mm and 14 mm, the compound is called sensitive. In addition, when the diameter is between 15 mm 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, twelve (12) imidazo[1,2-a]pyridinylhydrazone derivatives generated activity against *E. coli*. These compounds were sensitive to *E. coli* at a concentration of 500 µg/mL with inhibition diameters ranging from 8 mm to 11 mm. However, at the same concentration, five derivatives were found to be non-sensitive on the same strain. If in the absence of a substituent, compound **5a** showed the best activity with a diameter of 11 mm, the various substitutions made on the phenyl core did not improve the antibacterial activity. The introduction of a mesomeric donor group (OCH_3, F, and Cl) in position-4 did not improve the activity of compound **5a**. These different compounds each produced a diameter of 10 mm almost superimposed on that of compound **5a**. On the other hand, when a mesomeric donor group such as bromine in position-3 (compound **5m**) and a hydroxy in position-2 (compound **5e**) is introduced, there is a considerable decrease in activity with respective diameters of 9 mm and 8 mm. This same hydroxy group in position-4 (compound **5h**) leads to a loss of activity. In addition, the replacement of the groupings (OCH_3, F, and Cl) by an inductive donor group such as the 4-position methyl (compound **5j**) did not improve activity. The same applies when methyl is in the 2-position (compound **5d**). The **5j** and **5d** compounds produced diameters of 10 mm.

Other attempts to improve the activity did not yield better results. The addition of an EWG group by a mesomeric effect such as nitro in position-4 or -3 (compounds **5n** or **5l**) resulted in nearly superposable diameters equal to 10 mm and 9 mm respectively. This same grouping in position-2 leads to a loss of activity (compound **5i**). In addition, the presence of the cyano group, which is a mesomeric effect attractor in position-3 (compound **5g**) has generated an activity with a diameter of 9 mm. Similarly, double substitutions did not improve the activity of the compounds **5k**, **5o**, and **5p**, leading to a loss of activity. The replacement of phenyl by aromatic nuclei having a heteroatom like nitrogen did not allow to have better activity. Indeed, the pyridinic compound **5q** showed an activity of 10 mm comparable to that of compound **5a**. These various pharmacomodulations allow us to say that the improvement of the antibacterial activity of the imidazo[1,2-a]pyridinylhydrazone model is not only related to variations in phenyl and compounds with heteroatoms.

Conclusion

This work resulted in the development of seventeen imidazo[1,2-a]pyridine hydrazone derivatives. The structure of the synthesized compounds was characterized by ^{1}H, ^{13}C NMR spectroscopy, and HRMS. The antibacterial activity of the **5a-q** compounds showed that twelve compounds were active on *E. Coli*. Compound **5a** had the best potential antibacterial activity with a diameter of 11mm.

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