Mustansiriyah Journal of Pure and Applied Sciences, Print ISSN: 2957-9910. Online ISSN: 2957-9929, Vol. 3, No. 4, 2025, Pages 196-206

DOI: 10.47831/mjpas.v3i4.458

MJPAS

*MUSTANSIRIYAH JOURNAL OF PURE AND APPLIED SCIENCES*

Journal homepage:
https://mjpas.uomustansiriyah.edu.iq/index.php/mjpas

*RESEARCH ARTICLE – CHEMISTRY*

# Synthesis and Antimicrobial Evaluation of Mandelonitrile Derivatives

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**Article Info.**

*Article history:*

Received
19 June 2025

Accepted
24 July 2025

Publishing
30 September 2025

**Abstract**

The search for alternative antimicrobial agents has continued to be a top priority due to the growing cases of resistant strains of bacterial and fungal species. This work evaluated the antimicrobial activity of some known mandelonitrile derivatives. Thus, the compounds were successfully obtained by reacting the appropriate aldehydes with the solution of sodium metabisulphite and sodium cyanide at room temperature. The structures of the compounds were confirmed by the NMR and FTIR techniques. Evaluation of the susceptibility of the compounds against four bacterial and one fungal species using disc diff method showed excellent zones of inhibitions for compounds **2b**, **2d**, **2e**, and **2f** against *Pseudomonas aeruginosa*. (30.1 mm – 17.2 mm) compared to the control drug, piperacillin (25.8 mm – 13.4 mm). The minimum inhibitory concentration (MIC) and minimum inhibitory concentration (MBC) of compounds **2b**, **2d**, **2e**, and **2f** were similarly found to be lower against the same organism. All the synthesised compounds demonstrated mild activity against the fungal specie, *E. coli*. This work has demonstrated the potential of the studied nitrile-containing compounds against the investigated bacterial and fungal species.



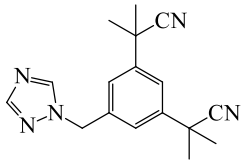
***The official journal published by the College of Education at Mustansiriya University***

***Keywords:*** Mandelonitriles; Nitrile-containing compounds; Antibacterial activity; Antifungal activity

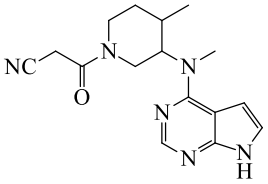
## 1. INTRODUCTION

Antimicrobial resistance (AMR) is increasingly threatening the public health. It was estimated that antibacterial resistance caused approximately 4.95 million deaths in 2019 globally [1]. While, more than 1 billion people are affected by fungal infections in which over 150 million accounts for severe and life-threatening cases [2]. Recently, a number of different compounds were synthesised and tested against various bacterial and fungal species in an attempt to discover a new generation of antimicrobial agents especially small molecules with novel mechanism of action. For instance, the antibacterial evaluation of benzyl acetate derivatives against *Staphylococcus aureus* and *Shigella spp* was reported by Umar et al., 2023 [3]. Also, Benzyl alcohol derivatives were evaluated for antifungal activity against *Candida albicans* and *Trichophyton rubrum* [4]. Similarly, the antibacterial activity of those benzyl alcohol derivatives was investigated against *Staphylococcus aureus* and *Pseudomonas aeruginosa* [5]. Some new aryl-substituted-1,2,3-triazoles containing carbohydrate moieties were evaluated against *Staphylococcus aureus* and *Pseudomonas aeruginosa* for antibacterial activity [6]. Another chemical scaffold found in different biologically important compounds is a nitrile group. Compounds containing a nitrile group are currently used for the treatment of various disease conditions as well as those in clinical development [7-14]. This claim is supported by a review which highlights more than thirty drugs approved by the Food and Drugs Agency of the United States; some examples (Figure

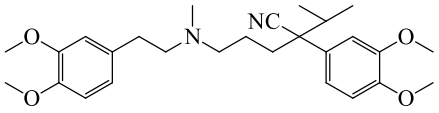
1) include anastrozole, verapamil, and tofacitinib [16]. The favourable properties associated with the nitrile group in drug action include enhanced binding affinity, improved pharmacokinetic profile, and reduced drug resistance [15]. Thus, the aim of the present work was to synthesise and evaluate the *in vitro* antimicrobial activity of some mandelonitrile derivatives against four bacterial and one fungal species.



**Anastrazole**
**(Anticancer Drug)**



**Tofacitinib**
**(Antirheumatic Drug)**



**Verapamil**
**(Antihypertensive Drug)**

**Figure 1**. Some Nitrile containing Drugs

## 2. MATERIALS AND METHODS

### 2.1.Chemistry

All chemicals were sourced from Sigma-Aldrich (Munich, Germany). NMR and FTIR spectroscopic techniques on Bruker AVANCE 500 spectrometer and Perkin–Elmer BX spectrophotometer respectively.

#### 2.1.1. Procedure for the Synthesis of Mandelonitrile Derivatives

Aldehyde (20 mmol) was added dropwise to a cold aqueous solution (10 mL) of $Na_2S_2O_5$ (12 mmol) and stirred continuously. Then a cold aqueous solution (10 mL) of NaCN (20 mmol) was added dropwise and the mixture stirred for 24 h at ambient temperature. The reaction mixture was extracted with $CH_2Cl_2$ (3 x 15 mL), dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure to furnish the desired products. Subsequently, NMR and FTIR spectroscopic techniques confirmed that the data of the synthesised compounds conforms with the literature [17-19].

Compound **2a**

White solid; Yield: 82%; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ (ppm): 4.51 (s, 1H, OH), 5.52 (s, 1H, CH), 7.38 – 7.41 (m, 5H, Ar). $^{13}$C-NMR (125 MHz, $CDCl_3$) δ (ppm): 63.2 (CH), 119.1 (CN), 128.2 – 135.1 (5C, ArC). FTIR ($cm^{-1}$): 3409 (OH), 2252 (CN).

Compound **2b**

White solid; Yield: 84%; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ (ppm): 2.53 (s. 3H, $CH_3$), 5.10 (s, 1H, OH), 5.28 (s, 1H, CH), 7.17 – 7.30 (m, 4H, Ar). $^{13}$C-NMR (125 MHz, $CDCl_3$) δ (ppm): 13.7 ($CH_3$), 54.4 (CH), 120.2 (CN), 128.2 (2C, Ar), 129.1 (2C, Ar), 139.3 (2C, Ar). FTIR ($cm^{-1}$): 3401 (OH), 2250 (CN).

Compound **2c**

Clear oil; Yield: 91%; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ (ppm): 3.63 (s, 1H, OH), 3.74 (s. 3H, $OCH_3$), 5.11 (s, 1H, CH), 5.98 – 7.68 (m, 4H, Ar). $^{13}$C-NMR (125 MHz, $CDCl_3$) δ (ppm): 55.3 O($CH_3$), 61.3 (CH), 120.6 (CN), 128.4 (2C, Ar), 129.3 (2C, Ar), 137.3 (2C, Ar). FTIR ($cm^{-1}$): 3401 (OH), 2250 (CN).

Compound **2d**

White solid; Yield: 83%; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ (ppm): 3.64 (s, 1H, OH), 5.23 (s, 1H, CH), 5.71 (s, 1H, Ar-OH), 7.41 - 7.65 (m, 4H, Ar). $^{13}$C-NMR (125 MHz, $CDCl_3$) δ (ppm): 64.1 (CH), 120.3 (CN), 129.5 (2C, Ar), 131.4 (2C, Ar), 137.4 (2C, Ar). FTIR ($cm^{-1}$): 3395 (OH), 2261 (CN).

Compound **2e**

Clear oil; Yield: 86%; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ (ppm): 3.72 (s, 1H, OH), 5.51 (s, 1H, CH), 6.95 - 7.61 (m, 4H, Ar). $^{13}$C-NMR (125 MHz, $CDCl_3$) δ (ppm): 64.3 (CH), 119.9 (CN), 128.1 (2C, Ar), 130.1 (2C, Ar), 133.2 (2C, Ar). FTIR ($cm^{-1}$): 3400 (OH), 2261 (CN).

Compound **2f**

White solid; Yield: 82%; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ (ppm): 3.69 (s, 1H, OH), 5.42 (s, 1H, CH), 6.81 (s, 1H, Ar), 7.10 – 754 (m, 3H, Ar). $^{13}$C-NMR (125 MHz, $CDCl_3$) δ (ppm): 60.9 (CH), 120.1 (CN), 127.9 (Ar-C), 129.5 (Ar-C), 132.5 (Ar-C), 133.1 (Ar-C), 134.0 (Ar-C), 135 (Ar). FTIR ($cm^{-1}$): 3407 (OH), 2251 (CN)

Compound **2g**

White solid; Yield: 87%; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ (ppm): 3.63 (s, 1H, OH), 3.74 (s, 3H, $OCH_3$), 5.52 (s, 1H, CH), 5.72 (s, 1H, Ar-OH), 6.81 (s, 1H, Ar-H), 7.23 – 7.61 (m, 2H, Ar). $^{13}$C-NMR (125 MHz, $CDCl_3$) δ (ppm): 61.2 (CH), 120.2 (CN), 128.1 (Ar-C), 128.9 (Ar-C), 130.1 (Ar-C), 132.4 (Ar-C), 133.1 (Ar-C), 135, 134.5 (Ar-C). FTIR ($cm^{-1}$): 3406 (OH), 2258 (CN).

### 2.2.Antimicrobial Activity

#### 2.2.1. Test Microorganisms

Five bacterial and one fungal species were clinical isolates obtained from the Department of Microbiology, Umaru Musa Yar'adua University, Katsina, Nigeria.

#### 2.2.2. Susceptibility Test

Concentrations of the synthesised compounds were prepared at 1000 µg/ml, 500 µg/ml, 250 µg/ml, and 125 µg/ml. Then, discs containing different concentrations of the synthesised compounds were dispensed into the various plates containing test organisms and incubated for 37°C h for 24 h. But *C. albicans* was at incubated at for 30°C h for 48 h. Ciprofloxacin and ketoconazole as positive controls for bacteria and fungi respectively were incubated at 37°C for 24 h. All experiments were performed in triplicate and zone of inhibition was recorded for each plate [4].

#### 2.2.3. Determination of Minimum Inhibitory Concentration (MIC)

The MIC of the compounds was determined using the tube dilution method as per the literature [4].

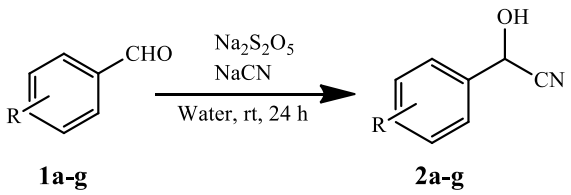
#### 2.2.4. Determination of Minimum Bactericidal/Fungicidal Concentration (MBC/MFC)

The resulting contents from the MIC testes were subjected to the MBC/MFC determination as reported by Benson et al., 2022 [4].

## 3. RESULTS AND DISCUSSION

### 3.1.Chemistry

The synthesised mandelonitrile derivatives were obtained according to Scheme 1. All respective benzaldehydes (**1a-f**) were reacted with the aqueous solutions of sodium metabisulphite and sodium cyanide for 24 h to yield the corresponding mandelonitrile products (**2a-2f**) in excellent yields. The formation of HO-CH-CN bonds was confirmed by the presence of CH peaks within 5.00 ppm – 5.50 ppm, and OH within 3.00 ppm – 3.60 ppm in the $^{1}$H NMR spectra. Similarly, the $^{13}$C spectra gave peaks within 119.0 ppm – 120.0 ppm for the CN carbons [17-19].




**1a-g** **2a-g**

| R | |
|---|---|
| **2a** | H |
| **2b** | 4-$CH_3$ |
| **2c** | 4-$OCH_3$ |
| **2d** | 4-OH |
| **2e** | 4-Cl |
| **2f** | 3-$NO_2$ |
| **2g** | 3-$OCH_3$, 4-OH |

**Scheme 1.** Synthesis of Mandelonitrile Derivatives

### 3.2. Antimicrobial Activity

The susceptibility test of the compounds against four bacterial and one fungal species was evaluated at four concentrations, 1000 µg/ml, 500 µg/ml, 250 µg/ml, and 125 µg/ml (Table 1). This was conducted using the disc diffusion method [4]. *Staphylococcus aureus* was found to be strongly susceptible to compounds **2a**, **2c**, and **2g** at all the tested concentrations compared to the control drug, ciprofloxacin. The range of the zones of inhibitions was 17.1 mm – 7.8 mm. While the control drug at the tested concentrations was 26.4 mm – 12.5 mm. There was no activity determined against *Escherichia coli* at the tested concentrations. *Streptococcus pneumoniae* appeared to be susceptible to compounds **2b**, **2d**, **2e**, and **2f** though mildly active compared to the the control drug, spiramycin. For instance, compound **2b** gave 16.1 mm zone of inhibition while spiramiycin exhibited 22.9 mm zone of inhibition. *Pseudomonas aeruginosa* was excellently inhibited by compounds **2b**, **2d**, **2e**, and **2f** at all the tested concentrations which appeared to be higher than the control drug, piperacillin. The range of inhibition zones of the compounds was 30.1 mm – 17.2 mm compared to piperacillin, 25.8 mm – 13.4 mm. *C. albicans* was the only fungal specie evaluated and was found to be reasonably inhibited by compounds **2b**, **2c**, **2d**, **2e**, **2f** compared to the control drug, clotrimazole. The range of the zone of inhibition was 18.1 mm – 12.0 mm compared to clotrimazole which gave 35.5 mm – 16.5 mm range. The minimum inhibitory concentration (MIC) for all the compounds was found to be 125 µg/ml against all the organisms with the exception of compound **2e** which gave an MIC value of 250 µg/ml against *Streptococcus pneumoniae*. Evaluation of the minimum bactericidal/fungal concentration (MBC/MFC) of the compounds against the organisms gave the highest value of 1,000 µg/ml, and the lowest MBC values of 250 µg/ml. The MFC values similarly gave the highest value of 1,000 µg/ml

and the lowest value of 125 μg/ml (Table 2). Generally, the best performance observed in compounds **2b**, **2d**, **2e**, **2f** may be attributed to the electronic effect of the different substituents. While compounds **2b**, **2d**, and **2e** possess electron activating groups, compound **2f** contains an electron withdrawing group. Similar trend was observed in our earlier studies on the antibacterial and antifungal activities of some simple aryl substituted compounds [3-5]. The antimicrobial activity observed in this work strengthened the potentiality of nitrile-containing compounds as future source of new antimicrobial agents as supported by other works which evaluated structurally different scaffolds containing nitrile group. Some of them include indole-acrylonitriles [20], acrylonitrile adducts [21], bi-α-amino nitrile compounds [22], polyhalo isophthalonitrile derivatives [23], imidazoline-sulphonamide nitriles [24]. The possible mode of antibacterial /antifungal activity of the compounds evaluated in this work could be associated with their binding affinity to the enzyme involved in the synthesis of peptidoglycan, a major component of bacterial cell walls and /or β-lactamase as had been found in the *in silico* studies of the indole-acrylonitriles [20].

**Table 1.** Zone of Inhibition of Compounds **2a** – **2f** against the Bacterial and Fungal Species

| Compound | Zone of Inhibition (mm)[a] | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *S. aureus* | | | | *E. coli* | | | | *S. pneumoniae* | | | | *P. aeruginosa* | | | | *C. albicans* | | | |
| | Concentration (μg/ml) | | | | Concentration (μg/ml) | | | | Concentration (μg/ml) | | | | Concentration (μg/ml) | | | | Concentration (μg/ml) | | | |
| | 1000 | 500 | 250 | 125 | 1000 | 500 | 250 | 125 | 1000 | 500 | 250 | 125 | 1000 | 500 | 250 | 125 | 1000 | 500 | 250 | 125 |
| **2a** | 16.6 | 16.0 | 15.3 | 13.2 | - | - | - | - | - | - | - | - | - | - | - | - | 8.5 | 7.9 | 7.0 | 7.0 |
| **2b** | - | - | - | - | - | - | - | - | 16.1 | 13.8 | 11.1 | 9.7 | 30.1 | 29.9 | 29.7 | 23.1 | 12.6 | 10.3 | 9.0 | 7.1 |
| **2c** | 17.1 | 14.2 | 11.6 | 9.5 | - | - | - | - | - | - | - | - | - | - | - | - | 16.0 | 13.0 | 12.6 | 12.0 |
| **2d** | - | - | - | - | - | - | - | - | 13.4 | 10.1 | 8.6 | 7.1 | 27.1 | 25.4 | 21.6 | 19.5 | 16.6 | 12.8 | 10.2 | 8.5 |
| **2e** | - | - | - | - | - | - | - | - | 12.8 | 10.1 | 8.3 | - | 27.7 | 24.1 | 21.8 | 17.2 | 16.3 | 11.9 | 9.1 | 7.0 |
| **2f** | - | - | - | - | - | - | - | - | 13.9 | 10.6 | 9.0 | 7.2 | 27.1 | 25.4 | 21.6 | 19.5 | 18.1 | 16.9 | 15.0 | 12.1 |
| **2g** | 14.7 | 13.3 | 11.9 | 7.8 | - | - | - | - | - | - | - | - | - | - | - | - | 9.6 | 8.2 | 8.1 | 7.5 |
| Cipr | 26.4 | 18.5 | 16.0 | 12.5 | 28.8 | 18.6 | 15.3 | 11.7 | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt |
| Spir | nt | nt | nt | nt | nt | nt | nt | nt | 22.9 | 18.3 | 16.1 | 14.9 | nt | nt | nt | nt | nt | nt | nt | nt |
| Pipe | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | 25.8 | 22.7 | 18.1 | 13.4 | nt | nt | nt | nt |
| Clot | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | 35.5 | 21.0 | 17.3 | 16.5 |

[a] = Mean values of triplicate tests; - = Not Determined; nt = Not Tested; Cipr = Ciprofloxacin; Spir = Spiramycin; Pipe = Piperacillin; Clot = Clotrimazole
*S. aureus = Staphylococcus aureus; E. coli = Escherichia coli; S. pneumoniae = Streptococcus pneumoniae; P. aeruginosa = Pseudomonas aeruginosa; C. albicans = Candida albicans*

**Table 2. Minimum Bactericidal/Fungal Concentrations of Compounds 2a – 2f**

| Compound | MIC (μg/ml) | | | | | MBC/MFC (μg/ml) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *S. aureus* | *E. coli* | *S. pneumoniae* | *P. aeruginosa* | *C. albicans* | *S. aureus* | *E. coli* | *S. pneumoniae* | *P. aeruginosa* | *C. albicans* |
| **2a** | 125 | - | - | - | 125 | 500 | - | - | - | 500 |
| **2b** | - | - | 125 | 125 | 125 | - | - | 500 | 250 | 125 |
| **2c** | 125 | - | - | - | 125 | 1000 | - | - | - | 500 |
| **2d** | - | - | - | 125 | 125 | - | - | - | 500 | 250 |
| **2e** | - | - | 250 | 125 | 125 | - | - | 1000 | 500 | 1000 |
| **2f** | - | - | 125 | 125 | 125 | - | - | 500 | 250 | 250 |
| **2g** | 125 | - | - | - | 125 | 500 | - | - | - | 500 |

- = Not Determined; *S. aureus = Staphylococcus aureus; E. coli = Escherichia coli, S. pneumoniae = Streptococcus pneumoniae; P. aeruginosa = Pseudomonas aeruginosa; C. albicans = Candida albicans*

## 4. CONCLUSION

Synthesis of some known mandelonitrile derivatives was carried out following the treatment of the corresponding aldehydes with sodium metabisulfite and sodium cyanide solutions. The obtained compounds were characterised using NMR and FTIR spectroscopic techniques. These techniques gave all the relevant peaks in agreement with the literature. Antimicrobial evaluation of the compounds at four different concentrations against five bacterial and one fungal species showed that the activity of the compounds was more potent against *Pseudomonas aeruginosa*. The potent compounds against *P. aeruginosa* were also found to have lower MIC as well as MBC values against the same organism. Although all the synthesised compounds showed mild activities against the fungal specie, *E. coli*. It was found that they all possessed similar MIC values but with variations in the MFC values. This work proved the efficacy of nitrile-containing compounds against the growth of the bacterial and fungal species evaluated. It further proved that nitrile-containing compounds could be a rich source of future pharmaceutics for various disease conditions [25].

## CONFLICT OF INTEREST

The authors declared no conflict of interest.

## ACKNOWLEDGEMENT

The Tertiary Education Trust Fund (TETFund) Nigeria is gratefully acknowledged for funding this work under the institution-based research (IBR) grant programme.

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