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Synthesis, Characterization and Antimicrobial Evolution of New Bi-α-amino Nitrile Compounds

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Abstract

This project is regarding the synthesis of new bi-α-amino nitrile compounds derived from the reaction of di-amine , aldehyde (vanillin or *o*-vanillin), and KCN in glacial acetic acid as a solvent . The three components-one pot reaction produced (2, 2' - (1, 2-phenylenebis (azanediyl)) bis(2-(4-hydroxy-3-methoxyphenyl) acetonitrile) (I) and (2, 2'-(1, 2- phenylenebis (azanediyl)) bis(2-(2-hydroxy-3-methoxyphenyl) acetonitrile) (II) considering the formation of bi-imine compounds as intermediate. α-amino nitrile compounds (I and II) were characterized using infrared spectroscopy and mass spectroscopy. The prepared compounds were screened for their anti-microbial activity. The bacteria are Gram positive (*Staphylococcus aurous*) and Gram negative (*Escherichia coli*) *in vitro*, the results were promising; due to the large inhibition zones.

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1. Introduction

Bifunctional compounds are versatile due to their ability to participate in two distinct chemical reactions [1]. These compounds had significant attention recently in various applications, due to their design to select and react with specific target molecules or sites [2]. In drug synthesis, these compounds have been increasing the efficiency of treatment and developed as potential cancer therapeutic [3-5], although small molecules of bifunctional compounds are designed to bind to protein and enhance biological effect [6]. In catalysis, many organic catalysts show great activity due to bifunctional unite and can catalyze two different types of reactions [7]. Bifunctional compounds can be designed to bind to multiple targets simultaneously, which can increase their efficiency and reduce the likelihood of resistance developing [8]. α-amino nitriles have occupied an essential position since Strecker`s original report in 1850, which is basic and considered valuable vital intermediate synthons [9-10]. These compounds are prepared by the addition of cyanide ion the nucleophilic part to the imines within Lewis acid or Lewis base catalyst [11]. Moreover a verity range of cyanation agents are been used, such as KCN, HCN, TMSCN, Bu_3SnCn [12] and ethyl cyanoformate [13] have been studied to optimize the results. Although, other types of catalysts, such as metal-catalysts, bio-catalysts and organcatalysts have been used in synthesis of α-amino nitriles [14]. Bi-molecule α-amino nitriles are vital intermediates synthon in organic synthesis due to the functional group of cyano group (CN) that can produce di-α-amino acids [15], di-amides [16] , and various nitrogen containing heterocyclic such as tetrazole [17-18]. Furthermore, these compounds demonstrate benefits in various fields of pharmacology therapeutic activities, such as anticancer [19], antioxidant [20] and antibacterial [21-22]. In addition, polydentate organic ligands enable chelating with metal

ions through oxygen or nitrogen donor atoms which are especially stable [23], these ligands were expected to be useful in creating intermediates in catalytic processes as a way to prepare binuclear complexes [24] due to polydentate nature and high coordination abilities. [25]. Multinuclear metal complexes can be categorized into macrocyclic and macroacyclic ones, physical and chemical properties are characterized by structural diversity. However, for the multipoint recognition of guest molecules, they can serve as hosts [26].

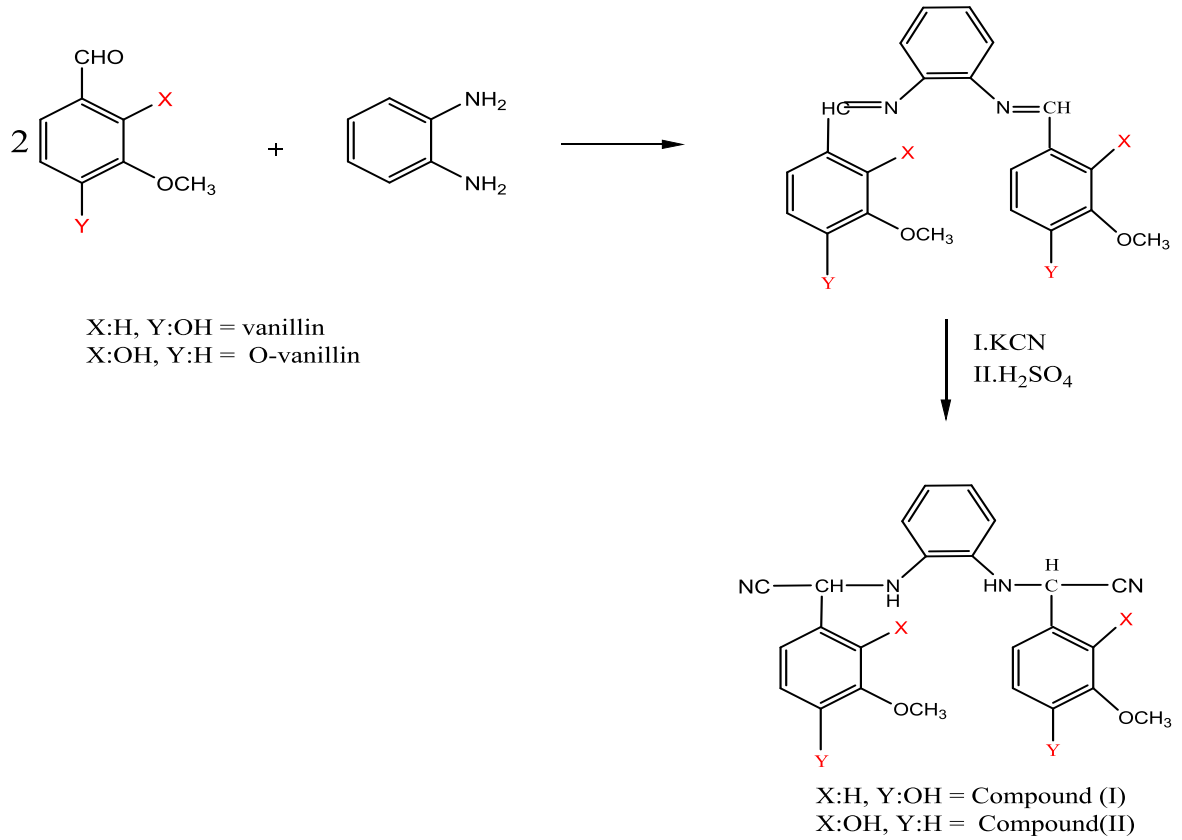
2. Materials and Methods

2.1. General techniques and equipment

The optimized synthons were characterized by FT-IR spectrometer using FTIR SHIMADZU spectroscopy type of 8300 with a range of (400-4000) cm^{-1} and Mass spectroscopy using GC-mass, Agilent Technologies 7820A USA GC Mass Spectrometer. The chemical obtained in this revision were provided and solid from original manufacturing.

2.2. Synthesis of Bi-α-amino nitrile compounds (I and II):

In 3 mL glacial acetic acid 2 mmol (0.6g) of aldehyde (vanillin or ortho vanillin) has been dissolved with stirring followed by (0.21g) of di-amine of 1 mmol compound (*o*-phenylenediamine). A small portion of acid (*p*-toluene sulfonic acid) was added to adjust the *P*H to around 4, then the reaction mixture refluxed for two hours. Potassium cyanide 4 mmol was added carefully to the reaction mixture. Meanwhile, H_2SO_4 (a few drops) was gradually added during this time and swirled for two days. The produced compound was poured on smashe ice, then gently alkalized with the addition of ammonia solution, then left overnight. To create the compounds I and II, the precipitates were filtered, rinsed with wate and dried, of yield percentages 67% and 86% respectively. The colors were; brown, olive and melting points were (120-122) °C and (185-187) °C of the synthesized compounds [I] and [II] respectively. Scheme 1. Shows the synthesis method of [I] and [II] compounds.



Scheme 1. Synthesis of the Bi-α-amino nitrile compounds (I and II)

3. Results and Discussion

3.1. Fourier infrared spectroscopy (FT-IR)

Both compounds showed signals around 3452cm^{-1} and 3436cm^{-1} for (I) and (II) respectively, that could be attributed to phenolic hydroxyl (OH-) which typically appeared at the range (3500-3300)cm^{-1}. It is obvious the major functionalities of the α-amino nitrile -C≡N absorbed at (2128-2220) cm^{-1} attributed to (I) and (II), which is generally appeared around (2250-2100)cm^{-1}. Addition, band of symmetrical –NH appeared at (3201-3186)cm^{-1} which is normally demonstrated at the range (3350-3180) cm^{-1} [27,28]. For (I) and (II) compounds. The mentioned and other characteristic bands are summarized and listed in Table 1.

Table 1. FT-IR absorption bands of the organic compounds

Compound	v(O-	v(N-H)	v(C-H)		*v* (C≡N)	δ(N-H)	Out of plane		
			Aromatic	*Aliphatic*			Ortho	meta	Para
I	3452	3201	3091	2937	2128	1606	748	748	817
II	3436	3186	3068	2935	2220	1676	744	788	NA

3.2. Mass and GC- Mass spectroscopies

It has been demonstrated that mass spectrometry is a useful and quick way to carry out chemical processes. Characterized throughout the gas phase by their mass to charge ratios (m/e+) and relative abundances. The directions and yields of chemical reactions in solution can occasionally be predicted from gas-phase reactions, which frequently show parallels to events in solution. Electrospray ionization, chemical ionization, and electron ionization are all made possible by positive ions. Compounds (I and II) start with 430 of ionized compounds ,which are isostere, mass spectroscopy of compound II spectrum showed peak at m/z = 426 attributed to[$C_{24}H_{18}N_4O_4$] structure due to lose 4 terminal hydrogens [29]. In measuring the peak at m/e+ = 222 is equivalent to the formula [$C_{14}H_{12}N_3$]. Another peak at m/z =175 is identical to the formula [$C_9H_7N_2O_2$] derived from the origin compound, although by losing CN the peak is m/e+ = 149 [30]. Furthermore, a signal was noticed at m/z = 123 which is attributed to [$C_7H_7O_2$] formula [29].

3.3. Antimicrobial Activity

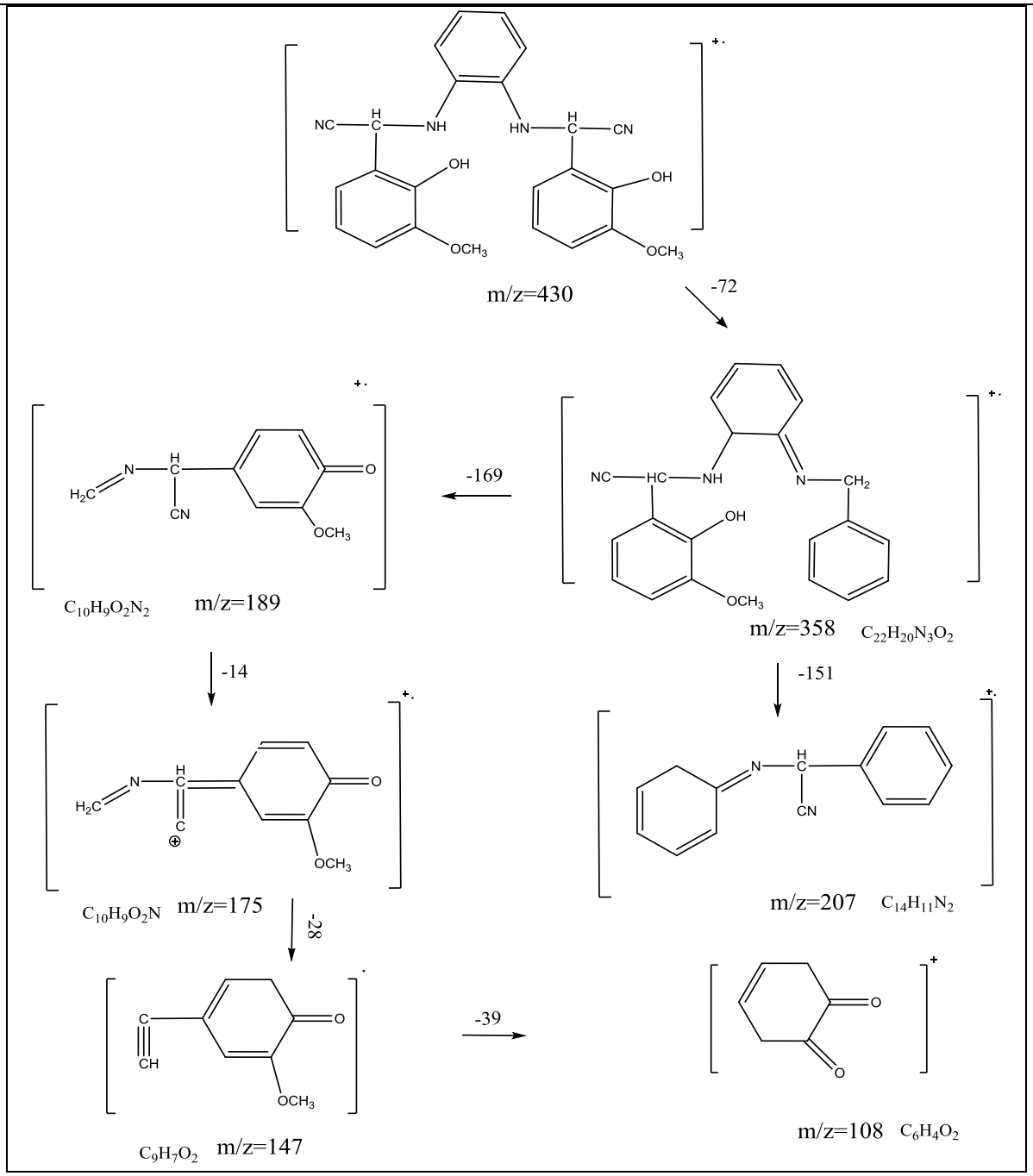
Microorganisms frequently cause serious infections in human. They are responsible for the significant increase in morbidity, Therefore Antimicrobials are crucial to addressing this healthcare issue. In this study, the synthesized bi functional α-amino nitrile compounds were assessed for their *in vitro* microorganism activity against some of the pathogenic bacteria. Two bacterial species were used: Gram positive (Staphylococcus aurous) and Gram negative bacteria (Escherichia coli) to figure out the activity of prepared compounds against the two bacteria.

3.4. Biological study

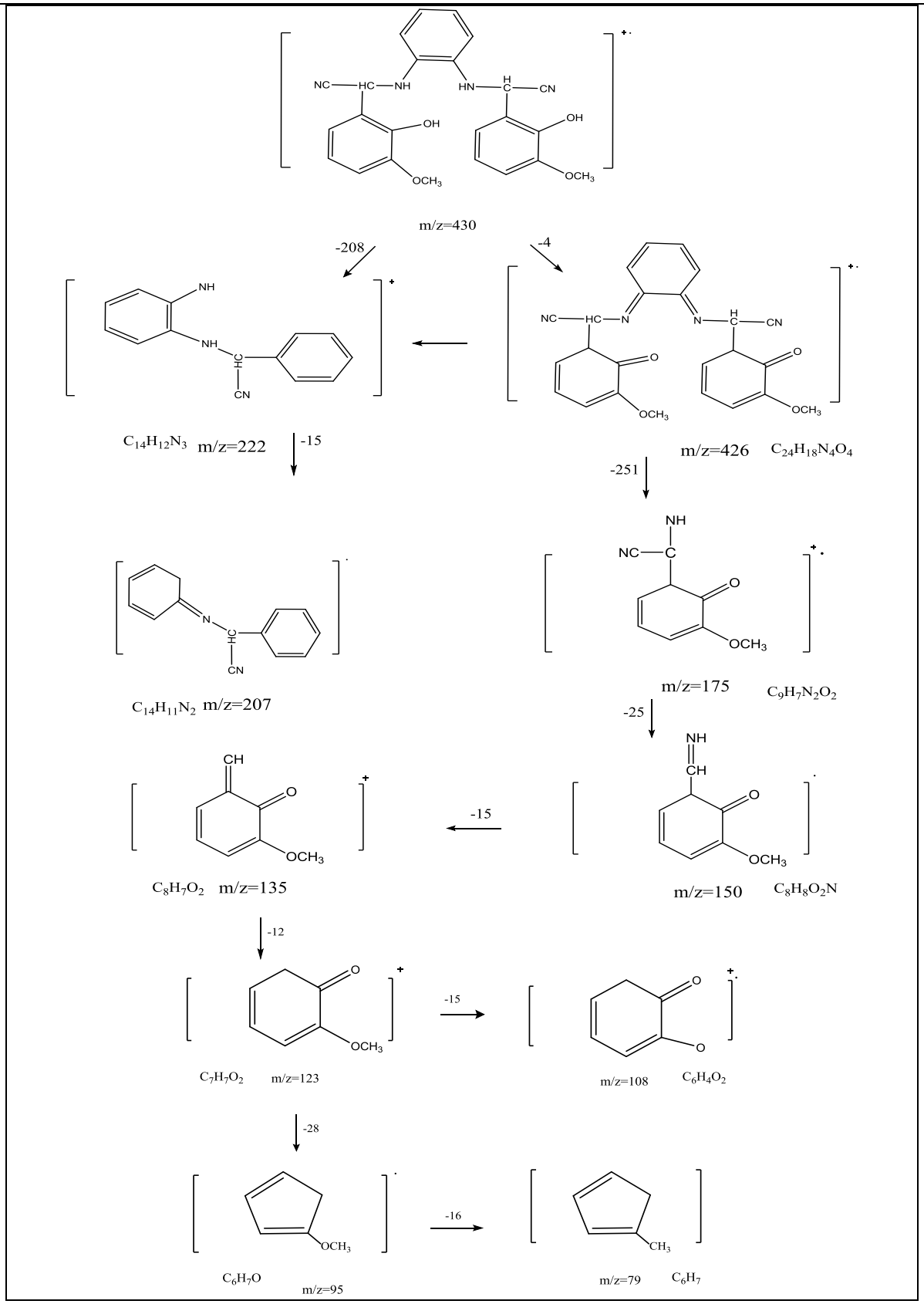
In our study, bi- α-amino nitrile compounds [I] and [II], were tested *in vitro* against two types of bacteria grams positive (Staphylococcus aurous) and grams negative (Escherichia coli). Using a reliable approach and the lowest inhibitor concentration possible to measure how much these ligands are inhibited; because the compounds have two terminal amino nitrile antibacterial groups, compounds I and II have promising results against bacteria. Bacteria-growth inhibition zones caused by test samples and standard references were measured in millimeter and the results were listed in Table 2. On an agar culture.

Table 2. The [I] and [II] compounds' bacterial-inhibiting zones.

Inhibition zone (mm)		
Compound	Staphylococcus aurous	Escherichia coli
[I]	20	20
[II]	18	20



Scheme 2. mass fragments of compound I.



Scheme 3. mass fragments of compound II.

4. Conclusions

Bi-functional compounds [I] and [II] were screened *in vitro* against two selected bacteria grams positive *(Staphylococcus aurous)* and grams negative *(Escherichia coli)* demonstrated an efficiency by preventing the spread of germs, due to the existence of the bi-functional compounds α-amino nitrile type, that demonstrated from the previous steps, which have been exhibited a good results with utilized methods. The results were approximately the same due to that compounds I and II are similar Furthermore, compounds are considered polydentate due to the presence of the N2 donor atoms. Furthermore, they have been attracted much consideration in our opinion upon to their interesting structures as ligands. Providing to synthesize complexes by chelation of polydentate ligand through donor atoms to metal ions forming more stable complexes.

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