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Synthesis, Characterization and Antimicrobial Activities of Novel Hg(II) Complex with 3-Amino-1-[2-phenyldiazenyl]-4*H*-thieno[3,4-*c*]chromen-4-one

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Abstract: *A novel mercury (II) complex of 3-amino-1-[2-phenyldiazenyl]-4H-thieno [3, 4-c] chromen-4-one* ***(3)*** *have been synthesized. The new coordination compound* ***4*** *was characterized on the basis of its IR, UV, NMR, elemental analysis, XRD and MS spectral data. From the data analysis, it was found that the ligand behaves as a bidentate chelating agent and bonds to the central metal ion through the nitrogen atom of the amino group and the oxygen atom of the carbonyl group to form a six-member ring coordination unit. Four such identical coordination units alternately interconnect to each other through four –O-(N=O)-O- bridges which link their central metal ions to each other through bonding to the external sp^3 hybridized oxygen atoms of the NO_3 linkers to form a Metal Organic Framework (MOF) consisting of a sixteen-member ring in which four mercury atoms bicoordinated each to one ligand unit are connected to each other by four NO_3 units. Both ligand (**3**) and new mercury coordination compound (**4**) were screened for their antimicrobial activities against four bacterial (Escherichia Coli, providencia stuartii, Klebsiella Pneumoniae, Staphylococcus aureus) and three fungal strains (Candida albicans ATCC 9002, Candida parapsilosis ATCC 22019, Candida parapsilosis). Data revealed that the synthesized complex (**4**) has the lowest minimum inhibitory concentration 8 µg/mL compared to that of the starting ligand (**3**)16 µg/mL.*

Key words*: Room temperature synthesis, antimicrobial, complexation reaction, 2-aminothiophene, mercury, MOF*

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I. Introduction

Drug resistance has become a growing problem in the treatment of infectious diseases caused by bacteria, fungi, parasites and viruses. So, it is important to find out safer, more effective and inexpensive chemotherapeutic agents. Substituted 2-aminothiophenes, arylazothienocoumarins derivatives and their metal complexes constitute one of the largest classes of industrially synthesized organic compounds because of their numerous applications. Their biological properties are also well known and include anticoagulant, antimicrobial, antitumor, antioxidant, and anti-HIV effect as reported recently [1-5]. Substituted 2-aminothiophene and azo compounds have been extensively used as pharmaceutical and chemotherapeutic agents [6-9]. This paper deals with the synthesis of a new azo coordination compound of mercury incorporating a fused 2-aminothiophene moiety and the investigation of its antimicrobial properties compared to that of the corresponding free ligand.

II. Material And Methods

Fourier-transform infrared spectroscopy (FTIR) spectra were obtained on a Genesis FTIRTM spectrometer (ATI Mattson) equipped with a DTGS (Deuterated Tri Glycine Sulfate) detector in the transmission mode from 400 to 4000 cm^{-1} after 20 scans. The UV spectra were recorded with a JENWAY 6715 UV-Vis Spectrophotometer. ^{1}H-NMR spectra were recorded in DMSO-d_6 on a Bruker DRX spectrometer operating at 300 MHz.^{13}C-NMR spectra were recorded in DMSO-d_6 on a Bruker DRX spectrometer operating at 75 MHz. TMS was used as internal reference. XRD data was collected on a STOE Stadi-p X-ray powder

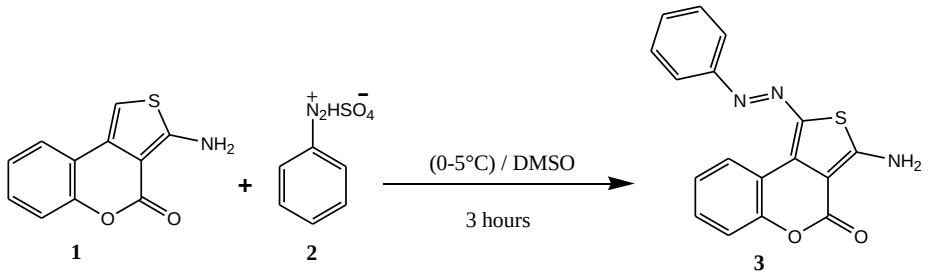
diffractometer (STOE & Cie GmbH, Darmstadt, Germany) with Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å; Gemonochromator; flat samples) in transmission geometry with a DECTRIS® MYTHEN 1K detector (DECTRIS, Baden-Daettwil, Switzerland). Elemental analyses were performed with a Euro Vector CHNS-O element analyzer (Euro EA 3000) or a vario MICRO Cube (Co. Elementar Analysen Systeme).

Procedure for synthesis of the ligand and the mercury complex

All the reagents mentioned in this work were purchased from Aldrich and Fluka and used without further purification.

Synthesis of ligand

The Ligand **(3)** was synthesized according to the literature procedure as published earlier [10]. 3-Amino-4H-thieno [3,4-c]chromen-4-one (**1**) (651 mg; 3 mmol) was dissolved in 10 mL of DMSO and cooled in a salt ice bath to a temperature between 0-5 °C. The diazonium ion (**2**) solution initially prepared over 30 min by mixing in the cool (0-5 °C) 0.93 mg (10 mmol) of aniline with 1.2 g (17 mmol) of dried $NaNO_2$ dissolved in 10 mL DMSO was added slowly for 1 h. The so obtained mixture was gently stirred for further 1h 30min and then 15 mL of a 10% sodium acetate solution were introduced into the reaction medium as described. The reaction's product was collected on a filter, washed in hot water and crystallized in ethanol to give ligand **3** (370 mg, 26%) as a brown powder; m.p. 238-239 °C [lit. [10] : 232-234 °C from DMF/ethanol (5:3)]; IR (KBr) υ_{max} 3207, 3107, 3062, 2896, 2875, 2845, 2580, 1874, 1731, 1683, 1488, 1404 cm^{-1}; λ_{max} (THF) (log ε) 211 (3.67); 253 (4.11); 291 (3.89); 336 (3.66); 478 nm (4.12); ^{1}H-NMR (DMSO-d_6, 300 MHz) 8.84 (1H; dd, *J* = 7.9 and 1.4 Hz; 9-H); 7.74 (1H; d; *J* = 7.4 Hz; 2' and 6'-H); 7.59 (1H; ddd; *J* = 1.5; 7.7 and 7.7 Hz; 7-H); 7.54 (1H; dd; *J* = 7.5 and 8.0 Hz; 3' and 5'-H); 7.45 (1H; ddd; *J* = 1.1; 7.7 and 7.6 Hz; 8-H); 7.35 (1H; d; *J* = 7.4 Hz; 4'-H); 7.40 (1H; dd; *J* = 7.4 and 8.3 Hz; 6-H); ^{13}C-NMR (DMSO-d_6, 75 MHz) 168.2 (C-3); 158.2 (C-4a); 152.6 (C-1' et C-8a); 151.9 (C-2); 134.9 (C-9); 133.0 (C-8b); 131.5 (C-7); 129.4 (C-3' and C-5'); 129.0 (C-6); 128.8 (C-8); 125.1 (C-4'); 121.7 (C-2' and C-6'); 117.2 (C-5);117.0 (C-2a); *m/z* (EI) (%) 321 (6), 280 (22), 247 (22), 208 (100), 190 (24). Anal. Calcd. for $C_{17}H_{11}N_3O_2S$: C, 63.54; H, 3.45; N, 13.08; S, 9.98. Found: C, 63.43; H, 3.34; N, 13.14; S, 9.75.

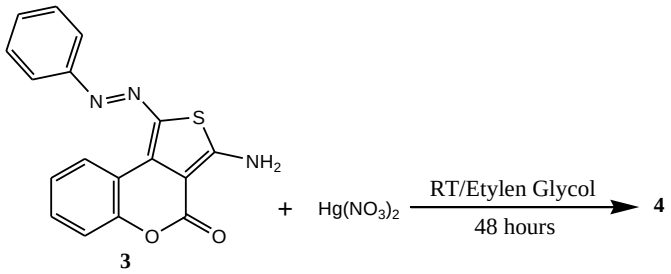


1 **2** **3**

Scheme 1: Synthesis of ligand

Synthesis of the mercury complex

In a warm solution of ethylene glycol (10 mL) was dissolved 0.30 g (0.93 mmol) of 3-amino-1-[2-phényldiazenyl]-4*H*-thieno[3,4-*c*]chromen-4-one **(3).** To this ligand solution, 4 mL a solution of mercury salt was gradually added. The latter one was obtained by dissolving 0.32 g of mercury salt (1 mmol) in a warm solution of ethylene glycol (4 mL). The reaction mixture was stirred at room temperature for 48 h (scheme 2). The precipitate formed was collected by filtration, washed several time in methanol and recrystallized in acetone to afford 0.56 g (71%) compound **4** as brown powder; m.p: 290 °C. IR (KBr) υ_{max} 3280, 1733, 1602, 1552, 1550, 1448 cm^{-1}; λ_{max} (DMSO) (log ε) 270 (4.58); 300 (4.60) ; 455 (4.33); 640 (4.21); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.98–11.41 (m, 4H), 10.57–10.09 (m, 5H), 9.13–8.73 (m, 4H), 8.70–8.36 (m, 5H), 8.26-8.08 (m, 9H), 8.04 (s, 5H), 7.95–7.12 (m, 4H), 7.13–6.73 (m, 4H). ^{13}C NMR (DMSO-d_6, 75 MHz) 184.70, 170.07, 169.39, 164.21, 160.12, 158.67, 158.02, 157.31, 156.47, 155.45, 154.38, 154.02, 153.56, 153.22, 151.57, 151.30, 148.33, 139.55, 137.52, 136.06, 135.83, 131.10, 130.85, 130.58, 130.32, 130.28, 130.15, 130.00, 129.93, 129.84, 129.60, 129.45, 128.67, 127.64, 127.21, 125.96, 125.87, 125.50, 125.36, 124.01, 123.82, 123.70, 123.58, 123.06, 123.03, 122.61, 121.54, 120.53, 118.64, 118.63, 118.61, 117.90, 117.86, 117.78. Elemental Analysis: $C_{68}H_{40}N_{16}O_{20}S_4Hg_4$; Calculated: C, 35.03; H, 1.73; N, 9.61; S, 5.50; Found: C, 35.33; H, 1.68; N, 9.21; S, 5.21.



Scheme 2: Synthesis of metal complex

Biological assay

Microorganisms

The microorganisms used in this study include four strains of bacteria (*Escherichia.coli ATCC 8739, Providencia stuartii ATCC 29916, Klebsiella pneumoniae ATCC 11296, Staphylococcus aureus*) and three yeast strains (*Candida albicans ATCC 9002, Candida parapsilosis ATCC 22019, Candida parapsilosis*). From Pasteur Institut (Paris, France). There were also three isolates of *Staphylococcus aureus*, *Candida Parapsilosis* and *Triclophyton ajeloi* from Pasteur Institute (Yaoundé, Cameroon).

Determination of Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC)

Minimum inhibitory concentrations (MIC) were determined by the liquid micro-dilution method as described earlier [11]. In micro titer plates (96 micro wells), 85 µL of Mueller Hinton (for bacteria) or Sabouraud Dextrose (for yeasts) were added followed by 5 µL of inoculum. The ligand **(3)** and the mercury complex (4) were made at concentrations of 2 mg/mL in 5% (v/v) aqueous solution of dimethylsulfoxide (DMSO) at 5% (v / v). One plate was used for each group of microorganisms. The positive control was contained the appropriate medium and the microbial suspension only. The negative control was done with an aqueous solution of DMSO or 10% Tween 20 instead of the inoculum. Then microliters of ligand **(3)** and the mercury complex **(4)** subsequently added corresponding wells to give a final volume of 100 µL. The plates were covered and incubated with shaking at 35 ° C for 24 h (for bacteria) and 48 h (for fungi). Microbial growth was determined by introducing 5 µL of a 0.2 mg / mL solution of para-iodonitrotetrazolium. Any change in color from yellow to purple indicates microbial growth. The MIC defined as the lowest concentration of the substance that resulted in color change was recorded. The minimum bactericidal or fungicidal concentrations (MBC or MFC), defined as the smallest concentration giving a negative subculture or only a colony was also determined by spreading 10 µL of the content of each well on to the surface of Mueller Hinton Agar or Sabouraud Dextrose Agar medium. Three repetitions were performed for each sample. Chloramphenicol for bacteria and nystatin for yeasts have been used as reference drugs.

III. Results and Discussion

Infrared spectrum

The infrared spectrum of the ligand was compared to that of the of the mercury complex in order to ascertain the coordination sites that might be involved in the chelations. Vibration bands of the free ligand and his complex were recorded in the region 4000-400 cm^{-1}. A summary of the characteristic bands of both molecules are shown in Table 1). The IR spectrum of the ligand displayed intensive bands at 3447 cm^{-1} and 3402 cm^{-1} which were assigned to υ (NH_2) stretching frequencies. In the spectrum of compound **4**, just one bands appeared at 3259 cm^{-1}. The absence of the second amine band is a clear evidence that the coordination process proceed with the deprotonation of this functional group. On the other hand, the down shift of the band, the change in shape, and the decrease intensity futher supports the involvement of the nitrogen atom in the coordination [7-9]. The band due to υ(C=O) shifted appreciably (about 12 cm^{-1}) to a higher wave number suggesting the involvement of the oxygen atom of the carbonyl group in the bonding with the mercury ion [8,9]. The characteristic vibrations of the benzene and thiophene moieties, as well as those of the –N=N- bridge were almost unaffected by the complexation thereby, excluding the possibility of their bonding to the mercury ion. The appearance of new absorptions bands in the spectrum of the complex (**4)** between 496–415 cm^{-1} was attributed to υ(M–O) and υ(M–N) vibrations [12, 13]. Meanwhile the bands of the nitrato groups of the complex appeared around 1522 cm^{-1}. [14, 15]

Table 1: Infrared data of the ligand and it mercury complex (cm^{-1})

Compounds	$\upsilon_{N=N}$	$\upsilon_{C=C}$ (benzene)	$\upsilon_{C=O}$	υ (NH_2)	υ(M–O); υ(M–N)	υ (NO_3)
Ligand	1487	1600	1733	3447-3402	/	/
Complex	1484	1602	1721	3259	496, 467, 436, 415	1552

Ultraviolet spectrum

The UV spectrum of the complex exhibits absorptions between 270 and 640 nm, in the visible range. Table **2** below recapitulates some characteristic wavelengths maxima and the corresponding molar extinction coefficients (in $L.mol^{-1}.cm^{-1}$). A comparison of the UV spectrum of the complex with that of the starting ligand allows us to observe a weak bathochromic effect and the appearance of new bands on the spectrum of the complex. The appearance of the new band in the visible UV (640 nm) is characteristic of a d-d transition, which confirms the coordination of the ligand to the metal. [16, 17]

Table 2: UV-vis data of ligand and it metal complex

	Ligand	complex
λ (nm)	245	270
	300	300
	340	350
	445	455
	/	640
ε ($L.mol^{-1}.cm^{-1}$)	4700.48	38520
	13007.88	40125
	7901.26	12623.6
	16050	21667.5
	/	91306.67

^{1}H-NMR and ^{13}C-NMR Spectrum.

The Analysis of the ^{1}H-NMR spectrum of this compound reveals a highly complex resonance pattern in the aromatic proton zone (6.3-9.25 ppm) suggesting a coordination macromolecule. The chemical shift due to other protons shifted to down field by about 0.6 to 1.0 ppm in the ^{1}H-NMR spectra of the metal complex.

The ^{13}C-NMR spectrum of the complex shows 50 signals attributable to 68 carbon atoms. However, the starting ligand has 17 carbon atoms. In addition, the characteristic signals of four carbonyl groups (C=O) appearing at δ = 184.70 ppm, 170.07 ppm, 169.39 ppm and 164.21 ppm, are in agreement with the presence of four ligands units bound to the four central mercury ions of a coordination spheres. Furthermore, to each of the other remaining signals of the carbon atoms of the starting ligand could be associated a set of the corresponding signals of the homologous carbon atoms in the mercury complex (table 3).

Table 3: NMR data of ligand and it metal complex

N° Carbon	**Chemical shift (ppm)**			
	Complex		**Ligand**	
	^{13}C-NMR	^{1}H-NMR	^{13}C-NMR	^{1}H-NMR
1	151.57, 151.30, 151.17, 148.30		134.9	
3	160.12, 158.67, 158.02, 157.31		158.2	8.85 (NH_2)
3a	101.40, 101.17, 100.9, 99.82		100.3	
4	184.70, 170.07, 169.39, 164.21		168.2	
5a	153.56, 153.28, 153.22, 153.16		151.9	
6	118.63, 118.57, 117.78, 117.66	6.95	117.2	7.35 (1H)
7	135.83, 135.77, 131.10, 130.85	7.84	131.5	7.59 (1H)
8	127.70, 127.21, 125.81, 125.36	7.21	125.1	7.45 (1H)
9	129.45, 127.70, 127.64, 127.58	8.76	128.8	8.84 (1H)
9a	117.56, 117.49, 117.43, 117.28		117.0	
9b	139.55, 137.52, 136.06 ; 135.89		133.0	
1’	156.47, 155.45, 155.00 ; 154,38		152.6	
2’ et 6’	125.96, 125.87	8.01	121.7	7.74 (1H)
3’ et 5’	130.58, 130.33	7.53	129.4	7.54 (1H)
4’	130.16, 129.98, 129.84, 129.65	7.48	129	7.40 (1H)

Elemental Analysis

The elemental analysis data of the ligand and the complex are given in table 4 below.

Table 4: elemental analysis data of ligand and complex

	C	H	N	S
Ligand	**63.54** (63.43)	**3.45** (3.34)	**13.08** (13.14)	**9.98** (9.75)
Complex	**35.03** (35.33)	**1.73** (1.68)	**9.61** (9.21)	**5.50** (5.21)

Bold = calculated; in bracket = found

The elemental analysis results are in agreement with the gross formula $C_{68}H_{40}O_{20}N_{16}S_4Hg_4$ for the complex.

XRD patterns of complex

The XRD patterns (Figure 1) of this complex shows many peaks well individualized. This observation is due to the good crystal structure of the complex in which atoms are organized in a regular manner.

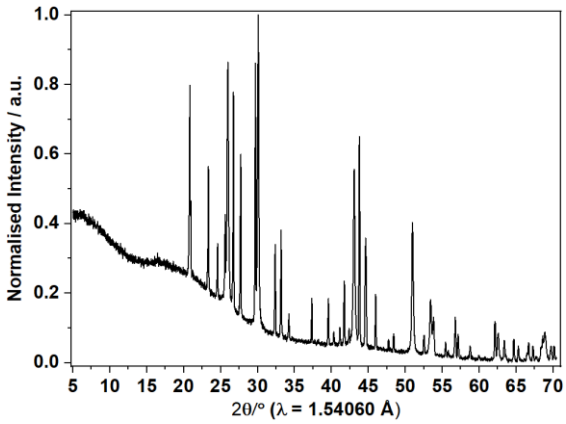


Figure 1: Powder XRD patterns of complex 4

From the above data and on the basis of relevant literature reports [18, 19, 20, 21] the structure shown in figure 2 was assigned to the metal complex **4**. It was assumed that the ligand is coordinated to a central mercury ion in a bidentate pattern through the bindings of the metal to the O atom of the C=O and the N atom of NH_2, giving a six member ring coordination unit. Four units of the coordinated ligand are interconnected by four bridging units of –O-N(=O)-O- through a bidentate binding way of each four mercury ions to the two external O atoms covalently bonded to the central N atoms of two nitrate groups. The larger ring (16-member) in the structure thus constructed contains four mercury atoms and four bridging nitrate groups. For stability reasons, the geometry about the mercury atoms should be a tetrahedral distorted one with the N=O orientations alternating above and under the mean plan of the complex molecule as shown on figure 3.

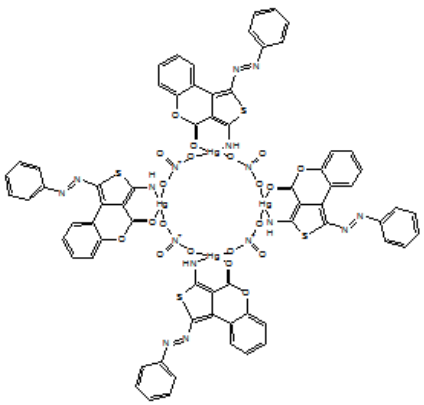


Figure 2: Structural representation of the mercury complex.

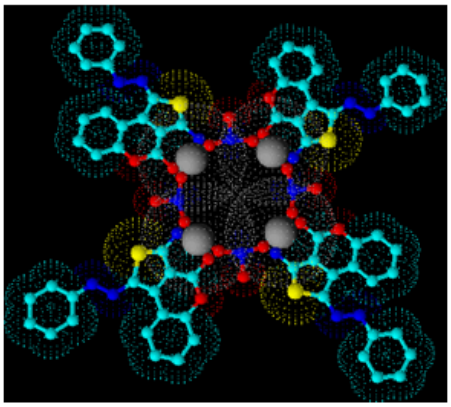


Figure 3: 3D-View of the coordination spheres of complex **4** drawn with ACD/Labs 3D viewer (freeware)

Antimicrobial properties.

The antimicrobial properties of the mercury complexes have been reported by several investigators [22, 23]. The coordination compounds, the 2-aminothiophenes and the diazo compounds have several interesting applications in various fields. In the pharmaceutical industry they are used as precursors in the search for new drugs. On the other hand, coordination compounds, 2-aminothiophene and their derivatives have various biological properties including antibacterial, antifungal, antidiabetic, anti-inflammatory activities [24-27] and anticancer activity [3]. This is why we have combined 2-aminothiophene derivatives and the diazo bridge, both chelated with a metal ion, in the same molecule. The aim is the hope to obtain biologically more active molecules that can be used in the pharmaceutical industries or which have other properties. Allured by these observations, biological experiments for evaluating the antibacterial and antifungal activities of the ligand and the complex have been performed using reported method [2-4]. The screening data obtained for some pathogenic bacteria and fungi are presented in Table 5.

These results show that the complex is significantly more active against certain bacteria (*Escherichia Coli*, *Staphylococcus aureus* and *Providencia stuartii*) and yeasts (*Candida albicans*) than the ligand alone. On the other hand, it appears from these results that the complex is more active than the reference drugs with regard to bacteria such as *EscherichiaColi*, *Staphylococcus aureus* and *Providencia stuartii*.

Table 5: Antibacterial and antifungal activities of ligand **3** and it metal complex **4**.

		Compounds		
Micro-organisms		Complex	Ligand	Standard Drug
Escherichia Coli ATCC 8739	MIC	8	256	64
	MBC	8	256	128
	MBC/MIC	1	1	2
Providencia stuartii ATCC 29916	MIC	8	128	64
	MBC	8	128	64
	MBC/MIC	1	1	1
Klebsiella Pneumoniae ATCC 11296	MIC	128	256	16
	MBC	256	256	64
	MBC/MIC	2	1	4
Staphylococcus aureus	MIC	8	64	128
	MBC	8	64	128
	MBC/MIC	1	1	1
Candida albicans ATCC 9002	MIC	256	128	8
	MBC	256	256	8
	MBC/MIC	1	2	1
Candida parapsilosis ATCC 22019	MIC	128	16	16
	MBC	128	16	16
	MBC/MIC	1	1	1
Candida parapsilosis	MIC	256	256	2
	MBC	>256	>256	2
	MBC/MIC	Inactive	Inactive	1

Ligand and complex was not active at concentrations up to 256 µg/mL; chloramphenicol and nystatin were used as standard drugs for bacteria and yeasts respectively; MIC: Minimum Inhibitory Concentration; MBC: Minimum Bactericidal Concentration

This increase in activity after chelation would be due to the presence of the metal ion in this molecule. This behavior had already been described in the literature with lanthanide complexes where it was observed that the activity of the complexes obtained was significantly higher compared to that of the starting ligand [28].

The increased activity in this complex is explained by the fact that chelation considerably reduces the polarity of the metal ion due to the sharing of the positive charge with the ligand donor groups. Moreover, the reduction of polarity increases the lipophilic character of the complexes and the interaction between the metal ion and the lipids is favored (because the cell membranes are essentially lipophilic). This can therefore lead to a failure of the permeability barrier of the cell resulting in a disturbance on the normal process of the cell. [29]

IV. Conclusion

In summary, we have synthesized and fully characterized a new Metal Organic Framework (MOF) containing Hg(II) with 3-amino-1-[2-phenyldiazenyl]-4H-thieno[3, 4-c]chromen-4-one at room temperature. Powder XRD confirms the crystalline nature of the complex obtained. Antimicrobial screening's results showed that complex was less antifungal than antibacterial in reference to standard drug. However, the antibacterial activities of the complex and ligand on *E. Coli, P. Stuartii, K. Pneumoniae* and *S. Aureus* were found to be equal or higher to that of chloramphenicol used as reference drug; highlighting their good antibacterial potency. In the case of *K. Pneumoniae*, the coordination process seems to have reduced to 50% the activity with the transformation of the ligand into the complex. In contrast, *C. Albicans* appeared to be 50% more sensitive with the same process. The overall results of this study indicated that the novel coordination compound exhibited prominent antibacterial and antifungal activities.

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