Journal of Molecular Structure 1242 (2021) 130812

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstr

Bis(Substituted Phenylamino)Glyoxime derivatives: Synthesis, characterization, and antimicrobial evaluation

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ARTICLE INFO

Article history:
Received 3 April 2021
Revised 25 May 2021
Accepted 28 May 2021
Available online 2 June 2021

Keywords:
Glyoxime
Oxime
vic-Dioximes
Antibacterial activity
Antifungal activity

ABSTRACT

In present work, a set of bis(substituted phenylamino) glyoxime derivatives are presented by the dropwise addition of corresponding primary aryl amines to the dichloroglyoxime (**1**). Reactions of corresponding primary aryl amines containing various substituents in different positions with dichloroglyoxime (**1**) gave thirteen compounds. The structural characterization of a set of bis(substituted phenylamino) glyoxime derivatives have been performed on the basis of FTIR, mass, proton, and carbon NMR methods. The crystal structure of compound **3a** has been determined by X-ray diffraction on a single crystal. The NMR spectrum and X-ray data of **3a** show that two hydroxyl groups of dioxime situated at *anti* position. Furthermore, all of the synthesized compounds (**3a-m**) were tested for *in vitro* both antimicrobial activity. The minimal inhibitory concentrations (MICs) against 7 bacteria and 3 yeasts were also determined. Among them, compound **3f** was the most potent compound against *S. aureus* with the value of MIC = 9.76 μg/mL for the antibacterial activity, in addition to this, compound **3i** has a good potency against *S. aureus* and *C. tropicalis* (MIC = 78.12 μg/mL) for both antibacterial and antifungal activities, respectively.

1. Introduction

It has been a long time recognized that the *vic*-dioximes are the important class of amongst the organic compounds having highly versatile applications in a variety of fields, for instance, medicine and bioinorganic chemistry. [1-3] Since the reaction of dimethylglyoxime with Ni(II) was reported for the first time, the complexation studies of these derivatives have been extensively studied comprehensively by a number of scientists due to their utilization as catalysts in chemical processes, biological model compounds such as vitamin B_{12}, and analytical reagents. [4-10] Another good example of an application based on the *vic*-dioximes is relevant to environmental perspectives. To develop an efficacious extractant that has a considerable influence, especially in the extraction process, on the separation and extraction efficiency used for the removal, separation, and concentration of metal ions from aqueous solutions, *vic*-dioximes are highly useful synthon. For this purpose, many *vic*-dioximes possessing different substituents and their complexes with different metal ions have been obtained and their extraction features were searched by solvent extraction. [11, 12]

Oximes and their derivatives, which are frequently used in organic synthesis, have a functional role as intermediates in the preparation of various heterocyclic compounds. [15] Compounds of *vic*-dioxime with two substituents (R-NH-) in 1,2-positions are among the most attractive precursors that are used to synthesize (hetero)cyclic compounds. [13] *vic*-Dioximes with two substituents (R-NH-) in 1,2-positions containing two carbonyl functional groups, play an important role in many areas. [14, 15] Given the unique chemical and structural properties of those compounds, they have been extensively investigated and applied in material science and medicinal chemistry. [15] *Vic*-dioximes containing slightly acidic hydroxy groups and slightly basic azomethine groups are amphoteric chelates that can form complexes of various types such as square-pyramidal and octahedral with transition metal ions [14]. The investigation of their coordination chemistry has been exceedingly amplified for different purposes mentioned above. [14, 16-19] Additionally, there are some important reports concerning antimicrobial activities of bis(substituted phenylamino)glyoxime deriva-

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https://doi.org/10.1016/j.molstruc.2021.130812
0022-2860/

tives and their complexes in the literature. [20-22] It has sparked interest in the exploration of their activities in bacteria and fungi, two main types of pathogenic organisms, causing infectious diseases that are one of the ten main reasons for mortality in the world. [23] What is currently the most needed is to make an efficient search for candidates to be assayed as antibacterial agents and highlight the role of organic compounds with a specific skeletons in their activities that have not been explored. Therefore, for a better understanding of antimicrobial properties of bis(substituted phenylamino)glyoxime compounds, this study is going to be a preliminary investigation for the synthesis of new derivatives and this will open the attractive perspectives for the design of new antimicrobial agents containing *vic*-dioximes.

The first aim of this work is to prepare novel bis(substituted phenylamino)glyoximes (**3a-m**) *via* the reaction of primary aryl amines with various substituents in different positions and dichloroglyoxime (**1**). The second aim is to confirm their structures by spectral data obtained X-ray single crystal, FTIR, NMR, and Mass spectrometers. The third aim is to understand their potential for antimicrobial properties as well.

2. Materials and methods

2.1. Materials and general techniques

General experimental method: All reactions were carried out in oven-dried glassware. The starting material dichloroglyoxime (**1**) for this research was prepared as reported previously. [24]

Reagents and solvents: All reagents used in the reactions and organic solvents used in the purification step were purchased from commercially available sources and they were used as sold.

Chromatography: Thin layer chromatography (TLC) was applied to monitor the reactions by using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under UV light (254 nm).

***Melting points*:** Melting points (mp) were obtained on a Buchi B-540 melting point without being corrected.

Mass spectra: Mass spectra were measured in ESI mode on a Thermo Finnigan LCQ Advantage MAX MS/MS spectrometer equipped or a BRUKER Microflex LT by MALDI-TOF technique *via* the addition of 1,8,9-anthracenetriol (DIT, dithranol) as matrix.

Infrared spectra: Infrared spectra were measured on Thermo Scientific Nicolet 6700 spectrometer or Alpha T FTIR spectrometer, and ATR on a Perkin Elmer Spectrum 100 Optical FT-IR Spectrometer.

NMR spectra*:* NMR spectra were recorded in DMSO-d_6 on a VarianUNITY INOVA spectrometer (500 MHz frequency for ^{1}H and 125 MHz frequency for ^{13}C NMR) in ppm. The coupling constants J are given in Hz.

X-Ray Diffraction Analysis: Data for the single crystal compound were obtained with Bruker APEX II QUAZAR three-circle diffractometer. Crystal structure validations and geometrical calculations were performed using the Platon software. [25] Mercury software [26] was used for visualization of the .cif files. The structure has been solved by the Bruker SHELXTL Software Package and refined using OLEX2.refine. [27, 28] The software used for molecular graphics: *OLEX2* 1.3 [29]; to prepare material for publication: *OLEX2* 1.3. [29] Data integration and reduction were carried out with SAINT. [30] The crystallographic and structure refinement data are summarized in Table 1. The selected bond lengths, torsion angles, bond angles, and hydrogen-bonding geometry are given in Tables 2-5. The crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, and CCDC reference number is 2072528 for **3a**. The data can be obtained available free of charge from http://www.ccdc.cam.ac.uk/conts/retrieving.html.

Table 1
Crystallographic data for the **3a**.

Identification code	**3a**
Chemical formula	$C_{16}H_{18}N_4O_4$
Formula weight (g mol^{-1})	330.346
Temperature (K)	273.15
Radiation λ (Å)	0.71073
Crystal system	Orthorhombic
Space groups, Z 4	$P2_12_12_1$, 4
Unit cell dimensions (Å)	a = 7.1630(15) b = 15.071(4) c = 15.305(3) α, β, γ = 90°
Volume (Å^3)	1652.3(6)
Crystal sizes (mm)	0.214 × 0.178 × 0.138
dcalc (g cm^{-3})	1.328
Absorption coefficient (mm^{-1})	0.098
Absorption correction, Tmin, Tmax	none, 0.979, 0.987
θ_{max}, deg	25.010
Goodness-of-fit on F^2	1.045
Index ranges	-8 ≤ h ≤ 8, -17 ≤ k ≤ 17, -18 ≤ l ≤ 10
Reflections collected	6890
Independent reflections	2872 [Rint = 0.0351, Rsigma = 0.0524]
Final R indices [I > 2σ(I)]	R1 = 0.0431, wR2 = 0.0925
R indices (all data)	R1 = 0.0658, wR2 = 0.1038
Refinement method	'\f and \w scans'
Data/restraints/parameters	2872/0/228
Largest diff. peak and hole (eÅ^{-3})	0.18/-0.19

Table 2
Selected bond lengths (Å) with e.s.d (in parentheses) for **3a**.

3a			
O2-N1	1.426(3)	C10-C15	1.392(4)
O3-N2	1.416(2)	C10-C11	1.373(4)
O4-C15	1.357(3)	C2-C3	1.379(4)
O4-C16	1.422(3)	C15-C14	1.385(4)
N1-C8	1.284(3)	C11-C12	1.387(4)
N2-C9	1.289(3)	C7-C2	1.384(3)
N4-C8	1.360(3)	C6-C5	1.381(4)
N4-C7	1.410(3)	C14-C13	1.370(5)
O1-C2	1.360(3)	C12-C13	1.372(4)
O1-C1	1.419(4)	C3-C4	1.377(5)
N3-C9	1.359(3)	C5-C4	1.363(5)
N3-C10	1.415(3)	C6-C5	1.381(4)
C8-C9	1.482(3)	C14-C13	1.370(5)
C7-C2	1.384(3)	C12-C13	1.372(4)
C7-C6	1.381(4)	C3-C4	1.377(5)

2.2. Experimental procedures, analytical, and spectroscopic data

2.2.1. Nucleophilic reaction between dichloroglyoxime and substituted aryl amines

General procedure.

Primary aryl amine (2.2 equiv.) in 3 mL ethanol was added into two necked RB flask that contained a solution of dichloroglyoxime (0.393 g, 2.5 mmol) in 3 mL ethanol (-10 °C). After triethylamine was added, the reaction was allowed to proceed with continued stirring of the solution at room temperature by the time TLC showed the absence of the starting materials (3-4 hours). The resultant solid was gathered by vacuum filtration to give the products (**3a-m**).

N^1,N^2-Dihydroxy-N^1,N^2-bis(2-methoxyphenyl)oxalamidine **(3a).**

It was synthesized from dichloroglyoxime (**1**) and 2-methoxybenzenamine (**2a**) as cream powder according to the general procedure. Yield: 0.63 g, 76%. IR and ^{1}H NMR spectra were found to be identical with the ones described in literature.

[31] FTIR (ATR): $\upsilon\ \overline{\nu}$ = 3400, 3296, 3067, 3022, 2952, 2833, 1655, 1621, 1597, 1512, 958, 927 cm^{-1}; ^1H NMR (500 MHz, *DMSO-d_6*): δ = 10.75 (s, 2H, -OH), 7.53 (s, 2H, -NH), 6.87-6.83 (m, 6H, Ar-H), 6.77-6.73 (m, 2H, Ar-H), 3.70 (s, 6H, -OCH_3) ppm; ^{13}C NMR (125 MHz, *DMSO-d_6*): δ = 148.5, 142.4, 128.2, 122.3, 120.9, 117.2, 111.2, 56.1 ppm; MS MALDI TOF: (m/z) = 331 $(M+H)^+$, Exact Mass. for $C_{16}H_{18}N_4O_4$ (330.13).

N¹',N²'-Dihydroxy-N¹,N²-bis(4-methoxyphenyl)oxalamidine **(3b).**

It was synthesized from dichloroglyoxime (**1**) and 4-methoxybenzenamine (**2b**) as light pink powder according to the general procedure. Yield: 0.53 g, 64%. IR and ^1H NMR spectra were found to be identical with the ones described in literature. [32] FTIR (ATR): $\upsilon\ \overline{\nu}$ = 3344, 3278, 3011, 2956, 2930, 2833, 1660, 1628, 934 cm^{-1}; ^1H NMR (500 MHz, *DMSO-d_6*): δ = 10.15 (s, 2H, -OH), 7.82 (s, 2H, -NH), 6.71 (d, *J: 9.2 Hz*, 4H, -OCH_2), 6.67 (d, *J: 9.2 Hz*, 4H, -OCH_2), 3.67 (s, 6H, -OCH_3) ppm; ^{13}C NMR (125 MHz, *DMSO-d_6*): δ = 155.0, 143.9, 133.4, 121.8, 114.0, 55.6 ppm; MS MALDI TOF: (m/z) = 330 $(M)^+$, Exact Mass for $C_{16}H_{18}N_4O_4$ (330.13).

N¹,N²-Bis(2-ethoxyphenyl)-N¹',N²'-dihydroxyoxalamidine **(3c).**

It was synthesized from dichloroglyoxime (**1**) and 2-ethoxybenzenamine (**2c**) as cream powder according to the general procedure. Yield: 0.48 g, 53%; M.p: 205-206 °C. FTIR (ATR): $\upsilon\ \overline{\nu}$ = 3376, 3240, 2979, 2903, 1625, 1510, 934 cm^{-1}; ^1H NMR (500 MHz, *DMSO-d_6*): δ = 10.75 (s, 2H, -OH), 7.54 (s, 2H, -NH), 6.88-6.84 (m, 2H, Ar-H), 6.82-6.79 (m, 4H, Ar-H), 6.77-6.71 (m, 2H, Ar-H), 3.89 (q, J: 6.9 *Hz*, 4H, -OCH2), 1.29 (t, *J:* 6.9 *Hz,* 6H, -CH_3) ppm; ^{13}C NMR (125 MHz, *DMSO-d_6*): δ = 147.6, 142.4, 128.4, 122.2, 120.8, 117.1, 112.3, 64.3, 15.1 ppm; MS (ESI+): *m/z* (%) = 359 (100, $(M+H)^+$), Exact Mass for $C_{18}H_{22}N_4O_4$ (358.16).

N¹,N²-Bis(4-ethoxyphenyl)-N¹',N²'-dihydroxyoxalamidine **(3d).**

It was synthesized from dichloroglyoxime (**1**) and 4-ethoxybenzenamine (**2d**) as off-white powder according to the general procedure. Yield: 0.58 g, 81%; M.p: 169 °C. FTIR (ATR): $\upsilon\ \overline{\nu}$ = 3371, 3173, 3060, 2975, 2930, 2885, 2811, 1636, 1619, 969, 921 cm^{-1}. ^1H NMR (500 MHz, *DMSO-d_6*): δ = 10.14 (s, 2H, -OH), 7.81 (s, 2H, -NH), 6.69 (d, *J: 9.2 Hz*, 4H, -OCH_2), 6.65 (d, *J: 9.2 Hz*, 4H, -OCH_2), 3.92 (q, *J: 6.9 Hz*, 4H, -OCH_2), 1.28 (t, *J: 6.9 Hz*, 6H, -CH_3) ppm; ^{13}C NMR (125 MHz, *DMSO-d_6*): δ = 154.2, 143.9, 133.3, 121.8, 114.5, 63.5, 15.2 ppm; MS MALDI TOF: (m/z) = 358 $(M)^+$, Exact Mass for $C_{18}H_{22}N_4O_4$ (358.16).

N¹,N²-Bis(4-butoxyphenyl)-N¹',N²'-dihydroxyoxalamidine **(3e).**

It was synthesized from dichloroglyoxime (**1**) and 4-butoxybenzenamine (**2e**) as off-green powder according to the general procedure. Yield: 0.29 g, 91%; M.p: 136-137 °C. FTIR (ATR): $\upsilon\ \overline{\nu}$ = 3366, 3189, 2972, 2905, 1646, 1620, 1509, 890 cm^{-1}; ^1H NMR (500 MHz, *DMSO-d_6*): δ = 10.14 (s, 2H, -OH), 7.80 (s, 2H, -NH), 6.69 (d, *J: 9.2 Hz*, 4H, -OCH_2), 6.65 (d, *J: 9.2 Hz*, 4H, -OCH_2), 3.86 (t, *J: 6.5 Hz*, 4H, -OCH_2), 1.68-1.62 (m, 4H, -CH_2), 1.46-1.38 (m, 4H, -CH_2), 0.92 (t, *J: 7.32 Hz*, 6H, -CH_3) ppm; ^{13}C NMR (125 MHz, *DMSO-d_6*): δ = 154.4, 143.9, 133.3, 121.8, 114.5, 67.7, 31.3, 19.2, 14.2 ppm; MS (ESI+): *m/z* (%) = 415 (100, $(M+H)^+$), Exact Mass for $C_{22}H_{30}N_4O_4$ (414.23).

N¹',N²'-Dihydroxy-N¹,N²-bis(2,4-dimethoxyphenyl)oxalamidine **(3f).**

It was synthesized from dichloroglyoxime (**1**) and 2,4-dimethoxybenzenamine (**2f**) as brown powder according to the general procedure. Yield: 0.78 g, 80%; M.p: 170 °C. FTIR (ATR): $\upsilon\ \overline{\nu}$ = 3404, 3299, 3015, 2959, 2833, 1653, 1616, 1596, 955, 940 cm^{-1}; ^1H NMR (500 MHz, *DMSO-d_6*): δ = 10.45 (s, 2H, -OH), 7.11 (s, 2H, -NH), 6.79 (d, *J: 8.8 Hz*, 2H, Ar-H), 6.40 (d, *J: 2.5 Hz*, 2H, Ar-H), 6.35 (dd, *J: 8.8, 2.5 Hz*, 2H, Ar-H), 3.68 (s, 6H, -OCH_3), 3.63 (s, 6H, -OCH_3) ppm; ^{13}C NMR (125 MHz, *DMSO-d_6*): δ = 155.8, 150.3, 143.4, 121.7, 119.4, 104.4, 99.0, 56.0, 55.7 ppm; MS MALDI TOF: (m/z) = 390 $(M)^+$, Exact Mass for $C_{18}H_{22}N_4O_6$ (390.15).

N¹',N²'-Dihydroxy-N¹,N²-bis(3,4,5-trimethoxyphenyl)oxalamidine **(3g).**

It was synthesized from dichloroglyoxime (**1**) and 3,4,5-trimethoxybenzenamine (**2g**) as white powder according to the general procedure. Yield: 0.48 g, 40%; M.p: 211-212 °C. FTIR (ATR): $\upsilon\ \overline{\nu}$ = 3407, 3348, 2978, 2944, 2848, 2822, 1653, 1631, 1594, 940, 918 cm^{-1}; ^1H NMR (500 MHz, *DMSO-d_6*): δ = 10.34 (s, 2H, -OH), 7.98 (s, 2H, -NH), 6.13 (s, 4H, Ar-H), 3.60 (s, 12H, -OCH_3), 3.56 (s, 6H, -OCH_3) ppm; ^{13}C NMR (125 MHz, *DMSO-d_6*): δ = 152.7, 144.0, 136.0, 133.0, 98.3, 60.6, 55.9 ppm; MS MALDI TOF: (m/z) = 451 $(M+H)^+$, Exact Mass for $C_{20}H_{26}N_4O_8$ (450.18).

N¹,N²-Bis(2,5-diethoxyphenyl)-N¹',N²'-dihydroxyoxalamidine **(3h).**

It was synthesized from dichloroglyoxime (**1**) and 2,5-diethoxybenzenamine (**2h**) as black powder according to the general procedure. Yield: 0.77 g, 76%; M.p: 137-138 °C. FTIR (ATR): $\upsilon\ \overline{\nu}$ = 3393, 3232, 3096, 2980, 2937, 2878, 1598, 931 cm^{-1}; ^1H NMR (500 MHz, *DMSO-d_6*): δ = 10.88 (s, 2H, -OH), 7.61 (s, 2H, -NH), 6.71 (d, *J: 8.8 Hz*, 2H, Ar-H), 6.51 (d, *J: 2.5 Hz,* 2H, -Ar-H), 6.32 (dd, *J: 8.8, 2.5 Hz*, 2H, Ar-H), 3.95-3.75 (m, 8H, -OCH_2), 1.38-1.30 (m, 12H, -CH_3) ppm; ^{13}C NMR (125 MHz, *DMSO-d_6*): δ = 153.0, 142.3, 141.5, 129.1, 113.7, 107.0, 103.8, 65.1, 63.4, 15.2, 15.1 ppm; MS MALDI TOF: (m/z) = 447 $(M+H)^+$, Exact Mass for $C_{22}H_{30}N_4O_6$ (446.22).

N¹,N²-Di(benzo [d] [1,3]dioxol-5-yl)-N¹',N²'-dihydroxyoxalamidine **(3i).**

It was synthesized from dichloroglyoxime (**1**) and 3,4-(methylenedioxy)aniline (**2i**) as grey powder according to the general procedure. Yield: 0.77 g, 86%; M.p: 210 °C. FTIR (ATR): $\upsilon\ \overline{\nu}$ = 3374, 3178, 3115, 2893, 2793, 1630, 1487, 1435, 928 cm^{-1}; ^1H NMR (500 MHz, *DMSO-d_6*): δ = 10.26 (s, 2H, -OH), 7.95 (s, 2H, -NH), 6.64 (d, *J: 8.3 Hz*, 2H, Ar-H), 6.37 (d, *J: 2.2 Hz*, 2H, Ar-H), 6.25 (dd, *J: 8.3, 2.2 Hz*, 2H, Ar-H), 5.90 (s, 4H, -OCH_2) ppm; ^{13}C NMR (125 MHz, *DMSO-d_6*): δ = 147.3, 143.8, 142.6, 134.7, 113.0, 108.0, 102.6, 101.1 ppm; MS MALDI TOF: (m/z) = 359 $(M+H)^+$, Exact Mass for $C_{16}H_{14}N_4O_6$ (358.09).

N¹-(2,3-Dihydrobenzo [b] [1,4]dioxin-6-yl)-N²-(2,3-dihydrobenzo [b] [1,4]dioxin-7-yl)-N¹',N²'-dihydroxyoxalamidine **(3j).**

It was synthesized from dichloroglyoxime (**1**) and 1,4-benzodioxan-6-amine (**2j**) as cream powder according to the general procedure. Yield: 0.62 g, 64%; M.p: 141-142 °C. FTIR (ATR): $\upsilon\ \overline{\nu}$ = 3667, 3341, 3202, 2979, 2904, 1607, 1506, 1062, 888 cm^{-1}; ^1H NMR (500 MHz, *DMSO-d_6*): δ = 10.20 (s, 2H, -OH), 7.87 (s, 2H, -NH), 6.58-6.56 (m, 2H, Ar-H), 6.38-6.31 (m, 4H, -ArH), 4.17-4.12 (m, 8H, -OCH_2CH_2O-) ppm; ^{13}C NMR (125 MHz, *DMSO-d_6*): δ = 143.6, 143.2, 138.9, 134.0, 116.7, 113.4, 109.3, 64.7, 64.2 ppm; MS (ESI+): *m/z* (%) = 387 (100, $(M+H)^+$), Exact Mass for $C_{18}H_{18}N_4O_6$ (386.12).

N¹',N²'-Dihydroxy-N¹,N²-bis(2-isopropylphenyl)oxalamidine **(3k).**

It was synthesized from dichloroglyoxime (**1**) and 2-isopropylbenzenamine (**2k**) as brown powder according to the general procedure. Yield: 0.57 g, 64%; M.p: 166-167 °C. FTIR (ATR): $\upsilon\ \overline{\nu}$ = 3667, 3404, 3071, 3170, 2966, 2905, 1643, 1596, 947 cm^{-1}; ^1H NMR (500 MHz, *DMSO-d_6*): δ = 10.65 (s, 2H, -OH), 7.06-6.92 (m, 10H, Ar-H and NH), 2.50-2.43 (m, 2H, -CH), 0.84 (d, *J: 6.8 Hz*, 12H, -CH_3) ppm; ^{13}C NMR (125 MHz, *DMSO-d_6*): δ = 144.2, 139.0, 136.3, 125.7, 123.8, 121.2, 115.2, 27.0, 22.9 ppm;

MS (ESI+): *m/z* (%) = 354 (100, $(M)^+$), Exact Mass for $C_{20}H_{26}N_4O_2$ (354.21).

N^1',N^2'-Dihydroxy-N^1,N^2-bis(4-isopropylphenyl)oxalamidine **(3l).**

It was synthesized from dichloroglyoxime (**1**) and 4-isopropylbenzenamine (**2l**) as light brown powder according to the general procedure. Yield: 0.7 g, 79%; M.p: 116-118 °C. FTIR (ATR): $\upsilon\ \overline{\nu}$ = 3667, 3380, 3179, 2964, 2905, 1604, 1512, 1056, 950 cm^{-1}; ^1H NMR (500 MHz, *DMSO-d_6*): δ = 10.31 (s, 2H, -OH), 8.01 (s, 2H, -NH), 6.93 (d, *J: 8.5 Hz,* 4H, Ar-H), 6.73 (d, *J: 8.6 Hz,* 4H, Ar-H), 2.76 (p, *J: 6.8 Hz*, 2H, -CH), 1.14 (d, *J: 6.8 Hz,* 12H, $-CH_3$) ppm. ^{13}C NMR (125 MHz, *DMSO-d_6*): δ = 143.3, 141.8, 137.9, 126.5, 126.3, 119.7, 33.2, 33.0, 24.5, 24.4 ppm; MS (ESI+): *m/z* (%) = 355 (100, $(M+H)^+$), Exact Mass for $C_{20}H_{26}N_4O_2$ (354.21).

N^1,N^2-Bis(4-(diethylamino)phenyl)-N^1',N^2'-dihydroxyoxalamidine **(3m).**

It was synthesized from dichloroglyoxime (**1**) and 4-diethylamino benzenamine (**2m**) as off-white powder according to the general procedure. Yield: 0.99 g, 95%; M.p: 209 °C. FTIR (ATR): $\upsilon\ \overline{\nu}$ = 3304, 3107, 2974, 2704, 1643, 944 cm^{-1}; ^1H NMR (500 MHz, *DMSO-d_6*): δ = 9.96 (s, 2H, -OH), 7.53 (s, 2H, -NH), 6.66 (d, *J: 9.0 Hz, 4*H, Ar-H), 6.44 (d, *J: 9.0 Hz, 4*H, Ar-H), 3.23 (q, *J: 6.8 Hz,* 8H, Ar-H), 1.03 (t, *J: 6.8 Hz,* 12H, $-CH_3$) ppm; ^{13}C NMR (125 MHz, *DMSO-d_6*): δ(ppm) = 144.5, 143.9, 129.3, 122.5, 112.6, 44.4, 12.8 ppm; MS MALDI TOF: (m/z) = 410 $(M-2H)^+$, Exact Mass for $C_{22}H_{32}N_6O_2$ (412.26).

2.3. In vitro *antimicrobial activity*

2.3.1. Determination of Minimum Inhibitory Concentrations (MIC)

The microbroth dilutions technique was performed to determine antimicrobial activity against *Staphylococcus aureus* ATCC 29213, *Staphylococcus epidermidis* ATCC 12228, *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 4352, *Pseudomonas aeruginosa* ATCC 27853, *Proteus mirabilis* ATCC 14153, *Enterococcus faecalis* ATCC 29212, *Candida albicans* ATCC 10231, *Candida parapsilosis* ATCC 22019, and *Candida tropicalis* ATCC 750 according to the Clinical Laboratory Standards Institute (CLSI) recommendations. [33, 34] Mueller-Hinton broth for bacteria and RPMI-1640 medium for yeast strain were used as the test medium. Serial twofold dilutions ranging from 2500 µg/mL to 4.88 µg/mL were prepared in the medium. The inoculum was prepared using a 4-6 h broth culture of each bacteria type and 24 h culture of yeast strains adjusted to a turbidity equivalent to 0.5 McFarland standard, diluted in broth media to give a final concentration of 5×10^5 cfu/mL for bacteria and 5×10^3 cfu/mL for yeast in the test tray. The trays were covered and placed into plastic bags to prevent evaporation. The trays containing Mueller-Hinton broth were incubated at 35°C for 18-20 h while the trays containing RPMI-1640 medium were incubated at 35°C for 46–50 h. The MIC was defined as the lowest concentration of compound giving complete inhibition of visible growth. As a control, antimicrobial effects of the solvents were investigated against test microorganisms. According to the values of the controls, the results were evaluated. The MIC values of the compounds are shown in Table 6.

3. Results and discussion

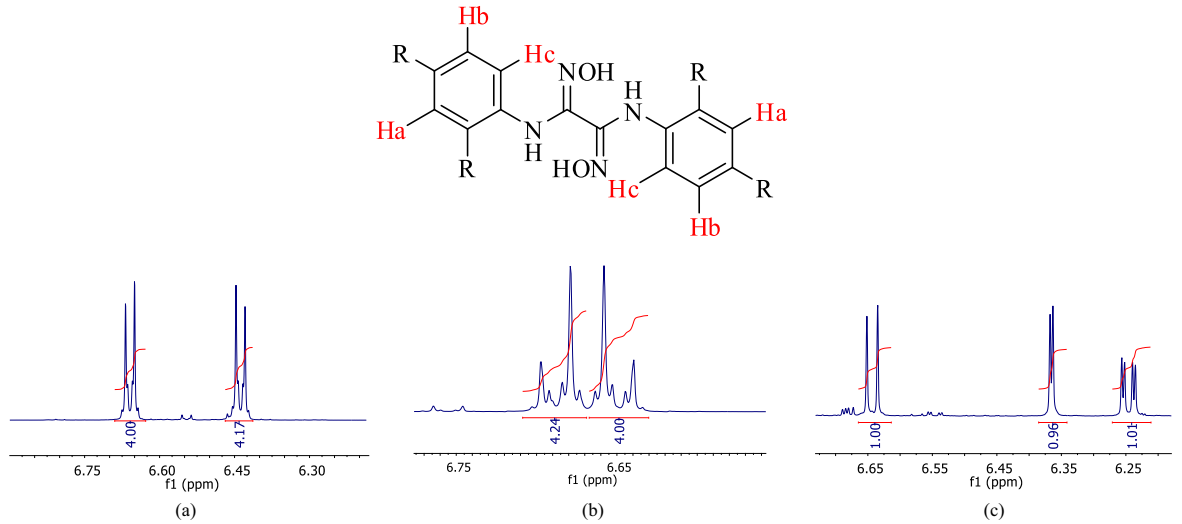
3.1. Chemistry

The starting material dichloroglyoxime (**1**) for this study was prepared as reported previously, following a modified method of van der Peet shown in Scheme 1. [24] The glyoxal (40% w/v) was reacted with hydroxylamine hydrochloride in the presence of triethylamine to prepare glyoxime in water at -10 °C. After this step, we have used *N*-Chlorosuccinimide in portions for chlorination of glyoxime in order to obtain dichloroglyoxime (**1**) in DMF at -10 °C as reported earlier. [24] Thirteen different bis(substituted phenylamino) glyoxime compounds (**3a-m**) have been synthesized which are examples of substituted *vic*-dioximes and summarized in Scheme 2. These derivatives were obtained according to the literature by the reactions of a wide range of primary aryl amines bearing divergent substituents with dichloroglyoxime (**1**) in ethanol at -10 °C. In most cases, the products obtained were solid in good yields and could be collected by filtration as the only purification method. ^1H and ^{13}C NMR, FTIR, and MS spectral data were used to determine the structures of these new compounds given in the Experimental Section.

FTIR data provide evidence for principal functional groups on the structure of the bis(substituted phenylamino)glyoxime derivatives (**3a-m**). Some of the characteristic bands such as OH and NH vibrations have been observed for these compounds. [17] In the FTIR spectral data of the synthesized compounds in this paper, the bands at expected areas pertain to N-H and O-H stretching vibrations, respectively, agreeing with previously reported values of the substituted *vic*-dioximes. [18]

Additional structural information can be deduced from both proton and carbon NMR spectra. The structures of **3a-m** are further confirmed by the study of proton magnetic resonance spectra in dimethyl sulfoxide-d_6 in which the hydroxyl and amine protons of these compounds resonated as two singlets at very similar values around 10.5 and 7.5 ppm, respectively. The aromatic protons of phenylamino moiety were observed at between 6.5-7.5 ppm. The proton-decoupled ^{13}C NMR spectral data were also in harmony with the structure of **3a-m**. The chemical shifts belong to the substituents on the aryl ring; methoxy, ethoxy, butoxy, *i*-propyl, *N,N*-diethyl, methylenedioxy, and ethylenedioxy derivatives were as expected in the ^{13}C NMR spectra of molecules. Assignment of the exchangeable protons of bis(substituted phenylamino)glyoxime was confirmed based on data from D_2O exchange, after the exchangeable protons peaks have clearly disappeared or decreased in intensity. From the present mass spectral data, it is concluded molecular ion peaks of glyoxime derivatives, which confirmed the proposed structures.

NMR spectra of the bis(substituted phenylamino)glyoxime compounds (***3a-m***) were taken first for structure determination. Bis(substituted phenylamino)glyoxime structure has NH and OH groups. The peaks around 9.5-10.5 ppm and 7.5-8.0 ppm belonged to the N-OH and NH group protons at ^1H NMR. As proof, when taken the D_2O exchange spectra of them, these peaks were disappeared. The compounds ***3b, 3d, 3e, 3l***, and ***3m*** had a common splitting pattern of two para-substituted rings in the aromatic region. Looked at the ^1H NMR of ***3l*** and ***3***, in the aromatic region, two doublet patterns were seen at around 6.93, and 6.73 ppm with J_{ortho} 8.5 Hz for ***3l*** and 6.66 ppm and 6.44 ppm with J_{ortho} 9.0 Hz for ***3m*** (Figure 1a). However, for the compound ***3b***, ***3d***, and ***3e*** these two doublets were too close to each other at 6.69 ppm (J_{ortho} 9.2) Hz) and 6.65 ppm (J_{ortho} 9.2 Hz) (Figure 1b). In the ^1H NMR spectra of ***3f, 3h***, and ***3i***, there were three splitting patterns of aromatic protons. It can be seen J_{ortho} and J_{meta} values for these structures. Proton **Ha** has no neighboring proton so it was just split by meta proton **Hb** as a doublet pattern with J_{meta} value around 2.5 Hz. Proton **Hb** was split by ortho proton **Hc** and meta proton **Ha** as a doublet of doublets (dd) pattern with J_{ortho} and J_{meta} values around 8.8 Hz and 2.5 Hz, respectively. Looked at proton **Hc**, it can be determined easily it was split by neighboring proton **Hb** as a doublet pattern with J_{ortho} value around 8.8 Hz (Figure 1c). In the ^{13}C NMR spectrum, the two symmetrically carbon of glyoxime backbone (C=NOH) were seen at around 156-143 ppm. The structure **3g** showed only two peaks of C_{arom}-OMe at around 144 and 136 ppm because of the symmetry even though it has three



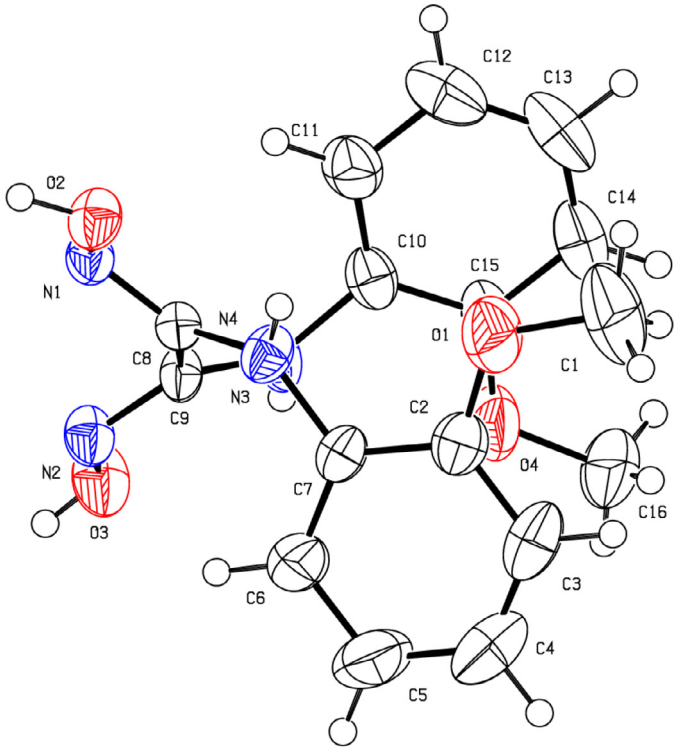
Fig; 1. The splitting patterns of substituted phenyl groups.

methoxy groups (OMe). The carbons (=CH) of para-alkoxy substituted phenyl groups were at around 113 and 122 ppm at ^{13}C NMR. When looked at the carbons (=CH) peaks of ortho-alkoxy substituted phenyl, the signals were seen at around 122, 120, 117, and 112 ppm as four peaks.

3.2. X-ray crystallographic analysis

An x-ray diffraction structural study was carried out on bis(substituted phenylamino)glyoxime on an automatic diffractometer using λ MoK radiation using 6890 reflections. The structure of **3a** was confirmed by X-ray diffraction analysis of a single crystal obtained by slow evaporation from an ethyl alcohol solution. The unit cell parameters of the crystal of ***3a*** compound, $C_{16}H_{18}N_4O_4$ at 273 K, which has three axes of different lengths (a = 7.1630, b = 15.071, c = 15.305) and whose axes intersect at 90 degrees (α, β, γ = 90°) with space groups $P2_12_12_1$, is compatible to ortothorhombic crystal system. In the X-Ray study, it is determined that the structure of ***3a*** has anti configurations of the oxime groups in symmetrically substituted glyoxime compound. The bond lengths of C8 -C9 (1.482 Å), N1-C8 (1.284 Å), and N2-C9 (1.289 Å) in the structure of ***3a*** are specific for glyoximes, featuring conjugation between the π systems (C=NOH) in the dioxime fragment. [35] The length of the N4-C8 and N3-C9 bonds between the sp^3 hybridized N and sp^2 hybridized C atoms in compound ***3a*** is about 1.360 Å, which is greater than 1.28 Å between the sp^2 hybridized N and the C atom of the disubstituted glyoxime compound. This is in line with the rule that bonds between sp^2-sp^2 hybridized atoms are shorter than bonds between sp^2-sp^3 hybridized atoms. The lengths of the aromatic C-C bonds in the phenyl group range from 1.363 to 1.402 Å. The O1-C1 and O4-C16 bond lengths of methoxy groups in the phenyl rings are 1.419 and 1.422 Å, respectively. The ORTEP drawing of the ***3a*** was reported at a 50% probability level in Figure 2. The crystallographic and structure refinement data for compound ***3a*** is summarized in Table 1. The molecular geometry with bond lengths and angles in the dioxime fragment is given in Tables 2 and 4. The C-C-C bond angles of the phenyl ring of ***3a*** are very close to 120.8º which supports structures involving sp^2 hybridized atoms.

The torsion angle of two phenyl amino groups bonded to the dioxime fragment is N4-C8-C9-N3 is -54.3º. Also, the dihedral angle between two oxime groups (N1-C8-C9-N2) is -59.3º. The N1-C8-C9-N3 and N2-C9-C8-N4 torsion angles are 124.0º and 122.4º, respectively. O2-N1-C8-NC9 (178.85º) and O3-N2-C9-C8 (-179.15º)

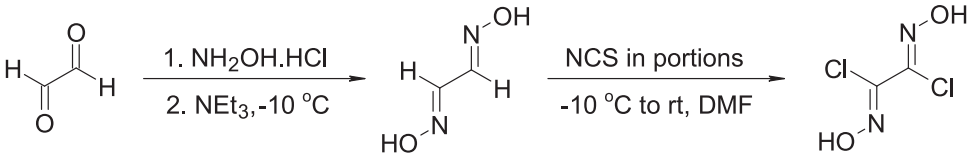


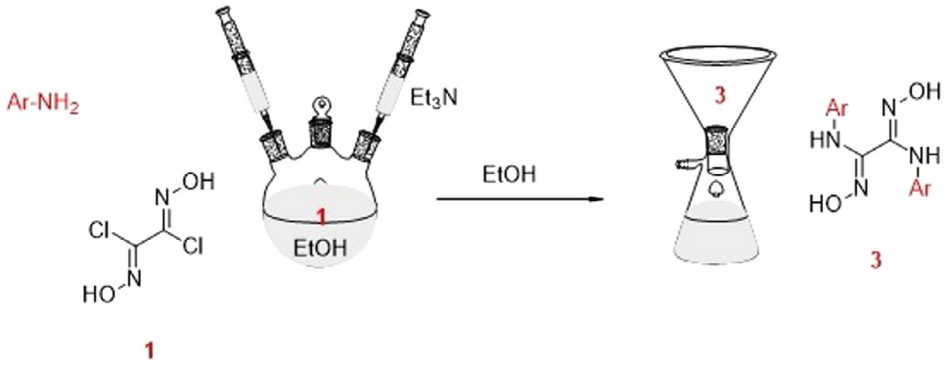
3a

Fig. 2. ORTEP drawings of the **3a** at 50% probability level.

show that two OH groups are anti position. Moreover, the NMR spectrum of **3a** shows OH peaks as a singlet at 10.75 ppm and this singlet peak proves the *anti*-configuration. [36] From the literature, this kind of isomeric structure is called *anti* (E,E). [14, 18, 37, 38] Some other torsion angles of compound **3a** given in Table 3 support the structure. In terms of bond distances and angles, the molecular geometry of ***3a*** is compatible with the expected.

In the structure of **3a**, there are hydrogen acceptor and donor groups. Therefore, the x-ray data shows possible both intermolecular and intramolecular hydrogen bonds. The corresponding distance and angle of hydrogen bonds are given in Table 5. All crystallo-





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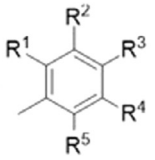

Compounds	R^1	R^2	R^3	R^4	R^5
3a	OMe	H	H	H	H
3b	H	H	OMe	H	H
3c	OEt	H	H	H	H
3d	H	H	OEt	H	H
3e	H	H	OBut	H	H
3f	OMe	H	OMe	H	H
3g	H	OMe	OMe	OMe	H
3h	OEt	H	H	OEt	H
3i	H	OCH_2O		H	H
3j	H	OCH_2CH_2O		H	H
3k	*i*-propyl	H	H	H	H
3l	H	H	*i*-propyl	H	H
3m	H	H	*N,N*-diethyl	H	H

graphic data of the compounds are presented in the supplementary material (Supplementary Material, SM).

3.3. Antimicrobial activity

All of the synthesized compounds (**3a-m**) were involved in a study to evaluate for their *in vitro* antimicrobial activity by comparing Ceftazidime, Cefuroxime-Na, Cefuroxime, Amikacin, Clotrimazole, and Amphotericin B. Tested Gram-negative were *P. aerugi-*

Table 3
Torsion angles (°) for **3a**.

3a			
O2-N1-C8-C9	178.95(17)	N1-C8-C9-N3	124.0 (2)
O2-N1-C8-N4	−2.9(2)	N2-C9-C8-N4	122.4(2)
O3-N2-C9-C8	-179.15 (18)	N4-C7-C2-C3	179.7(3)
O3-N2-C9-N3	-2.7 (2)	O1-C2-C3-C4	178.2(3)
N1-C8-N4-C7	159.0(2)	N4-C8-C9-N3	−54.3(2)
N2-C9-N3-C10	171.6(2)	O4-C15-C14-13	178.9(3)

Table 4
Selected bond angles (°) for with e.s.d (in parentheses) for **3a**.

3a			
C16-O4-C15	117.7(2)	C6-C7-C2	119.4(3)
C8-N1-O2	109.81(18)	C15-C10-N3	118.1(2)
C9-N2-O3	110.22(19)	C11-C10-C15	119.9(2)
C7-N4-C8	125.2(2)	C5-C4-C3	120.1(3)
C1-O1-C2	118.2(3)	C3-C2-O1	125.5(3)
C10-N3-C9	125.3(2)	C3-C2-C7	119.9(3)
N4-C8-N1	126.1(2)	C7-C2-O1	114.6(2)
C9-C8-N1	114.6(2)	C14-C15-O4	125.7(3)
C9-C8-N4	119.3(2)	C14-C15-C10	119.5(3)
N3-C9-N2	125.3(2)	C12-C11-C10	120.6(3)
C8-C9-N2	114.3(2)	C5-C6-C7	120.2(3)
C8-C9-N3	120.4(2)	C13-C14-C15	119.6(3)
C2-C7-N4	119.2(2)	C4-C3-C2	120.2(3)
C6-C7-N4	121.3(2)	C4-C5-C6	120.2(3)

Table 5
Hydrogen-bonding geometry (Å, °) for **3a**.

D-H…*A*	*D*-H	H…*A*	*D*…*A*	*D*-H…*A*
O2-H2…N1	0.90 (3)	2.56 (3)	3.132 (3)	122 (3)
O2-H2…N2	0.90 (3)	1.93 (3)	2.804 (3)	163 (3)
O3-H3…O2	0.820 (13)	1.984 (9)	2.783 (2)	165 (2)
N3-H3A…O3	0.860 (3)	2.247 (3)	2.572 (3)	102.4 (2)

nosa, E. coli, K. pneumoniae, and *P. mirabilis*, whereas Gram-positive bacteria were *S. aureus, S. epidermidis*, and *E. faecalis*. The tested fungi were *C. albicans, C. parapsilosis*, and *C. tropicalis*. The obtained results reflected variable antimicrobial activity and are given in Table 6.

Among the synthesized and tested compounds, compound **3f** had the best MIC value (MIC = 9.76 μg/mL) against *S. aureus*. In addition, **3i** showed good potency against *S. aureus* and *C. tropicalis* (MIC = 78.12 μg/mL). Both test-cultures *S. epidermidis* and *S. aureus* appeared to be susceptible to most of the synthesized compounds with MIC values of between 9.76–1250 μg/mL. The test-cultures *C. albicans* showed not to be susceptible to all of the synthesized compounds. The biological data also reveal that both compounds **3f** and **3i** were the most active among the synthesized compounds; they have both antibacterial and antifungal activities. Although **3m** did not show activity against fungi, it has moderate activity against two important pathogen microorganisms of the Gram-negative Enterobacteriaceae family (*Klebsiella pneumoniae* and *Escherichia coli*) and also Gram-positive microorganisms (*Staphylococcus aureus* and *Staphylococcus epidermidis*).

3.4. Structure-Activity Relationship (SAR) study

When we analyzed the structural features with their MIC values of the synthesized compounds by modification of various positions in the aryl amine moiety, the obtained results from the antibacterial activity are quite interesting because of the correlation against *S. aureus* strains. When all molecules were analyzed against the Gram-negative bacteria and the Gram-negative bacteria in addition to fungi, it seems difficult to abstract definite structure-activity re-

Table 6
In vitro antibacterial and antifungal activity results of the synthesized compounds.

		Microorganisms										
		Gram-negative Bacteria				Gram-positive Bacteria			Fungi			
		P. aeruginosa	*E. coli*	*K. pneumoniae*	*P. mirabilis*	*E. faecalis*	*S. epidermidis*	*S. aureus*	*C. albicans*	*C. parapsilosis*	*C. tropicalis*
MIC Values (μg/mL)	**3a**	-	-	-	-	-	-	-	-	-	-
	3b	625	625	-	-	-	625	1250	-	-	-
	3c	-	-	-	-	625	1250	-	-	-	-
	3d	-	-	-	-	-	-	-	-	-	-
	3e	-	-	-	-	-	-	-	-	-	-
	3f	-	-	-	625	-	1250	9.76	-	625	156.2
	3g	625	-	-	-	-	-	-	-	-	-
	3h	-	-	-	-	-	-	1250	-	-	312.5
	3i	-	-	-	-	-	1250	78.12	-	312.5	78.12
	3j	625	-	-	-	-	625	625	-	-	-
	3k	-	-	-	-	-	-	156.2	-	-	-
	3l	-	-	-	-	-	-	312.5	-	-	-
	3m	-	312.5	625	-	-	625	156.2	-	-	-
	Reference antimicrobials	2.4 Ceftazidime	4.9 Cefuroxime-Na	4.9 Cefuroxime-Na	2.4 Cefuroxime-Na	128 Amikacin	9.8 Cefuroxime	4.0 Amikacin	4.9 Clotrimazole	0.5 Amphotericin B	1.0 Amphotericin B

lationship except that *S. aureus* since there is not any sufficient data. We noticed that there is no significant activity against the rest of the microorganisms when we analyzed the effect of the position and presence of the substituent(s) on the phenyl ring in tested molecules. Among them, **3f** containing two alkoxy groups on the phenyl ring had the best antibacterial activity against *S. aureus*. The two substituents in a cyclic structure (**3i** and **3j**) was unfavorable in relation to the antibacterial activity against *S. aureus* when compared with the **3f**. Leading the loss of activity has been noticed for the **3g** containing the three alkoxy groups on the phenyl ring. Thus, it may be concluded that the presence of two substituents, in particular alkoxy groups, on the phenyl ring is vital for obtaining good activity against *S. aureus*.

4. Conclusion

In this paper, thirteen novel bis(substituted phenylamino) glyoximes were obtained, characterized by different spectral methods, and evaluated their antimicrobial activities using broth microdilution techniques. Assignment of the exchangeable protons of bis(substituted phenylamino)glyoxime was confirmed based on data from D_2O exchange, after the exchangeable protons peaks have clearly disappeared or decreased in intensity. From the X-ray analysis of **3a**, two OH groups of dioxime were placed anti position due to the torsion angles of O2-N1-C8-NC9 (178.85º) and O3-N2-C9-C8 (-179.15º). The structure of **3a** is an anti- dioxime as demonstrated by X-ray and NMR spectra. Testing in vitro these new compounds for their antimicrobial activity against several type strains revealed that the compound **3f** was the most potent compound against *S. aureus* (MIC = 9.76 μg/mL) for the antibacterial activity, whereas compound **3i** has a good potency against *S. aureus* and *C. tropicalis* (MIC = 78.12 μg/mL) for the antibacterial and antifungal activities, respectively. Although **3m** did not show activity against fungi, it could be evaluated for further studies due to its moderate efficiency for both gram-negative and gram-positive microorganisms. The simple access to bis(substituted phenylamino)glyoxime derivatives should pave the way for their applications in different areas.

Credit author statement

The corresponding author is responsible for ensuring that the descriptions are accurate and agreed by all authors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2021.130812.

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