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THE SYNTHESIS OF NOVEL NITRONS AND THEIR BIOLOGICAL ACTIVITIES

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ABSTRACT

In this study novel aldehydes were synthesised through diazoinium coupling reactions and used for the preparation of nitron compounds which were verified using mass spec., ^{1}H NMR and ^{13}C NMR. Also the biological activities were tested against four types of bacteria, two gram positive and two gram negative and the activities were compared with those of commercial antibiotics.

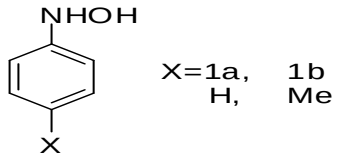
KEYWORDS: nitrons, azo compounds, n-oxides.

1. INTRODUCTION

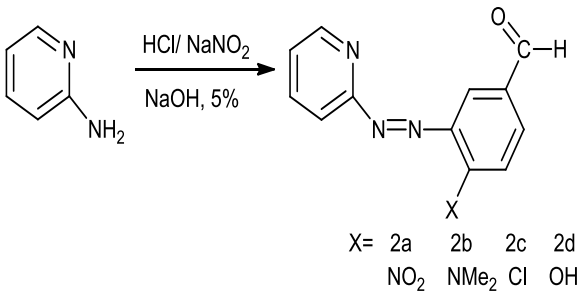
Nitrones are rather flexible intermediates in organic synthesis and are used[1-2], for instance, in the stereo-selective arrangement of synthetically important isoxazolidines oxadiazole[3] via their 1,3-dipolar cycloaddition[2,4,5] with alkenes and Schiff bases.[6,7] The most well known procedure in the preparation of nitrones is the condensation of *N*-monosubstituted hydroxylamines with ketones or aldehydes.[8] However, this procedure cannot easily be applied to ketonitrones with bulky alkyl groups or for the synthesis of non-conjugated cyclic nitrones.[9] The second procedure which has been studied over the last two decades is the oxidation of secondary amines to their equivalent nitrones, a method which was found to be useful in the preparation of nitrones.[10] Few efficient metal catalysts[11,12] and oxidizing agents[13-14] have been developed for this direct oxidation reaction. Another procedure for the synthesis of nitrones is the oxidation of *N*,*N*-disubstituted hydroxylamines[15- 16] in which a metal oxide[17-18] is normally used as an oxidant. Although this procedure is useful mainly for the synthesis of nitrones due to its mild reaction conditions, intramolecular and intermolecular and nitrone 1,3 dipolar cycloaddition reactions are also valuable methods for preparing biologically active heterocyclic compounds.[19-20, 21]

2. RESULTS AND DISCUSSION

In this study the nitrones were synthesised in a few steps. The target molecules were divided into two main parts, the first part being the portion containing the hydroxyl amine (1a, 1b). These were prepared by reduction of the nitro group using a mild reducing agent, (zinc dust in ammonium chloride solution) following the procedure described in the literature.[22,23]

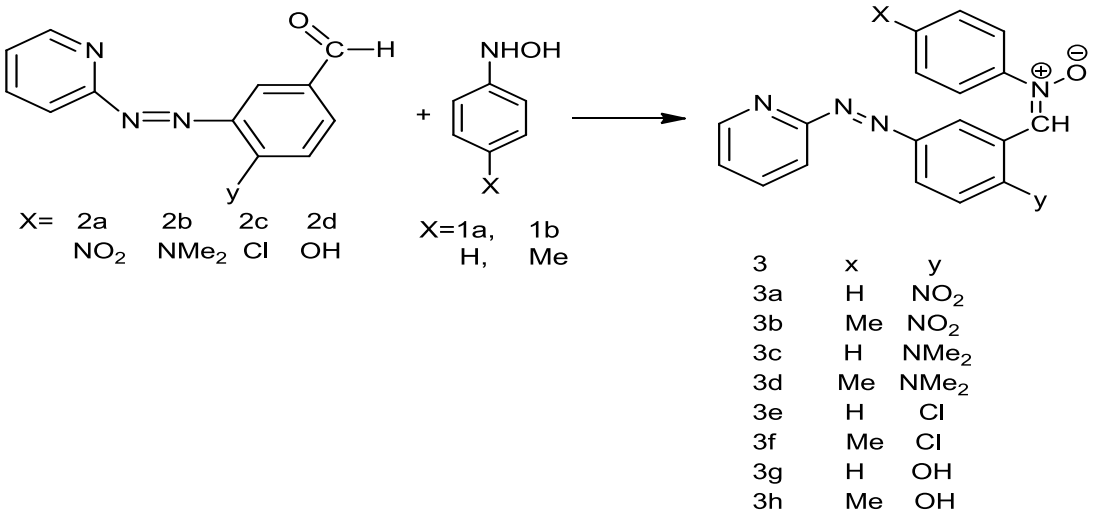


The second part is the portion which contains the aldehyde. This part was synthesised through diazonium coupling[24,25,26] between 2-amino pyridine and an aldehyde. The structures of the resulting aldehydes were confirmed using NMR and mass spectrometry. The NMR for the compounds (2a-d) displayed resonance between 9.34-10 ppm belonging to the aldehyde proton. The heterocyclic ring resonated between 7-8 ppm.



Scheme 1

The final step was the coupling between aldehydes (2a-d) and hydroxyl amines 1a and 1b to form the novel nitrons (3a-h) whose structures were confirmed using NMR, which showed 9.79-8.28 ppm for the nitron protons, while the rest of the protons resonated at around 7 ppm and mass spectrometry.



Scheme 2

2.1 Biological study

The synthesised compounds (**2a-d**) and (**3a-h**) were tested against both gram positive and negative bacteria in order to assess their biological activity. Table 1.

Table 1.

Symbol	Inhibition diameter *Staphylococcus aureus*	Inhibition diameter *Bacillus*	Inhibition diameter *Pseudo monas*	Inhibition diameter *Entero bacter*
2a	32 mm	28 mm	17 mm	25 mm
2b	15 mm	13 mm	2 mm	8 mm
2c	35 mm	27 mm	20 mm	11 mm
2d	32 mm	28 mm	26 mm	25 mm
3a	20 mm	15 mm	none	20 mm
3b	18 mm	15 mm	none	15 mm
3c	25 mm	20 mm	none	20 mm
3d	22 mm	20 mm	20 mm	20 mm
3e	10 mm	None	none	10 mm
3f	10 mm	None	none	10 mm
3g	27 mm	20 mm	20 mm	25 mm
3h	32 mm	30 mm	30 mm	30 mm
A.b (Erythro Mycin)	29 mm	19 mm	none	16 mm

Biological testing of the prepared compounds against four types of bacteria showed biological activity which was illustrated in the initial inhibition of the growth of certain gram positive and negative bacteria as shown in table (2). All the compounds which were prepared in this study displayed biological activity against the gram positive bacteria *Staphylococcus aureus* and *Bacillus*, except compounds 3e and 3f, while *Pseudo monas* showed a greater resistance to these compounds. Compound 2c showed the greatest biological activity of all the compounds. Compound 3h displayed the most consistent results against both gram positive and negative bacteria.

3. Experimental

All the chemicals were reagent grade unless stated otherwise and sourced from Sigma - Aldrich. Silica gel (Merck 7736), and silica gel plates for column and thin layer chromatography were Aldrich products, the separated components were detected using iodine vapour. Anhydrous sodium sulfate was used to dry organic solutions. Infrared (IR) spectra were carried out on an Infrared Reflection Absorption Spectroscopy (IRRAS) (4000-400 cm^{-1}) and recorded using Perkin-Elmer tensor 27 as thin film. Melting points were measured using a SMP31melting point apparatus. ^{1}H NMR spectra were carried out on a VARIAN spectrophotometer (300 MHz) and Brucker 500 in Tehran University Iran. The ^{13}C-NMR spectra were recorded using VARIAN spectrophotometer (75 MHz).

3.1 General procedure of azo dye preparation

3.1.1 Preparation of 2-nitro-5-(pyridin-2-yldiazenyl) benzaldehyde 2a

A solution of $NaNO_2$ (1.38 g, 0.02 mole) in water (6 ml) was added to 2-nitro benzaldehyde (3.02 g, 0.02 mole) in 10% NaOH aq (10 ml) and cooled to 0 ^{o}C. The resulting solution was added slowly to a stirred solution of 2-

amino pyridine (1.88 g, 0.02 mole) in HCl aq (6 ml conc. HCl: 6 ml water) keeping the temperature at 0°C. Following the addition (10 min) the pH of the mixture was adjusted to 7 and the precipitate which formed was filtered off and purified by recrystallization from EtOH to give 2-nitro-5-(pyridin-2-yldiazenyl) benzaldehyde 4.5 g (88 %) as a yellow crystalline solid with m.p. 38-40°C.

^{1}H-NMR (d_6-DMSO): 5.791-6.115(4H, m), 7.589-8.021(3H, m), 9.253 (1H, s).

^{13}C-NMR: 200.87, 153.02, 148.11, 135.80, 131.03, 130.04, 128.57, 126.09, 125.06, 123.48, 121.09, 120.17.

IR: 3103.52, 2865.55, 1693.81, 1606.00, 1571.63, 1524.02, 1447.15, 1396.6, 1345.03, 1270.24, 1188.50, 856.39, 786.96, 740.67, 694.37, 640.37.

3.1.2 Preparation of 4-(dimethylamino)-3-(pyridin-2-yldiazenyl) benzaldehyde 2b

Following the same procedure above, 2-amino pyridine (1.88 g, 0.02 mole) and 4-(dimethylamino)benzaldehyde (2.98g, 0.02 mole) were mixed together to give 4-(dimethylamino)-3-(pyridine-2-yldiazenyl)benzaldehyde 4.8 g (94 %) as a cream crystalline solid with m.p. 62-64 °C.

^{1}H-NMR (d_6-DMSO) δ: 9.250 (1H, s), 5.791-6.114 (4H, m), 7.589-8.024 (3H, m), 3.305 (6H, s).

^{13}C-NMR δ: 209.88, 159.73, 151.10, 139.17, 136.02, 131.34, 128.55, 125.22, 125.19, 122.15, 121.09, 117.95.

IR: 2905.07, 2815.71, 2795.31, 2713.36, 1683.89, 1654.43, 1585.57, 1530.64, 1483.20, 1432.90, 1367.95, 1306.11, 1229.23, 1163.17, 1123.33, 1102.39, 1063.94, 998.36, 938.02, 809.68, 725.99.

3.1.3 Preparation of 4-chloro-3-(pyridin-2-yldiazenyl)benzaldehyde 2c

Following the procedure outlined above, 2-amino pyridine (1.88 g, 0.02 mole) and 4-chloro benzaldehyde (2.81 g, 0.02 mole) were mixed together to yield 4-chloro-3-(pyridin-2-yldiazenyl) benzaldehyde 4 g (81 %) as a yellow crystalline solid with m.p. 40-42°C.

^{1}H-NMR (d_6-DMSO) δ: 9.253 (1H, s), 5.781-6.115 (4H, m), 7.580-8.018 (3H, m).

^{13}C-NMR ($CDCl_3$) δ: 201.99, 155.96, 149.01, 136.88, 136.82, 131.07, 130.00, 128.55, 125.08, 125.04, 123.06, 121.01.

IR: 3162.71, 2833.43, 1700.03, 1665.04, 1587.33, 1574.91, 1515.17, 1486.41, 1447.93, 1384.32, 1313.79, 1281.59, 1236.98, 1206.33, 1155.75, 1091.35, 1012.56, 818.82, 787.45, 696.95, 639.49, 600.34.

3.1.4 Preparation of 4-hydroxy-3-(pyridin-2-yldiazenyl)benzaldehyde 2d

Following the procedure outlined above, 2-amino pyridine (1.88 g, 0.02 mole) and 4-hydroxy benzaldehyde (2.44 g , 0.02 mole) were mixed together to give 4-hydroxy-3-(pyridin-2-yldiazenyl)benzaldehyde 4.2 g (92.5 %) as a white crystalline solid with m.p. 98-100 °C.

^{1}H-NMR (d_6-DMSO) δ: 9.248 (1H, s), 9.908 (1H, s), 5.790- 6.112 (4H, m), 7.589-8.022 (3H, m).

^{13}C-NMR (d_6-DMSO) δ: 205.76, 158.14, 150.07, 138.09, 136.80, 130.01, 128.55, 125.19, 125.09, 125.04, 123.09, 123.06.

IR: 3161.69, 3043.44, 2967.31, 1905.40, 1664.44, 1588.80, 1517.36, 1449.50, 1384.40, 1314.15, 1282.44, 1237.87, 1215.22, 1157.06, 1112.16, 857.60, 822.45, 787.55, 695.67, 640.27, 601.12.

3.2 PREPARATION OF NITRONES

3.2.1 Preparation of N-(2-nitro-5-(pyridine-2-yldiazenyl) benzylidene) anilineoxide 3a

In a 50 ml round bottom flask (0.5g, 0.0046 mole) of n-phenyl hydroxylamine was dissolved in 15 ml absolute ethanol and warmed to 40-50 °C. 2-Nitro-5-(pyridin-2-yldiazenyl) benzaldehyde (1.178g 0.0046 mole) was added to the reaction and the mixture was stirred overnight. When TLC showed the reaction to be complete, the solvent was removed under reduce pressure and the product was recrystallized from ethanol to give N-(2-nitro-5-(pyridin-2-yldiazenyl) benzylidene) anilineoxide 1.2g (75 %) as a white crystalline solid with m.p. 86-88°C.

^{1}H-NMR (d_6-DMSO) δ: 8.76 (1H, s), 8.51 (1H, d, J=9Hz), 8.08 (1H, d, J=9Hz), 7.92-7.84 (4H, m), 7.71 (2H, m), 7.59 (1H, s) 7.57-7.53 (3H, m).

^{13}C-NMR (d_6-DMSO) δ: 147.31, 133.69, 132.73, 131.67, 130.22, 130.01, 129.75, 129.29, 128.83, 128.78, 128.75, 128.40, 124.43, 123.97, 123.76, 123.70, 121.52, 120.94.

IR: 3104.02, 3074.04, 2851.06, 1699.73, 1600.34, 1568.20, 1517.90, 1466.27, 1483.50, 1410.38, 1339.55, 1224.45, 1191.24, 1090.02, 1068.51 , 1023.02, 1001.32, 968.80, 916.82, 885.98, 890.45, 804.96, 763.49, 735.67 , 685.06, 646.22, 586.34.

3.2.2 Preparation of 4-methyl-N-(2-nitro-5-(pyridin-2-yldiazenyl) benzylidene) anilineoxide 3b

Following the procedure outlined above, n-para toluidine hydroxylamine (0.5g, 0.004 mole) and 2-nitro-5-(pyridin-2 yldiazenyl) benzaldehyde (1.02g , 0.004 mole) were mixed together to give 4-methyl-N-(2-nitro-5-(pyridin-2-yldiazenyl) benzylidene) anilin oxide 1.12 g (78%) as a yellowish crystalline solid with m.p. 98-100°C.

^{1}H-NMR (d_6-DMSO) δ: 8.72 (1H, s), 8.52 (1H, d, J= 6 Hz), 8.04-8.16 (2H, m), 7.70-7.85(4H, m), 7.38 (4H, d, J=9 Hz), 2.39 (3H, s).

^{13}CNMR: 147.39, 145.07, 139.92, 133.68, 133.61, 132.96, 130.09, 129.67, 129.28, 129.09, 129.04, 128.84, 128.14, 123.94, 123.79, 123.75, 120.67, 120.60, 20.12.

IR: 3106.95, 2918.15, 2856.02, 1699.74, 1603.24, 1567.86, 1500.49, 1465.72, 1342.43, 1309.94, 1188.44, 1175.84, 1085.87, 1068.35, 1041.98 , 1015.09 , 946.19, 898.67, 862.99, 805.37, 781.11, 732.36, 674.47, 630.95, 524.15.

3.2.3 Preparation of N-(4-(dimethylamino)-3-(pyridin-2-yldiazenyl) benzylidene) anilineoxide 3c

The following the procedure outlined above, n-phenylhydroxylamine (0.5 g, 0.0046 mole) and 4-(dimethylamino)-3-(pyridin-2-yldiazenyl)benzaldehyde) (1.169 g, 0.0046 mole) were mixed to give N-(4-(dimethylamino)-3-(pyridin-2-yldiazenyl) benzylidene) aniline oxide 1.25 g (79%) as a cream crystalline solid with m.p. 120-122^{o}C.

^{1}H-NMR (d_6-DMSO) δ: 8.40 (2H, d, J=9 Hz), 8.28 (1H, s), 7.91 (2H d, J=9 Hz), 7.70 (2H, d, J=9 Hz), 7.54-7.44 (4H, m), 6.80 (2H, d, J=9Hz), 3.04 (6H, s).

^{13}C-NMR: 153.67, 150.90, 147.83, 132.59, 130.27, 128.79, 128.59, 128.41, 128.35, 127.91, 124.00, 120.46, 120.30, 119.66, 118.38, 110.91, 110.53, 110.50, 39.42, 39.28.

IR: 3082.54, 2902.11, 2796.48, 2713.82, 1659.56, 1591.52, 1526.54, 1482.66, 1444.11, 1433.43, 1368.71, 1329.54, 1312.80, 1231.56, 1162.05, 1122.66, 1056.75, 999.88, 946.82, 916.58, 884.88, 825.08, 804.25, 770.56, 727.36, 689.53, 658.30, 628.23, 595.32, 551.93.

3.2.4 Preparation of N-(4-(dimethylamino)-3-(pyridin-2-yldiazenyl) benzylidene)-4-methyl anilineoxide 3d

Following the procedre outlined above, n-para toluidine hydroxylamine (0.5 g, 0.004 mole) and 4-(dimethylamino)-3-(pyridin-2-yldiazenyl) benzaldehyde (1.017g, 0.004 mole) were mixed to give N-(4-(dimethylamino)-3-(pyridin-2-yldiazenyl) benzylidene)-4-methylaniline oxide 1.11 g (78%) as a yellowish crystalline solid with m.p. 82-84^{o}C.

^{1}H-NMR (d_6-DMSO) δ: 9.67 (1H, s), 8.38-8.04 (2H, m), 7.80 (1H, d, J= 9 Hz), 7.70 (1H. s), 7.67 (1H, d=J 9 Hz), 7.42-7.28 (2H, m), 6.79 (4H, d, J=9 Hz), 3.35 (3H, s), 3.04 (6H, s).

^{13}C-NMR: 153.66, 150.80, 145.03, 141.69, 140.75, 139.37, 130.99, 130.17, 129.09, 128.85, 128.70, 124.65, 124.00, 121.27, 120.19, 112.22, 111.87, 110.52, 39.41, 20.54, 20.26.

IR: 2911.63, 2795.85, 2713.80, 1660.07, 1592.82, 1525.01, 1444.86, 1432.33, 1366.97, 1312.74, 1230.86, 1161.22, 1124.36, 1062.26, 999.91, 941.46, 888.82, 811.20, 726.56, 594.40.

3.2.5 Preparation of N-(4-Chloro-3-(pyridin-2-yldiazenyl) benzylidene) anilineoxide 3e

Following the procedure outlined above, n-phenylhydroxylamine (0.45 g, 0.004 mole) and 4-chloro-3-(pyridin-2-yldiazenyl)benzaldehyde (0.98 g , 0.004 mole) to give N-(4-chloro-3-(pyridin-2-yldiazenyl)benzylidene) aniline oxide 1.09 g (81%) as white crystalline solid with m.p. 146-148^{o}C.

^{1}H-NMR (d_6-DMSO) δ: 8.55 (1H, s), 8.52 (2H, d, J=9Hz), 7.92-7.89 (2H, m), 7.58-7.51 (8H, m).

^{13}C-NMR: 147.84, 138.62, 133.96, 132.04, 130.02, 129.84, 129.45, 129.40, 128.77, 128.57, 128.39, 128.33, 128.31, 128.02, 124.44, 122.42, 121.44, 120.95.

IR: 3059.26, 2925.87, 2852.06, 1650.60, 1587.58, 1546.00, 1482.58, 1456.13, 1438.15, 1402.45, 1301.06, 1285.64, 1191.88, 1171.61, 1070.42, 1011.90, 916.45, 893.50, 839.43, 812.22, 762.54, 684.06, 634.80.

3.2.6 Preparation of N-(4-chloro-3-(pyridin-2-yldiazenyl)-4-methyl aniline oxide 3f

Following the procedure outlined above, n-para toluidine hydroxylamine (0.4 g, 0.003 mole) and 4-chloro-3-(pyridin-2-yldiazenyl) benzaldehyde (0.73 g, 0.003 mole) were mixed together to give N-(4-chloro-3-(pyridin-2-yldiazenyl)-4-methyl aniline oxide 0.9 g (86 %) as a white crystalline solid with m.p. 114-116^{o}C.

^{1}H-NMR (d_6-DMSO) δ: 8.53 (1H, d, J=9 Hz), 8.49 (1H, s), 8.14-8.03 (3H, m), 7.82 (1H, d, J=9 Hz), 7.57 (2H, d, J=9 Hz), 7.41 (2H, J=9 Hz), 7.35 (2H, d, J=9 Hz), 2.40 (3H, s).

^{13}C-NMR: 145.58, 144.93, 141.68, 140.75, 139.35, 139.27, 133.82, 131.37, 130.59, 129.78, 129.50, 129.09, 128.89, 128.84, 127.99, 124.64, 121.27, 120.66, 20.54.

IR: 2917.81, 2858.09, 1650.81, 1586.91, 1567.07, 1543.71, 1500.07, 1453.52, 1420.10, 1401.24, 1380.51, 1294.13, 1193.84, 1165.06, 1076.82, 1012.00, 499.78, 894.72, 819.16, 782.02, 706.13, 677.66, 650.98, 609.48, 590.03.

3.2.7 Preparation of N-(4-hydroxy-3-(pyridin-2-yldiazenyl)benzylidene)aniline oxide 3g

Following the procedure outlined above, n-phenylhydroxylamine (0.5 g, 0.0046 mole) and 4-hydroxy-3-(pyridin-2-yldiazenyl)benzaldehyde (1.045 g, 0.0046 mole) were mixed to give N-(4-hydroxy-3-(pyridin-2-yldiazenyl) benzylidene) aniline oxide 1 g (68 %) as a white crysilline soild with m.p. 124-126^{o}C.

^{1}H-NMR (d_6-DMSO) δ: 8.40 (1H, d, J=9Hz), 8.34 (1H, s), 7.89 (1H, d, J=9 Hz), 7.77 (2H, d, J=6 Hz) 7.52-7.49 (2H, m), 7.66 (1H, s), 6.94-6.86 (5H, m).

^{13}C-NMR: 162.8, 159.12, 147.91, 132.65, 131.56, 130.64, 128.79, 128.78, 128.44, 128.41, 127.89, 124.44, 122.09, 121.53, 120.74, 115.32, 115.11, 114.73.

IR: 3153.58, 2965.45, 2878.29, 1665.00, 1597.08, 1572.76, 1507.61, 1473.76, 1437.84, 1384.67, 1314.79, 1285.19, 1236.85, 1215.21, 1154.38, 1108.03, 1053.10, 1021.29, 878.59 , 857.88, 831.25, 758.16, 683.08, 638.81, 602.86.

3.2.7 Preparation of N-(4-hydroxy-3-(pyridin-2-yldiazenyl)benzylidene)-4-methyl anilineoxide 3h

Following the procedure outlined above, n-para toluidine hydroxylamine (0.5 g, 0.004 mole) and 4-hydroxy-3-(pyridin-2-yldiazenyl)benzaldehyde (0.9 g, 0.004 mole) were mixed to give N-(4-hydroxy-3-(pyridin-2-yldiazenyl) benzylidene)-4-methylaniline oxide 1.2 g (91%) as white crystalline solid with m.p. 102-104^{o}C.

^{1}H-NMR (d_6-DMSO) δ: 9.79 (1H, s), 8.15 (1H, d, J=9 Hz), 8.07 (1H, d, J=9 Hz), 7.77-7.79 (2H, m), 7.75 (1H, s), 7.42 (1H, d, J=6 Hz), 7.36 (1H, d, J=6 Hz), 6.95 (2H, d), 6.92 (2H, d, J=6 Hz), 2.42 (3H, s).

^{13}C-NMR: 162.78, 145.01, 142.57, 141.70, 140.76, 140.29, 139.36, 134.59, 133.79, 131.55, 129.10, 128.85, 127.91, 124.64, 123.62, 121.29, 115.30, 115.08, 115.02, 20.54.

IR: 3163.42, 1665.37, 1594.90, 1517.80, 1451.30, 1385.08, 1314.63, 1284.78, 1238.76, 1216.03, 1158.40, 1112.40, 857.85, 822.64, 787.97, 705.15, 640.89, 602.30.

3.3 Biological study

The antibacterial activities of the prepared samples were determined by the agar well diffusion method, using aboratory strains of four bacterial species which included two gram-positive bacteria, *Staphylococcus aureus* and *Bacillus cereus* and two gram-negative bacteria, *Pseudomonas aeruginosa* and *Enterobacter*. Erythromycin was used as the standard antibacterial agent.

The prepared compounds in this study, 2a-d and 3a-h were tested for their activity against the above bacteria using the disc diffusion method. Mueller Hinton Agar was sterilized in a round bottom flask, cooled to 40–50°C and homogenously spread onto pre-sterilized Petri dishes. The bacteria were separately introduced on the agar plates. The test compounds were introduced to the Petri dishes by soaking discs in a 0.25 mg concentration of the test compounds (2a-d) and (3a-h) and then applying then to the surface of the agar plates. A sterile disc was use as blank and this disc was soaked in the solvent (DMSO) and applied to the agar as a negative control on each Petri dish along with the standard drug (erthrymicine). The Petri dishes were incubated at 37 °C (overnight) for bacterial strains.

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