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Antimicrobial studies of novel 2, 5 –Dimercapto-1, 3, 4 –thiadiazole derivatives

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Abstract

A series of novel chalcone derivatives of 2, 5 –Dimercapto-1, 3, 4 –thiadiazole *(3a-h) were synthesized by Claisen-Schmidt condensation between terephthaldehydyl -2, 5 –dimercapto (acetichydrazide)-1, 3, 4 –thiadiazole (1) and substituted aromatic ketones (2a-h). All the synthesized compounds (3a-h) were characterized by UV, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. The synthesized compounds were subjected to antibacterial studies against Staphylococcus aureus, Bacillus subtilis (gram-positive), Escherichia coli and Salmonella enteritidis (gram-negative) bacteria and antifungal studies against Candida albicans, Trichophyton rubrum, Trichoderma viride and Aspergillus niger and the Minimum Inhibitory concentration of each compound was determined by liquid broth method. The results indicated that all the synthesized compounds 3a-h showed considerable antibacterial and antifungal activities.*

Keywords: 2, 5 –Dimercapto-1, 3, 4 –thiadiazole, anti-fungal and anti-bacterial activity.

Introduction

Chalcones are a major class of natural products belonging to the flavonoid family. They areconsidered as the precursors of flavonoids and isoflavonoids. They are also the precursors of a number of biologically important heterocycles such as benzothiazepines, pyrazolines, and flavones[1,2]. They are widely distributed in fruits, vegetables, tea, spices, soy based foods and other plant products. From a chemical point of view an important feature of chalcones and their heteroanalogs is the ability to act as activated unsaturated systems in conjugate addition reactions of carbanions in presence of base catalysts[3]. Chalocnes have been popular substrates for the generation of variety of heterocyclic, carbocyclic and flavonoids[4].

The compounds with the backbone of chalcones have been reported to possess various biological activities such as antibacterial[5], antifungal[6], insecticidal[7], anaesthetic, anti-inflammatory, analgesic, antiulcerogenic[8-9], antiplatelet, antimalarial[10], anticancer, antiviral, antileishmanial, antioxidant, antituberculosis[11], anti hyperglycemic, immunomodulatory, inhibition of chemical mediators release, inhibition of leukotriene B_4, inhibition of tyrosinase and inhibition of aldose reductase activities[12].

In the present work we report the reaction of terephthaldehydyl-2,5 -dimercapto (acetichydrazide)-1,3,4 –thiadiazole with different substituted aromatic ketones to form chalcones (3a-h). Many reports were available for the preparation of chalcones[13-16] but the reports on antibacterial and antifungal activity of chalcones associated with thiadiazole nucleus are rarely found. This prompted us to synthesize chalcones containing 1, 3, 4 –thiadiazole moiety and to carry out the antibacterial and antifungal activity.

Material and Methods

Chemistry: All melting points (uncorrected) were determined using a Guna melting point apparatus. UV spectra were obtained UV 2460 shimadzu spectrophotometer. IR spectra were carried out on a Perkin-Elmer 1650 spectrophotometer. NMR spectra were recorded in $CDCl_3$ on a Bruker AM 400 MHz spectrometer, using residual $CHCl_3$ and TMS as an internal standard. Mass spectra were recorded on a VG-70-S instrument. Elemental analysis was carried out in a Perkin Elmer 240C model instrument. The purity of the compound was checked by TLC using silica gel 'G' plates. All the chemicals used are of AR grade.

General procedure for the preparation of compounds 3a-h: Terephthaldehydyl 2,5 –Dimercapto (Acetichydrazide)-1,3,4 –thiadiazole.1 (0.01 mol) was dissolved in 100 ml ethanol and the substituted aromatic ketones (2a-h) (0. 02mol) were added and heated for 7-8 hrs with constant stirring in a magnetic stirrer and a catalytic amount of NaOH was added in drops. The reaction was poured into ice-cold water, neutralized with con.HCl and left over night in a refrigerator. The precipitate formed was filtered, dried and the purity of the compound was checked by TLC using chloroform as the solvent.

Terephthalphenyl-2,5 –Dimercapto (Acetichydrazide)-1,3,4 –thiadiazole -(3-nitrophenyl)-prop-2-en-1-one (3a): Yield 65%; m.p.: 201^{o}C; UV λ max: 651.50,561.50; 333.00;IR (KBr) cm^{-1}: 3466, 1697, 1458; ^{1}H-NMR (400MHz $CDCl_3$) δ: 7.11 (d, 1H, J=1.6Hz, H-1'), 7.38 (dd, 1H, J=8Hz,1.6Hz, H-3'), 6.88 (d, 1H, J=8Hz, H-4'), 6.98 (d, 1H, J=8Hz, H-5'), 6.76 (td, 1H, J=8, 1.6Hz, H-6'), 6.93 (dd, 1H, J=8, 1.6Hz, H-7'), 6.48 (dd, 1H, J=8, 1.6Hz, H-8'), 7.68 (d, 1H, J=16Hz, H-2),7.23 (d, 1H, J=16Hz,

H-3), 7.51 (d, 2H, J=8Hz, H-2", 6"), 6.85(m, 2H, H-3", 5"), 3.79 (s, 3H, 0CH3), 8.79 (s, 1H, NH); ^{13}CNMR δ:193.71,184.0, 150.0, 169.92, 162.12, 129.72, 40.58; MS (EI)m/z = 820.95(M^+); Anal. Calcd.for $C_{38}H_{28}N_8O_8S_3$: C, 77.64%; H,3.52%; N, 4.11%; Found: C, 77.58%; H, 3.67%; N, 4.23%.

Terephthalphenyl-2,5 –Dimercapto (Acetichydrazide)-1,3,4 –thiadiazole --(4-Fluorophenyl)-prop-2-en-1-one(3b) :: Yield 64%; m.p.: 218^{o}C; UV λ max: 792.50,672.00, 335.50; IR (KBr) cm^{-1}: 3465, 1692, 1452; ^{1}H-NMR(400MHz $CDCl_3$) δ : 7.31 (d, 1H, J=1.6Hz, H-1'), 7.46 (m, 1H,H-3'), 7.09 (d, 1H, J=7.8Hz, H-4'), 6.91 (d, 1H, J=7.8Hz, H-5'),6.77 (t, 1H, J=7.8Hz, H-6'), 6.99 (td, 1H, J=7.8Hz, H-7'), 6.67(d, 1H, J=7.8Hz, H-8'), 7.46 (m, 2H, H-3",5"), 7.87 (m, 2H, H-2", 6"), 7.63 (d, 1H, H-4"), 7.77 (d, 2H, J=16Hz, H-2,3), 8.89 (s,1H, NH). ^{13}C-NMR δ: 121.90, 141.10, 126.24, 127.94, 126.11,114.57, 128.75, 112.92, 142.82, 115.19, 143.72, 123.58, 188.02,122.52, 143.72, 136.85, 122.08, 128.90, 130.57, 134.66, 126.40,62.91,40.58.MS (EI)m/z = 766.62(M^+);; Anal. Calcd.for$C_{38}H_{28}N_6O_4S_3F_2$: C, 6.59%; H,4.55%; N, 4.25%; Found: C, 76.67%; H, 4.44%; N, 4.34%.

Terephthalphenyl-2,5 –Dimercapto (Acetichydrazide)-1,3,4 –thiadiazole -(4-chlorophenyl)-prop-2-en-1-one (3c): Yield 66%; m.p.: 210^{o}C. UV λ max: 570.50,328.50,259.50;IR (KBr) cm^{-1}: 3450, 1670, 1451; ^{1}H-NMR (400MHz $CDCl_3$) δ: 7.30 (d, 1H, J=1.6Hz H-2'), 7.63 (dd, 1H, J=8,1.6Hz, H-3'),7.09 (d, 1H, J=8Hz, H-4'), 6.93 (dd, 1H, J=8Hz, H-5'), 6.78 (dt,1H, J=8, 1.6Hz, H-6'), 7.00 (td, 1H, J=8, 1.6Hz, H-7'), 6.52 (dd,1H, J=8, 1.6Hz, H-8'), 7.71 (d, 1H, J=16Hz, H-2), 7.83 (d, 1H,J=16Hz, H-2), 7.91 (d, 2H, J=8Hz, H-2",6"), 7.53 (d, 2H, H-3",5"), 8.79 (s, 1H, NH); ^{13}C-NMR δ: 193.71, 184.00, 150.0, 169.92, 162.12, 129.73, 40.58.MS (EI)m/z = 798.03(M^+);; Anal. Calcd.for$C_{38}H_{28}N_6O_4S_3Cl_2$: C, 69.34%;H, 3.85%; N, 3.85%; Found: C, 69.29%; H, 3.80%; N, 3.91%.

Terephthalphenyl- 2,5 –Dimercapto (Acetichydrazide)-1,3,4 –thiadiazole --((4-methylphenyl)-prop-2-en-1-one(3d) :Yield 61%; m.p.: 198^{o}C. UV λmax: 492.00, 465.50, 342.00; IR(KBr) cm^{-1}: 3458, 1685, 1454; ^{1}H-NMR (400MHz $CDCl_3$) δ:7.30 (d, 1H, J=1.6Hz, H-1'), 7.61 (dd,1H, J=8, 1.6Hz, H-3'), 7.08 (d, 1H, J=8Hz, H-4'), 6.91 (dd, 1H, J=8, 1.6Hz, H-5'), 6.76(td, 1H, J=8, 1.6Hz, H-6'), 6.92 (td, 1H, J=8, 1.6Hz, H-7'), 6.65(dd, 1H, J=8, 1.6Hz, H-8'), 7.71 (d, 1H, J=16Hz, H-2), 7.75 (d,1H, J=16Hz, H-3), 7.71 (d, 2H, H-2",6"), 7.28 (d, 1H, J=8Hz, H-3",5"), 2.35 (s, 3H, CH3), 8.77 (s, 1H, NH); ^{13}C-NMR δ:164.87,164.3,156.12,155.96,139.67,135.57,132.27,131.30,126 .50.122.70,117.28,115.97,51.32.MS (EI)m/z = 758.02(M^+); Anal. Calcd.for $C_{40}H_{34}N_6O_4S_3$: C, 76.96%; H, 4.95%; N, 4.07%; Found: C, 76.93%; H, 4.84%; N, 4.23%.

Terephthalphenyl-2,5 –Dimercapto (Acetichydrazide)-1,3,4 –thiadiazole --(3-Bromophenyl)-prop-2-en-1-one (3e): Yield 63%; m.p.: 199^{o}C.; UV λ max: 657.00, 630.50,329.00; IR (KBr) cm^{-1}: 3452, 1685, 1456; ^{1}H-NMR (400MHz $CDCl_3$) δ: 7.31 (d, 1H, J=1.6Hz, H-1'), 7.68 (dd, 1H, J=8,1.6Hz, H-3'), 7.08 (d, 1H, J=8Hz, H-4'), 6.93 (dd, 1H, J=8,1.6Hz, H-5'), 6.79 (td, 1H, J=8, 1.6Hz, H-6'), 6.99 (td, 1H, J=8,1.6Hz, H-7'), 6.67 (d, J=8, 1.6Hz, 1H, H-8'), 7.80 (d, 1H,J=16Hz, H-2), 8.02 (d, 1H, J=16Hz, H-3), 8.74 (m, 1H, H-2"),8.26 (dd, 1H, J=8, 1.6Hz, H-4"), 7.74 (t, 1H, J=8Hz, H-5"), 8.28(m, 1H, H-6"), 8.75 (s, 1H, NH); ^{13}C-NMR δ: 173.14, 169.62, 161.86,153.42,149.62,133.32,129.72,126.56,123.65,119.30,40.47; MS (EI)m/z = 888.64(M^+); Anal. Calcd.for $C_{38}H_{28}N_6O_4S_3Br_2$: C, 67.38%; H, 3.74%; N, 7.48%; Found: C,67.48%; H, 3.65%; N, 7.54%.

Terephthalphenyl- 2,5 –Dimercapto (Acetichydrazide)-1,3,4 –thiadiazole -(4-Bromophenyl)-prop-2-en-1-one (3f): Yield 61%; m.p.: 204^{o}C. UV λ max: 765.00,758.00,334.50; IR (KBr) cm^{-1}: 3450, 1685, 1456; ^{1}H-NMR(400MHz $CDCl_3$) δ: 7.30 (d, 1H, J=8Hz, H-1'), 7.61 (dd, 1H,J=8Hz, H-3'), 7.09 (d, 1H, J=8Hz, H-4'), 6.91(dd, 1H, J=8,1.6Hz, H-5'), 6.77 (td, 1H, J=8, 1.6Hz, H-6'), 7.00 (td, 1H, J=8,1.6Hz, H-7'), 6.68 (dd, 1H, J=8, 1.6Hz, H-8'), 7.67 (m, 1H, J=16Hz, H-2), 7.83 (m, 1H, J=16Hz, H-3), 7.80 (m, 2H, H-2",6"), 7.67 (m, 2H, H-3",5"), 8.78 (s, 1H, NH); ^{13}C-NMR δ:173.12,149.58,134.15,126.02,118.79;MS (EI)m/z = 888.97(M^+); Anal. Calcd.For $C_{38}H_{28}N_6O_4S_3Br_2$: C, 61.78%; H, 3.43%; N, 3.43%; Found: C,61.84%; H, 3.51%; N, 3.45%.

Terephthalphenyl-2,5 –Dimercapto (Acetichydrazide)-1,3,4 –thiadiazole --(4-nitrophenyl)-prop-2-en-1-one (3g): Yield 62%; m.p.: 213^{o}C; UV λmax:583.50,576.00,328.50; IR (KBr) cm^{-1}: 3462, 1692, 1452; ^{1}HNMR(400MHz $CDCl_3$) δ: 7.31 (d, 1H, J=1.6Hz, H-1'), 7.61 (dd,1H, J=8, 1.6Hz, H-3'), 7.09 (d, 1H, J=8Hz, H-4'), 6.91 (dd, 1H,J=8, 1.6Hz, H-5'), 6.78 (td,1H, J=8, 1.6Hz, H-6'), 7.00 (td, 1H,J=8, 1.6Hz, H-7'), 6.67 (d, 1H, J=8, 1.6Hz, H-8'), 7.90 (m, 2H,H-2",6"), 8.09 (m, 2H, H-3",5"), 7.78 (d, 1H, J=16Hz, H-2), 7.91(d, 2H, J=16Hz, H-3), 8.79 (s, 1H, NH), 10.05 (s, 1H, CHO);^{13}C-NMR: δ 173.12,149.58,134.15,126.02,118.79;MS (EI)m/z = 820.94(M^+); Anal. Calcd.for $C_{38}H_{28}N_8O_8S_3$: C, 73.39%; H,4.20%; N, 3.91%; Found: C, 73.47%; H, 4.25%; N, 4.31%.

Terephthalphenyl-2,5 –Dimercapto (Acetichydrazide)-1,3,4 –thiadiazole -3-(4-methoxyphenyl)-prop-2-en-1-one(3h) : Yield 63%; m.p.: 209^{o}C; UV λ max:635.00, 308.50, 212.00; IR (KBr) cm^{-1}: 3464, 1692, 1456; ^{1}HNMR(400MHz $CDCl_3$) δ: 7.31 (d, 1H, J=1.6Hz, H-1'), 7.61 (dd,1H, J=8, 1.6Hz, H-3'), 7.09 (d, 1H, J=8Hz, H-4'), 6.91 (dd, 1H,J=8, 1.6Hz, H-5'), 6.78 (td,1H, J=8, 1.6Hz, H-6'), 7.00 (td, 1H,J=8, 1.6Hz, H-7'), 6.67 (d, 1H, J=8, 1.6Hz, H-8'), 7.90 (m, 2H,H-2",6"), 8.09 (m, 2H, H-3",5"), 7.78 (d, 1H, J=16Hz, H-2), 7.91(d, 2H, J=16Hz, H-3), 8.79 (s, 1H, NH), 10.05 (s, 1H, CHO); ^{13}C-NMR:δ173.14,169.62,161.86, 153.42,149.61, 133.32, 129.72, 126.56, 123.65,119.30,40.47; MS (EI)m/z = 850.68(M^+);; Anal. Calcd.for$C_{42}H_{38}N_6O_8S_3$: C, 73.39%; H, 4.20%; N, 3.91%; Found: C, 73.47%; H, 4.25%; N, 4.31%.

Antibacterial and antifungal activity: The results of the antibacterial and antifungal activity of the tested compounds were given in table 1 and 2. Significant inhibitory activity with a

MIC value of 15to 20 µg/mL was observed against the studied pathogenic bacteria. *B. sustilis*, *S.aureus* was the most sensitive strain. Tetracycline was used as a standard compound for screening the antibacterial activity. Most of the compounds had remarkable antifungal activity against the microorganisms employed in this study. Two out of eight studied compounds exhibited a good antifungal activity with a MIC value of 15 to 20µg/mL against *C. albica,T. rubrum, T. viride*, and *A.flavus*. As it can be seen in Table 2, *A. flavus* was more susceptible than *C. albicans,T. rubrum, T. viride* to the studied compounds. Ketoconazole was used as a standard compound for screening antifungal activity. From the outcome of antimicrobial screening, it is apparent that the compounds 3a, 3c, 3d and 3g possess very good antibacterial and antifungal activity with MIC values ranging from 15 to 20µg/mL and the compounds 3b, 3e, 3f and 3h showed moderate antimicrobial and antifungal activity.

Results and Discussion

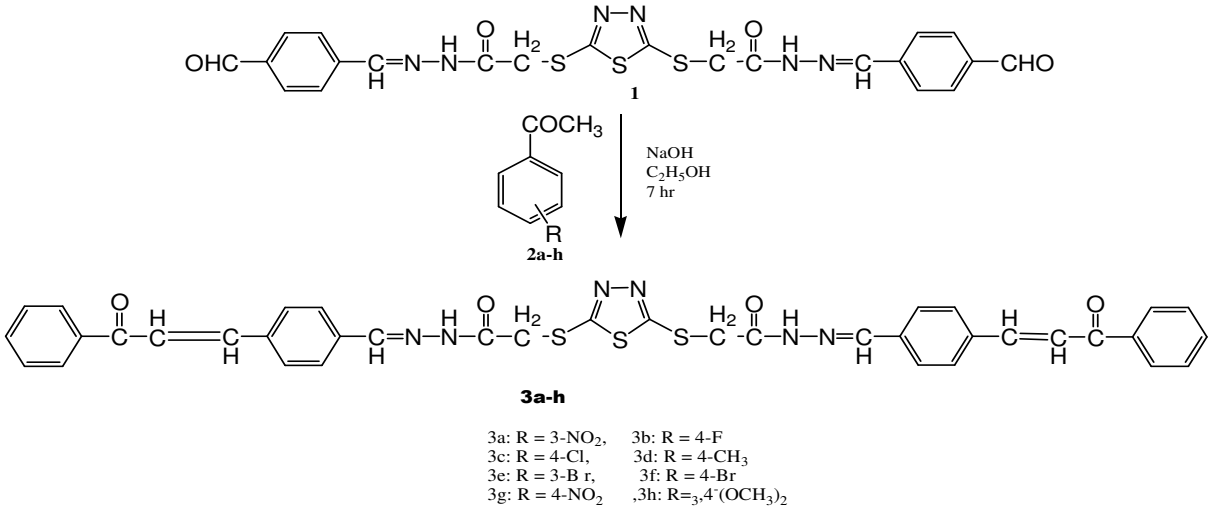
Compounds 3a-h were synthesized by the reaction between terephthalphenyl -2,5 –dimercapto (acetichydrazide)-1,3,4 – thiadiazole with various substituted aromatic ketone by Claisen-Schmidt condensation reaction as shown in scheme 1. For the compounds 3a-h, IR spectra showed characteristic absorption bands to show the presence of carbonyl group at 1670 cm^{-1}, C=C at 1600 cm^{-1} and NH stretching at 3450 cm^{-1}. For all the synthesized compounds,the signals for the aromatic carbons and protons were assigned using known effects of substituents, position, multiplicities and integral values. In ^{1}H-NMR spectra for the compound 3a-h the H-2 and H-3 protons are found to be in the Trans positions by appearing as doublets at δ 7.30 and 7.77 with a coupling constant of 16Hz. NH proton appeared as a singlet at δ 8.79. In compound 3a, the methoxy protons appeared as a single t δ 1.18, similarly in 3d, CH_3 appeared at δ 2.35. In 3g, the singlet at δ 10.05 is due to CHO group and all the aromatic protons appeared between δ 6.50- 8.28. The ^{13}C – NMR signals were assigned based on their positions and intensities. The ^{13}C-NMR spectrum were recorded in $CDCl_3$ and spectral signals were in good agreement with the proposed structures; C=O group appeared at δ 187.92. In the compound 3a, the methoxy carbon appeared at δ 55.42 and in compound 3d, the methyl carbon appeared at δ 21.05. For 3g, the keto carbon appeared at δ192.59 and all the aromatic carbon and unsaturated Carbons appeared between 100-160. Characteristic molecular ion peaks were observed in the mass spectra of the compounds 3a-g and shown in experimental section

Table-1
Antibacterial activity of the compounds 3a-h

Tested compound	Minimum inhibitory concentration expressed in µg/mL			
	B. sustilis	***S. aureus***	***E. coli***	***S. enteritidis***
	Gram positive		**Gram negative**	
3a	20	15	25	10
3b	45	35	40	55
3c	15	25	20	15
3d	20	30	25	15
3e	35	40	30	45
3f	25	35	20	35
3g	30	20	25	15
3h	35	25	30	25
Tetracycline	20	20	20	20

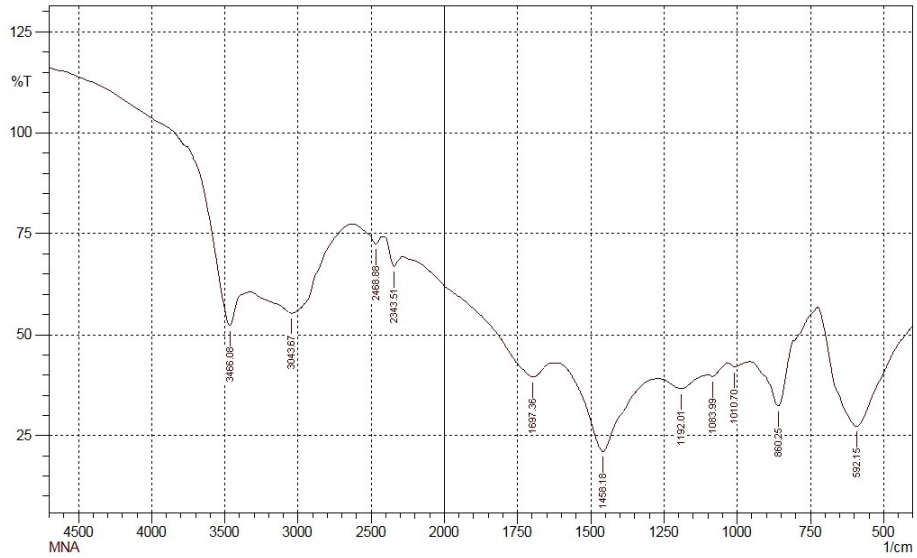
Table-2
Antifungal activity of the compounds 3a-h

Tested compound	Minimum inhibitory concentration expressed in µg/mL			
	Candida albicans	***Trichophyton rubrum***	***Trichoderma Viride***	***Aspergillus flavus***
3a	25	30	15	20
3b	40	55	50	45
3c	25	15	30	20
3d	35	25	40	30
3e	40	50	35	45
3f	30	40	30	25
3g	30	35	20	30
3h	30	40	35	25
Ketoconazole	**10**	**10**	**10**	**10**



3a: R = 3-NO_2, 3b: R = 4-F
3c: R = 4-Cl, 3d: R = 4-CH_3
3e: R = 3-B r, 3f: R = 4-Br
3g: R = 4-NO_2 ,3h: R=$_3$,4$^-$$(OCH_3)_2$

Scheme-1
Synthesis of Chalcones 3a-h



	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	592.15	27.264	27.706	723.31	399.26	133.143	47.627
2	860.25	32.354	16.625	956.69	725.23	83.357	13.085
3	1010.7	41.961	1.063	1029.99	958.62	26.421	0.357
4	1083.99	39.612	1.149	1101.35	1031.92	26.859	0.35
5	1192.01	36.658	2.923	1271.09	1103.28	70.065	2.571
6	1458.18	21.036	20.208	1610.56	1273.02	164.579	33.896
7	1697.36	39.512	6.208	2285.65	1629.85	165	5.783
8	2343.51	66.914	4.477	2426.45	2287.58	21.493	1.578
9	2468.88	72.501	2.495	2625.12	2428.38	24.546	0.968
10	3043.67	55.352	12.119	3329.14	2627.05	140.614	25.767
11	3466.08	52.25	19.621	3765.05	3331.07	67.046	17.668

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Figure-1
IR Spectral data of compound 3a

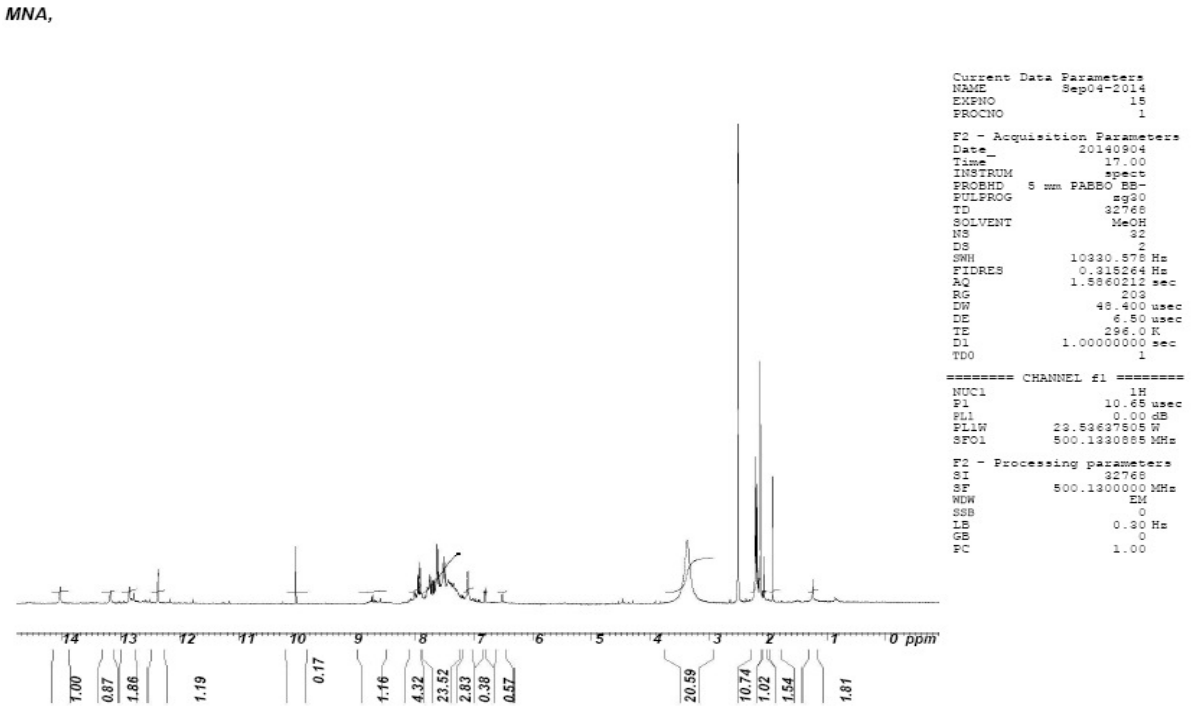

Figure-2
^{1}H - NMR Spectral data of compound 3a

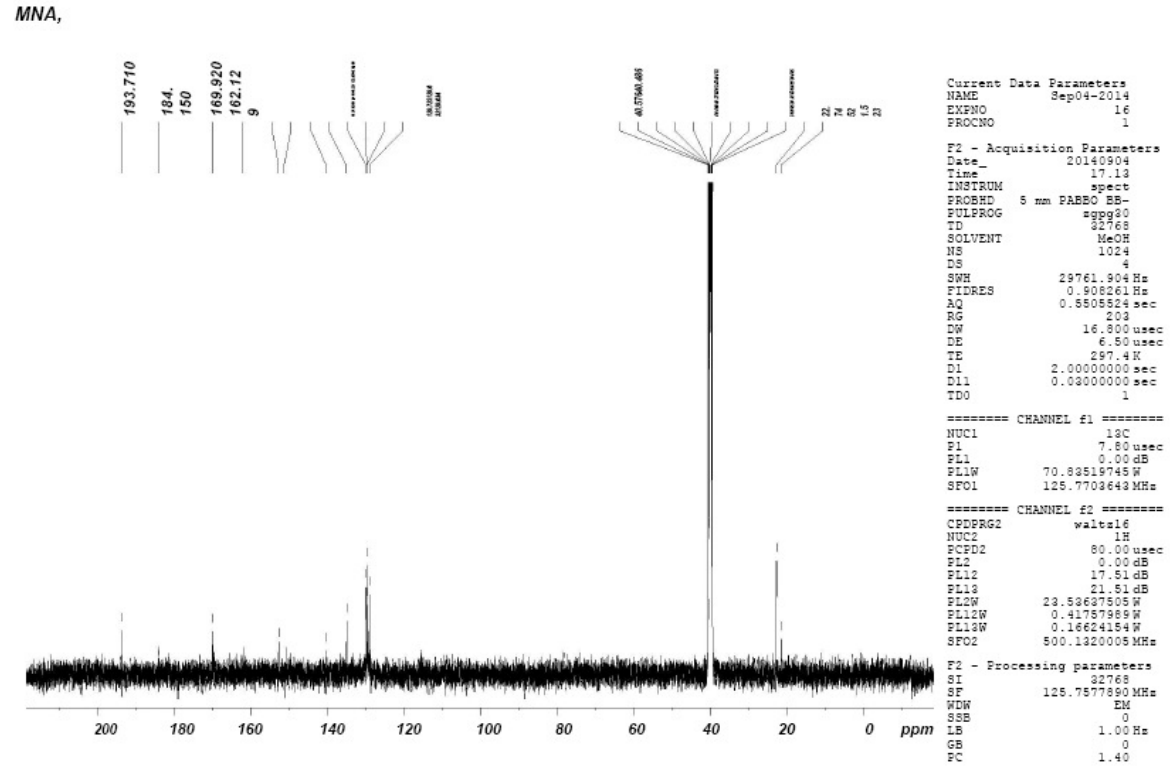

Figure-3
^{13}C- NMR Spectral data of compound 3a

Conclusion

In conclusion, a series of chalcones (3a-h) were synthesized and characterized by Claisen-Schmidt condensation reaction. They were screened for their potential antimicrobial activities in comparison with the standard drugs tetracycline and ketoconazole . The compounds 3aand 3c,3d exhibited the most intensive and consistent antimicrobial activitywith a MIC value of 15-20 μg/mL.

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