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Synthesis and in Vitro Anti Microbial Study of Some Novel Schiff Bases Synthesized By Different Methods

Sharma N.R. and Parmar J.M. *

Department of Chemistry, Maharaja Shree MahendraSinhji Science College,
Morbi-363642, (Gujarat), India.
E-mail: sharmanitish48@gmail.com

ABSTRACT

Schiff bases containing heterocyclic scaffolds such as coumarin derivatives are an important class of heterocyclic compounds which show wide spectrum of biological and pharmacological activities. Hence, in the present work, some new heterocyclic Schiff bases have been synthesized by two different methods; conventional and microwave irradiation methods. The effect of solvents on reaction time and yield was also graphically represented. Further these synthesized compounds were characterized by different methods such as IR, ^{1}H NMR and mass spectral data. The in vitro anti-microbial activities of these compounds were studied in DMF and DMSO against some selected bacterial and fungal strain.

KEYWORDS: Schiff base, conventional method, microwave irradiation method.

***Corresponding author**

J.M. PARMAR

Department of Chemistry,

Maharaja Shree MahendraSinhji Science College,

Morbi-363642, (Gujarat), India.

E-mail: sharmanitish48@gmail.com

INTRODUCTION

The compounds containing -C=N- are the group are generally termed as Schiff bases[1]. The imine grouppresent in such compounds has been shown to be critical totheir biological activities[2]. The Schiff bases containing wide range of biological activities including biological, pharmacology, medicinal etc. As per Literature survey it is observed that Schiff bases are known to exhibit various activities such as antibacterial[3,4] antifungal[5,6] antiviral[7], antimalarial[8], antipyretic properties[9], cytotoxic[10], anticonvulsant[11,12], antitumor[13], etc. further these biological activities are enhanced by introducing heterocyclic compounds especially coumarin derivative[14, 15]. Hence, syntheses of such compounds are of considerable interest. Many medicinal interest compounds are containing heterocycles especially nitrogen and oxygen containing[16-18].

A literature survey shows that various workers have reported the synthesis of heterocyclic compounds containing pyridine and coumarin scaffold and shows that these heterocycles enhanced biological and pharmacological activities of the Schiff bases[19, 20].

Multi-step reactions are sometimes not efficient tools in modern synthetic organic chemistry due to their decreases in significant features such as atom economy and straight forward reaction designing. Further in conventional or tradition methods are required much energy effort. Now a days microwave assisted reactions getting more attention in comparison of traditional method because of better energy and atomic efficiency. Microwave Induced Organic Reaction enhancement (MORE) chemistry is nonconventional technique for rapid synthesis of heterocyclic compound in last few year [21, 22].

The structural characterizations of these synthesized compounds were carried out by various spectroscopic methods such as Infra-red, mass spectrometry and 1H nuclear magnetic resonance. Further, *in vitro* antibacterial and antifungal activities of these derivatives have been studied in *N,N*-dimethyl formamide and dimethyl sulphoxide solvents against some selected gram positive and gram negative as well as fungal strains.

METHODS

Chemicals

For the synthesis different substituted benzaldehydes, hydrazine hydrates etc., was purchased from Spectrochem Pvt. Ltd. (Mumbai, India) and was used without any further purification.

The solvents used in anti-microbial activities were of AR grade supplied by Spectrochem Pvt. Ltd. (Mumbai, India) and were purified according to standard distillation process[23].

The melting points of all these compounds were taken by open capillaries method. The purity of the synthesized compounds was checked by Thin Layer Chromatography.

INSTRUMENT

The structure confirmation of these synthesized Schiff bases was done by Infra-red, ^{1}H Nuclear magnetic resonance and mass spectral data. For Infra-red analysis of synthesized compounds IRaffinity-1S (Shimadzu furrier transport infrared spectrophotometer) instrument was used.^{1}H NMR spectra were taken on a Bruker AVANCE III (400 MHz). In all the cases, NMR spectra were obtained in deuterated dimethyl sulfoxide (DMSO-d_6) using tetra methyl silaneas an internal standard. The NMR signals are reported in δ ppm. Mass spectra were determined using direct inlet probe on a Shimadzu GC-MS (Model No.- QP 2010) mass spectrometer.

ANTI-MICROBIAL ACTIVITY

The effective antimicrobial agents; chloramphenicol and tetracycline are used as reference for comparison with activity of synthesized compounds. Similarly, for fungal activity, nystatin and itraconazole were used as a reference.

For the anti-microbial activity various bacterial and fungal strains are used mention as given below; As Gram positive *Bacillus cereus* ATCC11778 *(BC)*, *Corynebacterium rubrum* ATCC14898 (*CR*), *Bacillus subtilis* ATCC1912 (*BS*), *Staphylococcusaureus* ATCC29737 (*SA*) bacterial strains were used. As Gram negative *Klebsiella pneumoniae* NCIM2719 (*KP*), *Staphylococcus typhimurium* ATCC23564 (*ST*), *Escherichia coli* NCIM2931 (*EC*), *Pseudomonas aeruginosa*ATCC27853 (*PA*) were used.

For fungal activity, the *Candida albicans* ATCC2091 (*CA*), *Candida glabrata* NCIM3448 (*CG*), *Candida epicola* NCIM3367 (*CE*), *Cryptococcus neoformans* NCIM3542 (*CN*) fungal strains were used.

PREPARATION OF SOLUTIONS OF COMPOUNDS

For all the compounds, solution of 20 mg/ml concentration was prepared in DMF and DMSO. *In vitro*, antimicrobial activity of all the compounds was studied against selected bacterial and fungal strains by the Agar well diffusion method.

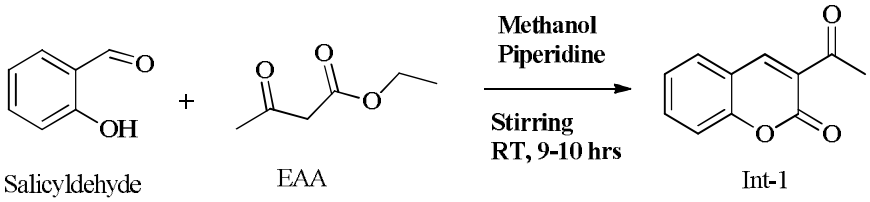
For that Mueller Hinton No. 2 / Sabouraud dextrose agar (Hi-media) was used for the antibacterial and antifungal susceptibility test respectively. The Mueller Hinton agar and Sabouraud

dextrose agar were melted and were cooled to 48-50°C. A standardized inoculum (1.5×10^8 CFU/ ml, 0.5 McFarland) was then added aseptically to the molten agar and was poured into sterile Petri dishes. Wells of 8.5 mm were prepared in the seeded agar plates. The test compound was introduced into the well. The petri plates were incubated overnight at 37°C and 28°C for 24 h and 48 h respectively, for bacteria and fungi. DMSO/DMF was used as negative control. The microbial growth was determined by measuring the diameter of the zone of inhibition and the mean values are considered.

EXPERIMENTAL

❖ Synthesis of 3-acetyl-2H-chromen-2-one (Int-1):

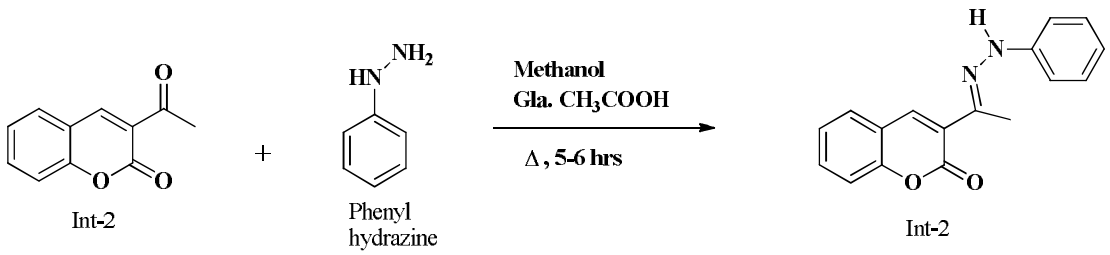
A mixture of salicyldehyde (0.01 mmol) and ethyl acetoacetate (0.012 mmol) in methanol was stirred for 9-10 hrs at room temperature (RT) in presence of 0.5 ml piperidine. The completion of reaction was checked by analytical thin layer chromatography (TLC) (Performed on aluminium coated plates Gel $60F_{254}$ (E. Merck)) using (0.6:0.4-Hexane: Ethyl acetate) as a mobile phase. After the completion of reaction, the resulting solid was filtered, washed with cold methanol and dried. The crude product was used for the next step without further purification.



Salicyldehyde EAA Int-1

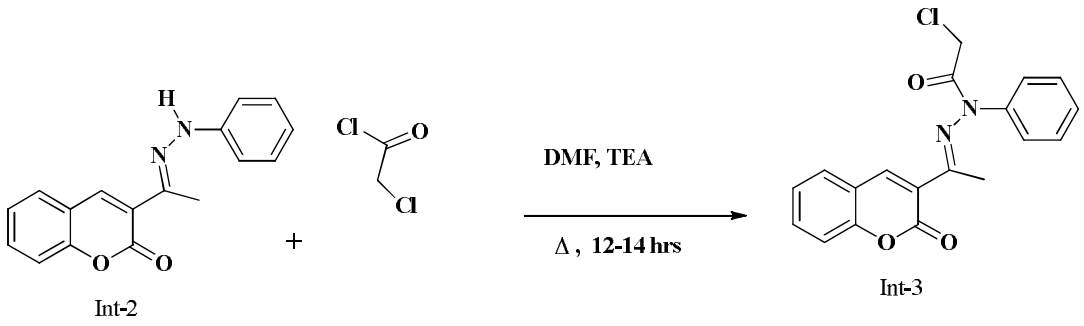
❖ Synthesis of 3-(1-(2-phenylhydrazono)ethyl)-2*H*-chromen-2-one (Int-2):

Equimolar mixture of 3-acetyl-2H-chromen-2-one(Int-1) and phenyl hydrazine was refluxed for 5-6hrsusingglacial acetic acid as catalyst. The progress of reaction was checked by TLC using (0.3:0.7 v/v-Hexane: Ethyl acetate) as mobile phase. After completion of reaction, the temperature of reaction mass was allowed to decrease to room temperature. The solid product was separated by filtration, washed with cold methanol and dried. The product was crystallized from methanol. This product was used in the next step.



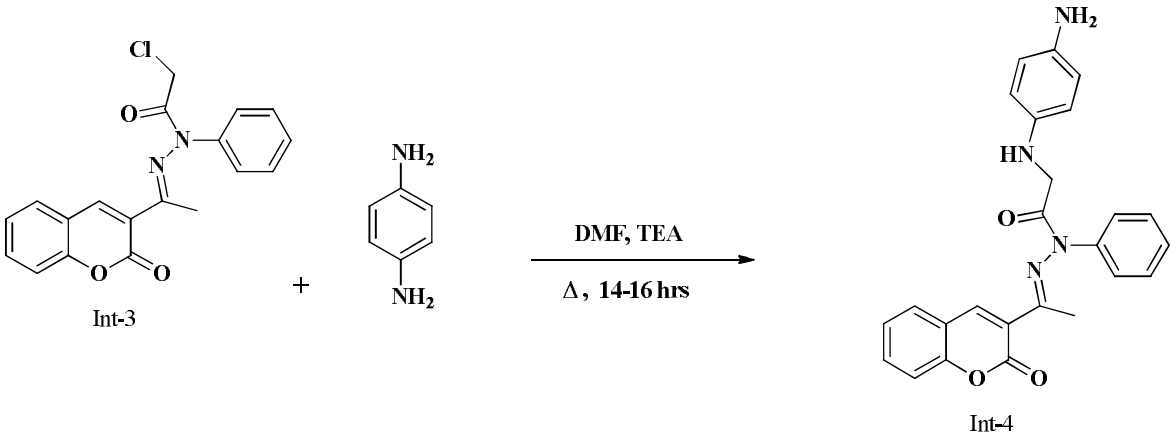
❖ Synthesis of 2-chloro-N'-(1-(2-oxo-2H-chromen-3-yl)ethylidene)-N-phenylacetohydrazide (Int-3):

Equimolar mixture of 3-(1-(2-phenylhydrazono)ethyl)-2*H*-chromen-2-one (Int-2) and chloro acetyl chloride was refluxed for 12-14 hr sin the presence of triethyl amine (TEA) using as catalyst. The progress of reaction was checked by TLC using (0.4:0.6 v/v-Hexane: Ethyl acetate) as mobile phase. The progress of reaction was checked by thin layer chromatography. After completion of reaction, the reaction mass was poured in cold water with stirred. The obtained solid product was separated by filtration, washed with cold water and dried.



❖ Synthesis of 2-((4-aminophenyl)amino)-N'-(1-(2-oxo-2H-chromen-3-yl)ethylidene)-N-phenylacetohydrazide (Int-4):

The mixture of **2**-chloro-N'-(1-(2-oxo-2H-chromen-3-yl) ethylidene)-N-phenylacetohydrazide (Int-3)and1,4-phenyldiamine was prepared in DMF and add few drops of triethyl amine (TEA) using as catalyst. The resultant mixture was refluxed for 14-16 hrs. The progress of reaction was checked by TLC using (5.0:5.0 v/v-Hexane: Ethyl acetate) as mobile phase. After completion of reaction, the reaction mass was poured in cold water with stirring. The obtained solid product was separated by filtration, washed with cold water then cold methanol and dried. This product is directly used for final steps without further purification.



❖ Synthesis of Schiff bases:

Schiff bases were synthesized by two ways:

[1] Conventional method

[2] Microwave irradiation method

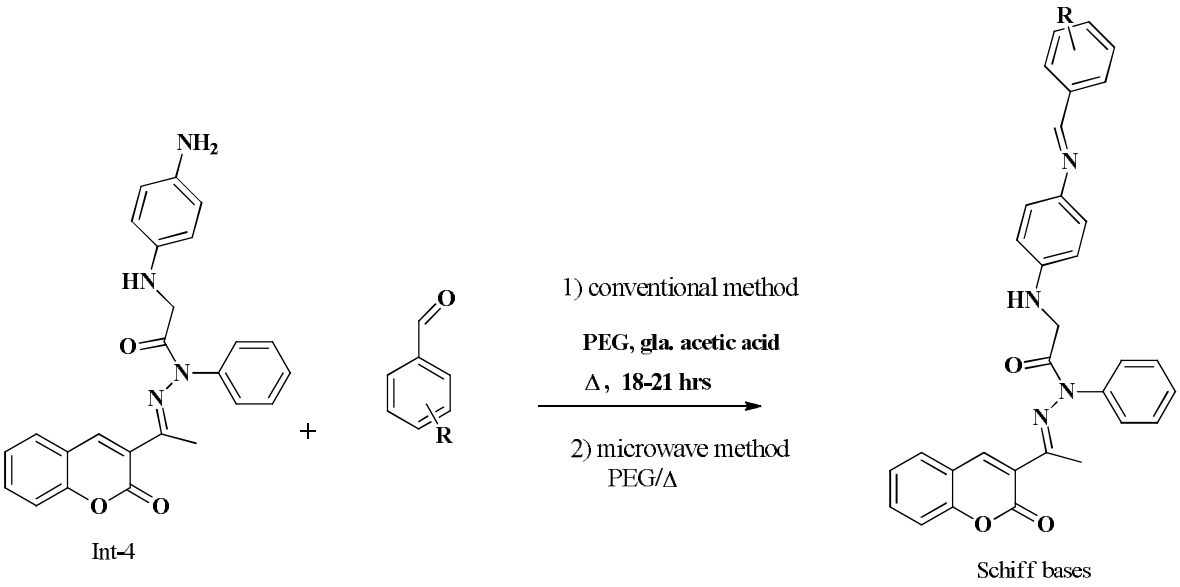
[1] Conventional method:

In this method, a mixture of 3-(2-oxo-2H-chromen-3yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (0.01 mmol) and different substituted aryl aldehydes (0.011 mmol) was refluxed in poly ethylene glycol 400 (PEG 400) for 8-12 hrs in presence of few drops of glacial acetic acid used as catalyst.

The progress of reaction was checked by TLC using (0.7:0.3-Chloroform Methanol) as a mobile phase. After completion of reaction, the reaction mass was cooled to room temperature and then was poured in to water. The resulting solid mass was filtered.

[2] Microwave irradiation method:

A mixture of 3-(2-oxo-2H-chromen-3yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (0.01 mmol) and different substituted aryl amines (0.011 mmol) was subjected to microwave irradiation for 15-20 minutes at 450 Watt. The reaction status was checked by TLC using (0.7:0.3-Chloroform: Methanol) as a mobile phase. After completion of reaction, the content was poured in to water and was allowed to stirrer for 10-12 hrs. The obtained crude product was filtered.



RESULT AND DISCUSSIONS

The physical properties of synthesized Schiff bases are given in Table 1.

Table 1: The physical data of synthesized Schiff base

Compound Code	*Substitution R*	*Molecular formula*	*Molecular weight (g/mol)*	*Melting points (°C)*	R_f^* *value*
SHA-1	H	$C_{32}H_{26}N_4O_3$	514	320-324	0.58
SHA-2	4-Br	$C_{32}H_{25}N_4O_3Br$	592	298-302	0.55
SHA-3	4-Cl	$C_{32}H_{25}N_4O_3Cl$	548	340-345	0.63
SHA-4	2-F	$C_{32}H_{25}N_4O_3F$	532	241-244	0.49
SHA-5	4-F	$C_{32}H_{25}N_4O_3F$	532	244-247	0.60
SHA-6	4-NO_2	$C_{32}H_{25}N_5O_5$	559	241-245	0.53
SHA-7	3-Cl-4-F	$C_{32}H_{24}N_4O_3ClF$	567	248-252	0.51
SHA-8	2-Br	$C_{32}H_{25}N_4O_3Br$	592	251-254	0.59

*0.7:0.3 v/v- chloroform: methanol

Table 2 shows the % Yield and reaction time for the synthesis of Schiff bases by both conventional and microwave irradiation methods.

Table 2: The % yield and reaction time for the Schiff base synthesis by conventional and microwave irradiation methods

Compound Code	% Yield		Reaction Time	
	Microwave Irradiation	Conventional	Microwave Irradiation (min.)	Conventional (hrs.)
SHA-1	67	49	20	10-11
SHA-2	78	55	18	8-9
SHA-3	84	58	15	8-9
SHA-4	75	61	17	8-9
SHA-5	79	69	14	8-9
SHA-6	81	62	15	8-9
SHA-7	60	52	20	11-12
SHA-8	71	63	15	9-10

It is evident from Table 2 that % yields of Schiff bases increased significantly using microwave irradiation method. The Schiff bases containing nitro aryl side chains have higher % yield than other halide containing bases. In conventional method, reaction time is in hours whereas in microwave irradiation method, it is reduced into minutes.

Further PEG-400 used as solvent in microwave irradiation method. The choice of PEG-400 as reaction medium is due to its solubility in water and various organic solvents. So, it can be easily recovered/ removed from the reaction mixture. Further, PEG-400 is thermally stable, inexpensive, environmentally friendly and non-toxic hydrophilic polymer.

Hence, it is concluded that the microwave irradiation method is more favorable for the synthesis of Schiff bases. Figures 1 shows the IR spectrum of SHA-1. Figure 2 and 3 show ^{1}H NMR and Mass spectrum of SHA-1 compound respectively.

From the Figure 4 it is observed that against *Bacillus cereus* in DMF, all the studied compounds exhibited significant inhibition and SHA-6 showed maximum inhibition. In DMSO, few compounds had no effect on *Bacillus cereus* and SHA-6 showed maximum inhibition. Against *Corynebacteriumrubrum*, SHA-1 and SHA-6 showed significant inhibition in DMF whereas in DMSO only SHA-6 showed inhibition. The inhibition is higher for SHA-6 and in DMF it is almost up to same extent as that of chloramphenicol.

SHA-6 containing 4-nitro group substituted phenyl ring. Overall, both these compounds showed significant inhibition against all selected Gram-positive bacteria (except *Bacillus subtilis* in DMSO) in both DMF and DMSO. This suggests that compound having methyl group substituted

phenyl ring showed significant inhibition against selected Gram positive bacteria. Out of these four strains, *Bacillus subtilis* is most resistant bacteria.

Against Gram negative bacteria, Figure 5 shows the zone of inhibition for the studied compounds along with two standard antibiotics in DMF and DMSO.

In DMF against *Klebsiellapneumonia*, except SHA-7, all the studied compounds showed inhibition and SHA-5 and SHA-6 showed same extent of inhibition. Thus, SHA-5 and SHA-6 containing 4-fluoro and 4-nitro groups respectively are found to be most effective than other groups against *Klebsiellapneumonia* in DMF. Against *Escherichia coli*, few compounds exhibited inhibition in DMF and had almost equal effect. However in DMSO, against this strain only SHA-7 showed inhibition. Thus, again type of substituent plays an important role in inhibition. Comparison of inhibition of studied compounds with those of standard antibiotics shows that all the compounds exhibited less inhibition than that of antibiotics against selected Gram negative bacteria in both DMF and DMSO.

Figure 6 shows the zone of inhibition for the studied compounds and two antibiotics against some selected fungal strains in DMF and DMSO. It is observed that against *Candida albicans*, many compounds are effective. Against *Candida glabrata*, SHA-4 with SHA-5 containing 2-fluoro and 4-fluoro groups are effective in DMF whereas in DMSO, only SHA-8 containing 2-bromo group showed inhibition.

Figure-1: IR spectrum of SHA-1

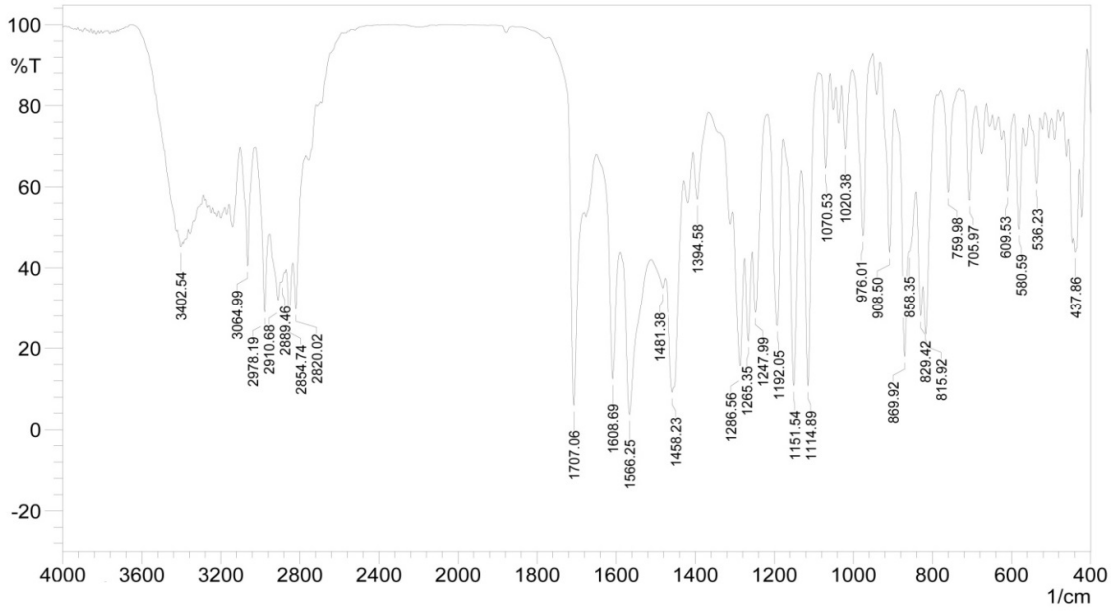


Figure-2: ^{1}H NMR spectrum of SHA-1

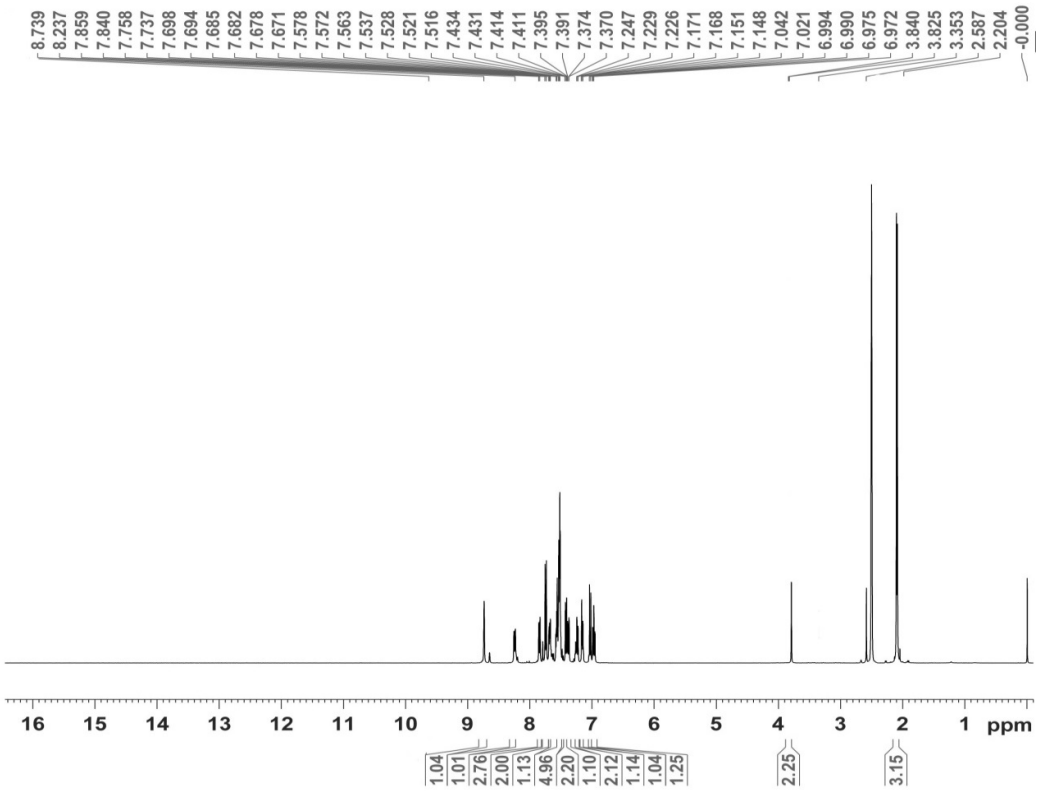
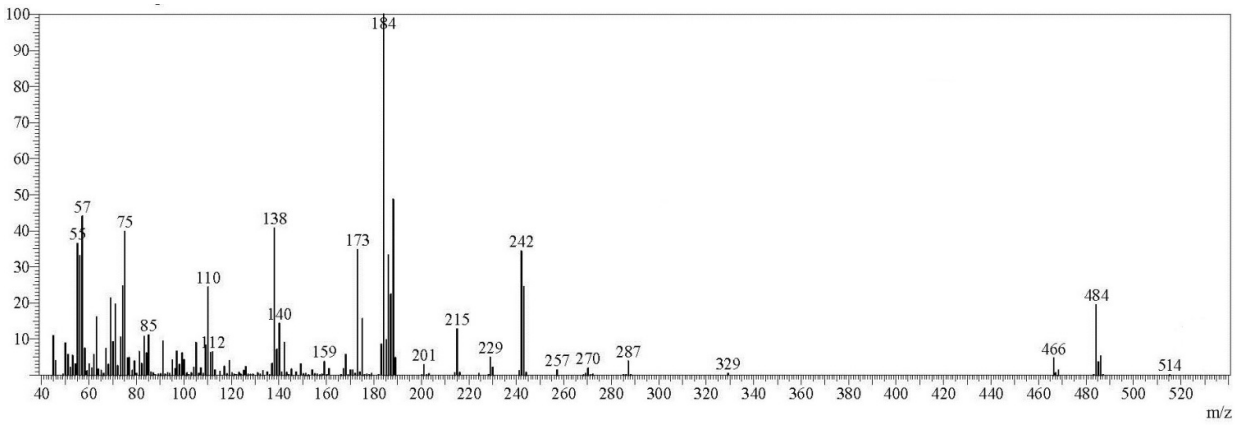


Figure-3: Mass spectrum of SHA-1



Spectral data

SHA-1

IR (v, cm^{-1}): 3402.54 (-OH stretching), 3064.99, 2978.19, 2910.68, 2889.46, 2854.74, 2820.02 (N-H stretching), 1707.06, 1608.69, 1566.25, 1286.56, 1265.35 (-CO- stretching), 1458.23, 1394.58 (-CH-), 976.01, 908.50 (C=C stretching), 815.92 (di-substituted), 759.98, 705.97 (-CH- stretching).

^{1}H NMR (400 MHz, DMSO-d$_6$) (δ ppm): 2.204 (s, 3H, -CH_3), 3.840 (s, 2H, -CH_2-), 6.972-7.859 (m, 19H, Ar-CH), 8.237 (s, 1H, -CH-), 9.627 (s, 1H, -CH=N-)

Mass (m/z): 514.

SHA-2

IR (v, cm^{-1}): 3410.34 (-OH stretching), 3065.12, 2974.23, 2882.34, 2851.39, 2829.82 (N-H stretching), 1713.47, 1612.14, 1569.29, 1281.01 (-CO- stretching), 1453.98, 1391.24 (-CH- stretching), 976.54, 915.67 (C=C stretching), 811.23 (di-substituted), 682.80 (C-Br stretching).

^{1}H NMR (400 MHz, DMSO-d$_6$) (δ ppm): 2.212 (s, 3H, -CH_3), 3.843 (s, 2H, -CH_2-), 6.975-7.879 (m, 18H, Ar-CH), 8.249 (s, 1H, -CH-), 9.641 (s, 1H, -CH=N-)

Mass (m/z): 592.

SHA-3

IR (v, cm^{-1}):3734.19, 3082.25(O-H stretching), 2212.14 (-CN stretching), 1747.51(-C=O stretching), 1649.14, 1585.49 (-NH- bending), 1471.69 (-CH- bending, alkanes), 1398.39, 1340.53 (-CH- rock, alkanes), 1274.95, 1213.25, 1089.78 (C-O stretching, ether), 995.27 (O-H bending), 873.75 (di-substituted benzene ring).

^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 2.215 (s, 3H, -CH_3), 3.829 (s, 2H, -CH_2-), 6.969-7.871 (m, 18H, Ar-CH), 8.265 (s, 1H, -CH-), 9.656 (s, 1H, -CH=N-)

Mass (m/z): 548.

SHA-4

IR (v, cm^{-1}):3731.22, 3078.25(O-H stretching), 1742.52(-C=O stretching), 1644.14, 1582.44 (-NH- bending), 1476.65 (-CH- bending, alkanes), 1395.35, 1344.52 (-CH- rock, alkanes), 1278.95, 1215.25, 1084.78 (C-O stretching, ether), 992.22 (O-H bending), 871.18 (di-substituted benzene ring), 681.19 (C-F stretching).

^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 2.205 (s, 3H, -CH_3), 3.811 (s, 2H, -CH_2-), 6.957-7.878 (m, 18H, Ar-CH), 8.249 (s, 1H, -CH-), 9.646 (s, 1H, -CH=N-)

Mass (m/z): 532.

SHA-5

IR (v, cm^{-1}):3732.89 (O-H stretching), 1745.78 (-C=O stretching), 1648.11, 1585.78 (-NH- bending), 1478.45 (-CH- bending), 1397.11, 1345.77 (-CH- rock, alkanes), 1279.91, 1212.13 (C-O stretching, ether), 992.45 (O-H bending), 870.87 (di-substituted benzene ring), 680.01 (C-F stretching).

^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 2.209 (s, 3H, -CH_3), 3.819 (s, 2H, -CH_2-), 6.947-7.865 (m, 18H, Ar-CH), 8.242 (s, 1H, -CH-), 9.685 (s, 1H, -CH=N-)

Mass (m/z): 532.

SHA-6

IR (v, cm^{-1}):3734.19, 3083.14 (O-H stretching), 1716.65 (-C=O stretching), 1649.14, 1598.99 (-NH- bending), 1490.97, 1471.69 (-CH- bending, alkanes), 1367.53, 1334.74 (-CH- rock, alkanes), 1288.45, 1234.44, 1074.35 (C-O stretching, ether), 968.27 (O-H bending), 865.25 (di-substituted benzene ring).

^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 2.250 (s, 3H, -CH_3), 3.889 (s, 2H, -CH_2-), 6.986-7.871 (m, 18H, Ar-CH), 8.264 (s, 1H, -CH-), 9.699 (s, 1H, -CH=N-)

Mass (m/z): 559.

SHA-7

IR (v, cm^{-1}):3724.69, 3337.56 (O-H stretching), 1746.41 (-C=O stretching), 1579.70 (-NH- bending), 1450.11 (-CH- bending, alkanes), 1393.53 (-CH- rock, alkanes), 1256.58, 1019.90 (C-N stretching),

1291.48 (C-O stretching, ether), 929.33 (O-H bending), 831.18 (di-substituted benzene ring), 688.71 (C-F stretching)..

^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 2.221 (s, 3H, -CH_3), 3.845 (s, 2H, -CH_2-), 6.924-7.878 (m, 17H, Ar-CH), 8.212 (s, 1H, -CH-), 8.463 (s, 1H, -CH-), 9.743 (s, 1H, -CH=N-)

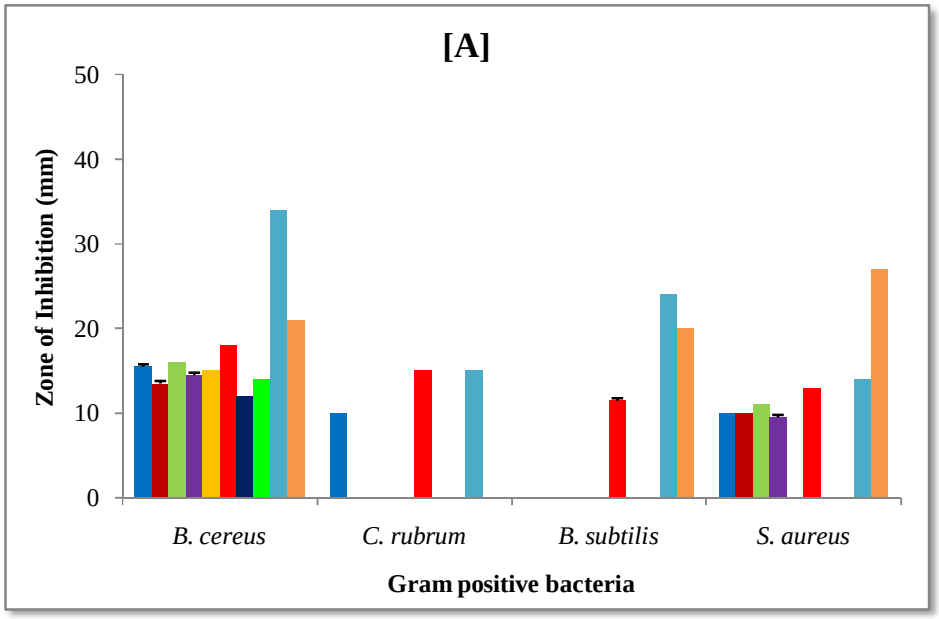
Mass (m/z): 567.

SHA-8

IR (v, cm^{-1}): 3418.34 (-OH stretching), 3064.67, 2885.83, 2858.83, 1579.70 (-NH- bending), 1460.11 (-CH- bending, alkanes), 1394.53 (-CH- rock, alkanes), 1276.88, 1029.99 (C-N stretching), 1230.58 (C-O stretching, ether), 939.33 (O-H bending), 835.18 (di-substituted benzene ring), 682.80 (C-Br stretching).

^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 2.223 (s, 3H, -CH_3), 3.845 (s, 2H, -CH_2-), 6.968-7.887 (m, 18H, Ar-CH), 8.267 (s, 1H, -CH-), 9.646 (s, 1H, -CH=N-)

Mass (m/z): 592.



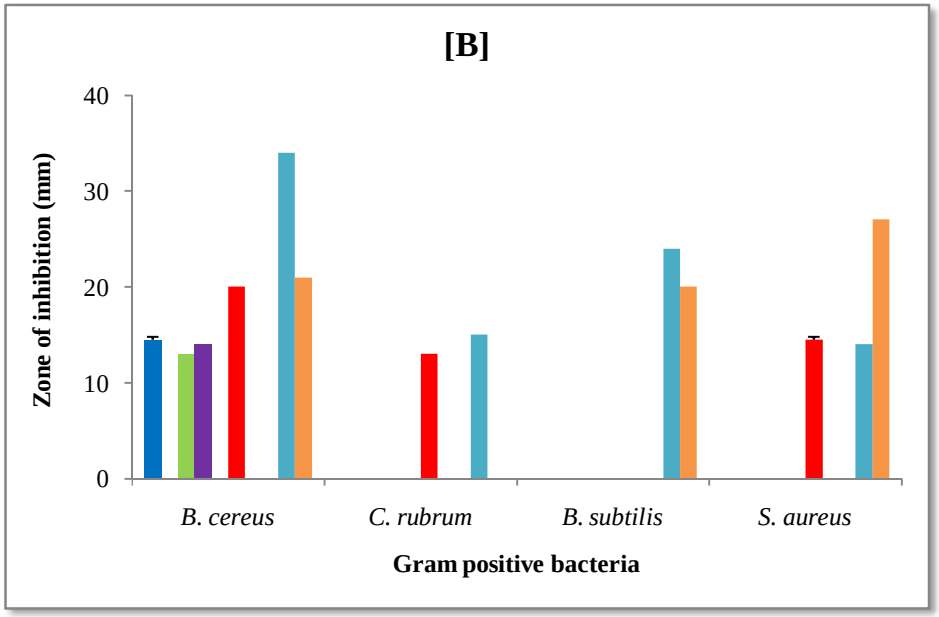
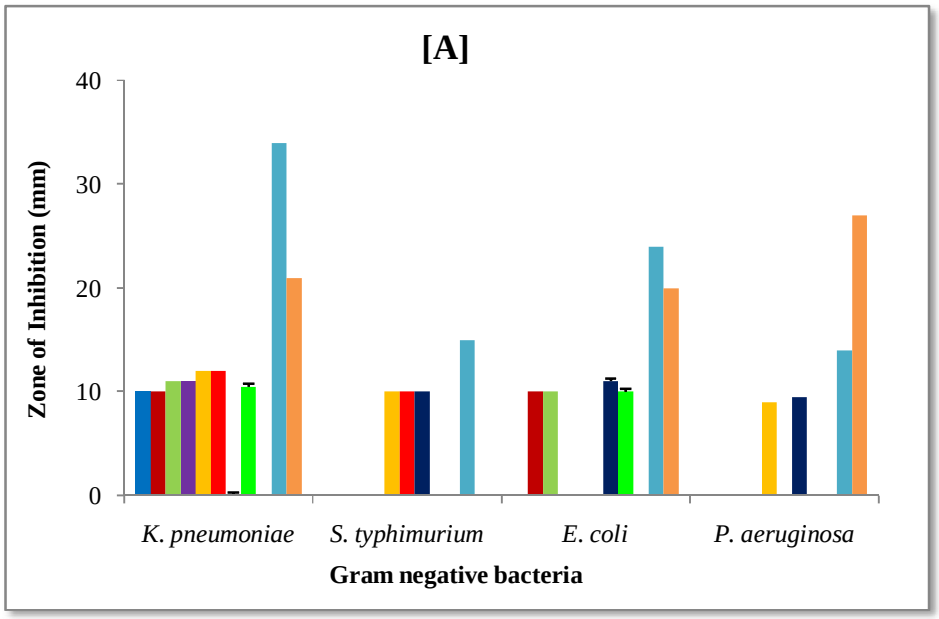


Figure 4:Zone of inhibition of Schiff basesagainst Gram positive bacteria in [A] DMF and [B] DMSO [SHA-1, (■); SHA-2, (■); SHA-3, (■); SHA-4, (■); SHA-5, (■); SHA-6, (■); SHA-7, (■); SHA-8, (■); Chloramphenicol (■); Tetracycline (■)]



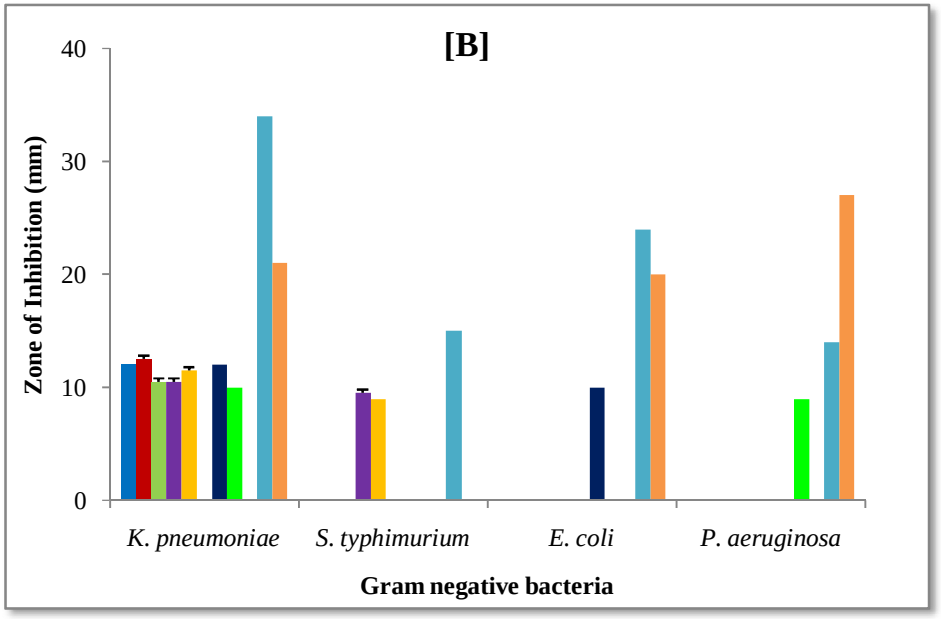
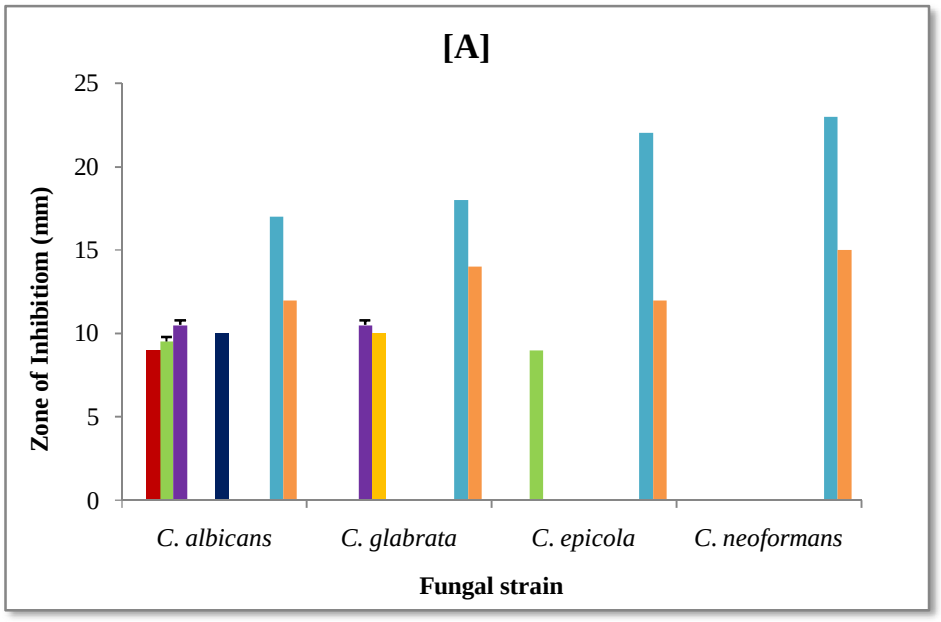


Figure 5:Zone of inhibition of Schiff basesagainst Gram negative bacteria in [A] DMF and [B] DMSO [SHA-1, (■); SHA-2, (■); SHA-3, (■); SHA-4, (■); SHA-5, (■); SHA-6, (■); SHA-7, (■); SHA-8, (■); Chloramphenicol (■); Tetracycline (■)]



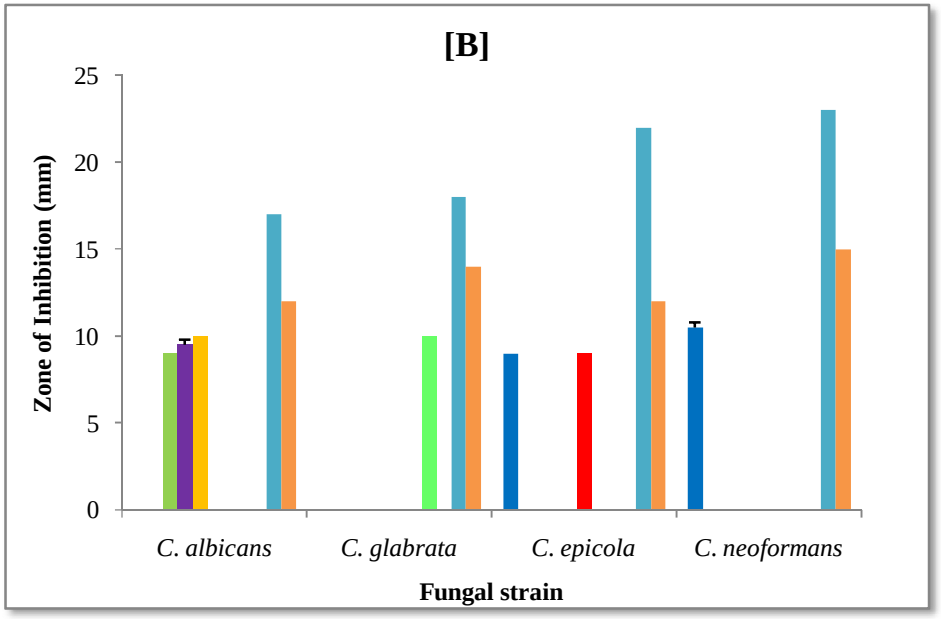


Figure 6:Zone of inhibition of Schiff basesagainst fungal strains in [A] DMF and [B] DMSO [SHA-1, (■); SHA-2, (■); SHA-3, (■); SHA-4, (■); SHA-5, (■); SHA-6, (■); SHA-7, (■); SHA-8, (■); Nystatin (■); Itroconazole, (■)]

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