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Full Length Research Paper

Synthesis, characterization and antimicrobial screening of some novel coumarin-pyrazolo Schiff bases

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Some novel coumarin-pyrazolo substituted Schiff bases were synthesized by two different methods; conventional and microwave irradiation from coumarin-pyrazole aldehyde and different substituted aryl amines. The structure conformation of these synthesized compounds was done by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. All these synthesized compounds were also tested for *in-vitro* antimicrobial activity against some bacterial as well as fungal strains in DMF and DMSO. It is observed that some of Schiff bases showed excellent antibacterial activity in both solvents.

Key words: Schiff bases, gram positive bacteria, gram negative bacteria, DMF, DMSO.

INTRODUCTION

The chemistry of the carbon-nitrogen (-C=N-) double bond i.e., Schiff base plays a vital role in the progress of chemistry science (Bodowska et al., 2014; Xavier and Srividhya, 2014; Chetana et al., 2015). Schiff bases are used as intermediate for synthesis of many biological active compounds such as azetidinones, thiazolidinones, and arylacetamide (Wadher et al., 2009; Kumar et al., 2012; Mauf et al., 2014). Further, Schiff bases and their metal complexes are used as catalyst in various biological systems, in synthesis of polymer, as fluorimetric analytical reagents (Khan et al., 2011; Khoo et al., 2014; Xin and Yun, 2012; Ibrahim and Sharif, 2007).

Schiff bases having different heterocyclic scaffolds e.g. pyrazole, coumarin etc. show many biological and pharmacological activities such as anti-microbial (Bhatt et al., 2013; Hishmat *et al.,* 1989; Deckie *et al.*, 2010), antibacterial (Al-Mosawi, 2014), antihistaminic (Buckie et al*.*, (1984), anti-inflammatory and analgesic (Ghate et al., (2005), anti-tuberculosis (Manvar et al., 2008), antifungal (Al-Amiery et al., 2012); Guerra et al., 2015), anticancer (Klenkar and Molnar, 2015), antioxidant (Arora et al., 2014) and many other pharmacological activities (Freires et al., 2016); Ferraroni et al., 2016) etc.

Owing to these interesting applications of Schiff bases, in the present work, some novel Schiff bases have been synthesized by two different methods, (i) conventional and (ii) microwave irradiation. The structure of these compounds was confirmed by different spectroscopic techniques likes FT-IR, ^{1}H NMR, ^{13}C NMR and mass. The *in vitro* screening for antimicrobial activity of the synthesized compounds was also carried out against some Gram positive and Gram negative bacteria as well as fungi in *N,N*-dimethyl formamide (DMF) and dimethyl sulfoxide (DMSO).

EXPERIMENTAL

Materials

The solvents, DMF and DMSO used for the study of antimicrobial activity were of Analytical Reagent (AR) grade supplied by LOBA Chemie Pvt. Ltd. (Mumbai-INDIA) and were purified according to the standard reported procedure (Riddick et al., 1986).

Synthesis

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

Literature survey shows that 3-acetyl-2*H*-chromen-2-one

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has been synthesized by many different methods (Hasnah et al., 2012; Rajesh et al., 2015; Mohammad et al., (2016).

Equimolar mixture of salicyldehyde and ethyl acetoacetate (EAA) in methanol was stirred for 2 h in the presence of piperidine used as catalyst. The progress 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 v/v-hexane: ethyl acetate) as a mobile phase. After the completion of reaction, the resulting solid is filtered, washed with cold methanol and was dried under vacuum. The obtained crude product is used for the next step without further purification.

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

To a mixture of 3-acetyl-2*H*-chromen-2-one (Int-1) (0.01 mmol) and phenyl hydrazine (0.011 mmol) in methanol, 4 - 5 drops of glacial acetic acid was added and then it was refluxed for 5-6 hours. The status 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 up to room temperature. The obtained solid was separated by filtration, washed with cold methanol and dried. The obtained crude product was used in the next step without any further purification.

Synthesis of 3-(2-oxo-2*H*-chromen-3yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (Int-3)

To a well stirred and cooled (0°C) solution of 3-(1-(2-phenylhydrazono)ethyl)-2*H*-chromen-2-one (Int-2) (0.01 mmol) in anhydrous DMF (0.1 mmol), phosphorus oxychloride ($POCl_3$) (0.03 mmol) was added drop wise. After complete addition of $POCl_3$, the reaction mixture was further stirred at 0°C for additional one hour. The reaction mixture was then refluxed and the progress of reaction was checked by TLC using (0.4:0.6 v/v-hexane: ethyl acetate) as a mobile phase. After completion of reaction, the reaction mixture was poured into crushed ice and was left for 10 - 12 hours in a refrigerator during which a solid product was separated out. The obtained product was collected by filtration, washed with 20% Na_2CO_3 aqueous solution and was dried under vacuum.

Synthesis of Schiff bases

Schiff bases were synthesized by two different methods:

Conventional method
Microwave irradiation method

Conventional method: An equimolar mixture of 3-(2-oxo-2*H*-chromen-3yl)-1-phenyl-1*H*-pyrazole-4 carbaldehyde (Int-3) and different substituted aryl amines was refluxed in poly ethylene glycol 400 (PEG 400) for 8 - 10 h in the presence of 2 - 3 drops of glacial acetic acid. The progress of reaction was checked by TLC using (0.7:0.3-v/v chloroform: methanol) as a mobile phase. After completion of reaction, the reaction mass was poured into crushed ice and was allowed to stirrer for 10 - 12 h. The obtained solid was filtered, washed with cold water and was dried under vacuum.

Microwave irradiation method: In this method, an equimolar mixture of 3-(2-oxo-2*H*-chromen-3yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (Int-3) and different substituted aryl amines was prepared in PEG 400 and was subjected to microwave irradiation for 15-20 minutes at 450 watt. The reaction progress was checked by TLC using the same mobile phase as conventional method. After completion of reaction, the reaction mixture was poured in to cold water and was stirred for few hours. The obtained crude product was filtered, washed with cold water and was then dried.

Following are the five Schiff bases which were synthesized (Figure 1).

QAS-1:3-(4-(((4-fluorophenyl)imino)methyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*- chromen-2-one
QAS-2: 3-(4-(((4-nitrophenyl)imino)methyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one
QAS-3: 3-(4-(((3-chloro-4-flourophenyl)imino)methyl)-1-phenyl-1*H*-pyrazol-3-yl)-2H-chromen -2-one
QAS-4: 3-(4-(((4-methoxyphenyl)imino)methyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one
QAS-5: 3-(4-(((2-bromophenyl)imino)methyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one

All the synthesized Schiff bases were crystallized from N, N-dimethylformamide before use. The purity of these synthesized compounds was checked by GC-MS (SHIMADZU Model-QP2010) and was found to be greater than 99.95 %.

Spectroscopy study

The structure of the compounds was confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The IR spectra were taken on Furrier Transform Infra-Red Spectrophotometer (SHIMADZU Model-IRaffinity-1S). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III at 400 MHz frequency. In all the cases, NMR spectra were obtained in deuterated dimethyl sulfoxide ($DMSO-d_6$) and in presence of tetra methyl silane used as an internal standard. The NMR signals are reported in δ ppm. Mass spectra were determined using direct inlet probe on a GC-MS (SHIMADZU Model-QP2010) mass spectrometer. The melting points of compounds were measured by Different Scanning Calorimeter

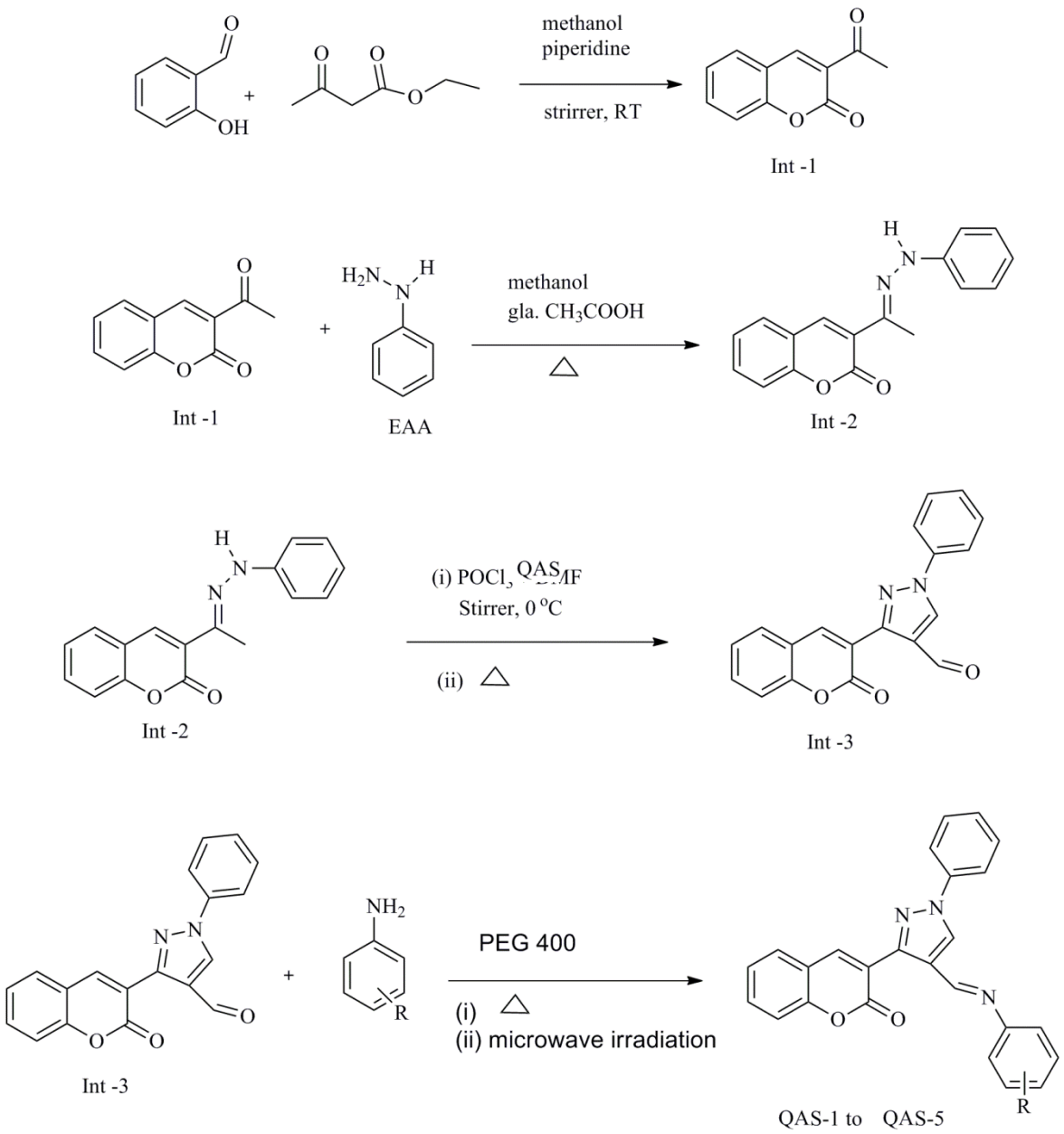


Figure 1. Reaction scheme for the synthesis of Schiff bases.

(SHIMADZU Model-DSC-60) under nitrogen atmosphere (flow rate 100 ml/min) and at 10 ˚C/min heating rate.

Figures 2 to 5 show FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectra respectively for QAS-5.

Microorganisms tested

The studied microorganisms were obtained from National Chemical Laboratory (NCL), Pune, India. The microorganisms were maintained at 4°C. The Gram positive bacteria studied were *Bacillus cereus* (*B. cereus*) ATCC11778 (BC), *Corynebacterium rubrum* (*C. rubrum*) ATCC14898 (CR), *Bacillus subtilis* (*B. subtilis*) ATCC6633 (BS) and *Staphylococcus aureus* (*S. aureus*) ATCC29737 (SA). Gram negative bacteria were *Klebsiella pneumoniae* (*K. neumoniae*) NCIM2719 (KP), *Staphylococcus typhimurium* (*S. typhimurium*) ATCC23546 (ST), *Escherichia coli* (*E.coli*) NCIM2931 (EC), *Pseudomonas aeruginosa* (*P. aeurginosa*) ATCC27853 (PA) and fungi were *Candida albicans* (*C. albicans*) ATCC2091 (CA), *Candida glabrata* (*C. glabarata*) NCIM3448 (CG), *Candida epicola* (*C. epicola*) NCIM3367 (CE) and *Cryptococcus neoformans* (*C. neoformans*) NCIM3542 (CN).

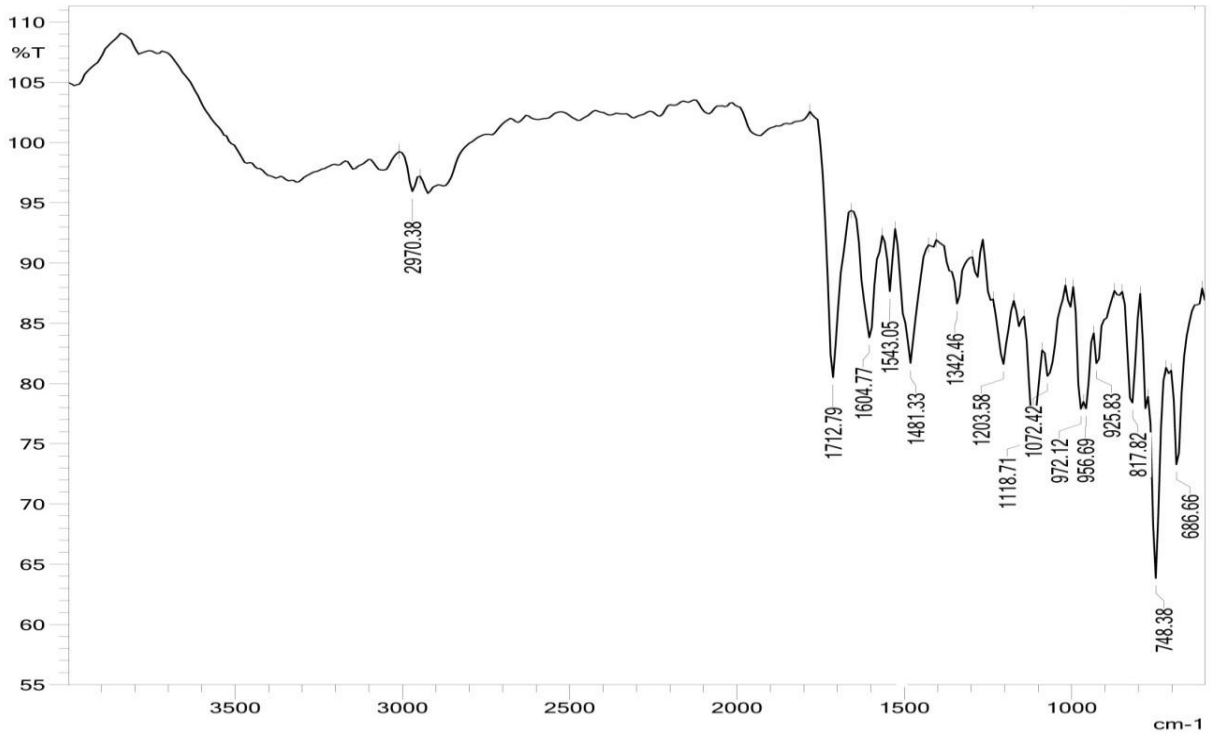


Figure 2. IR spectrum of QAS-5.

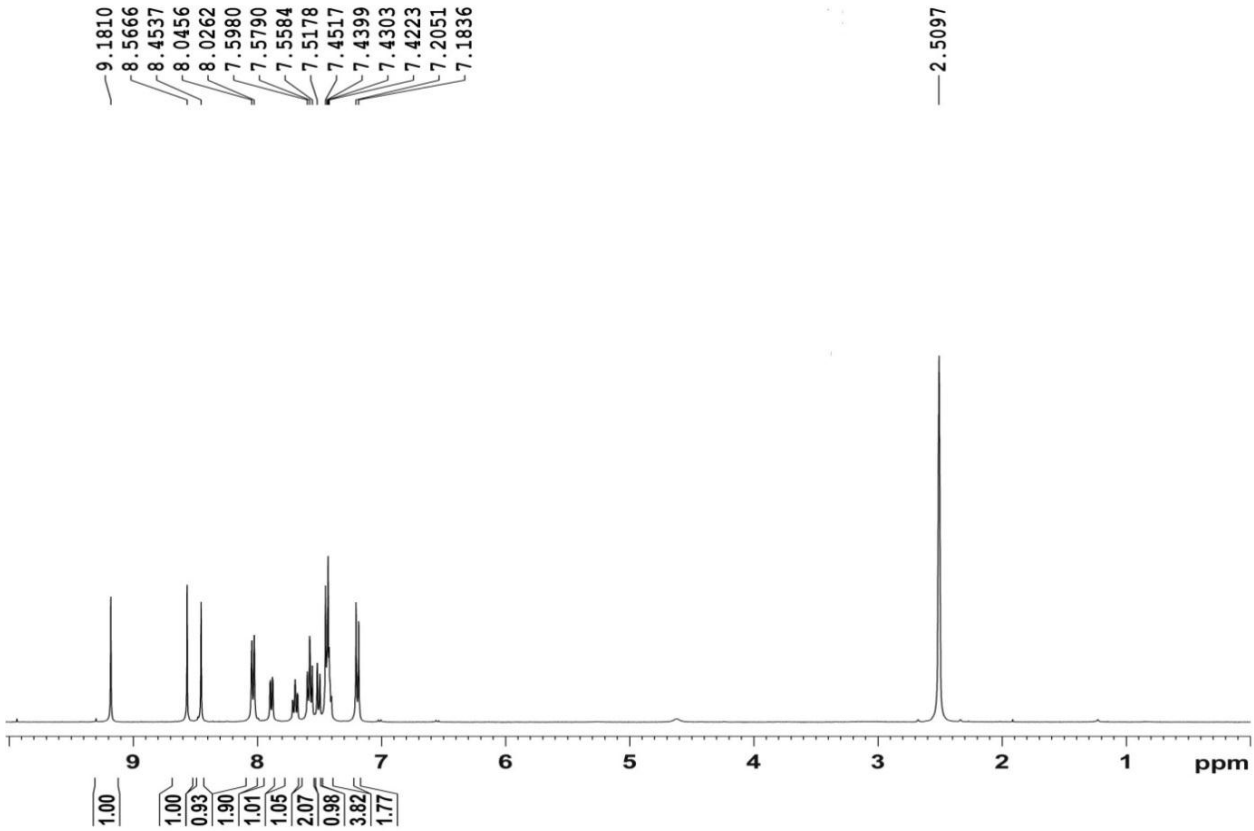


Figure 3. ^{1}H NMR spectrum of QAS-5.

Table 1. Physical constants of Schiff bases.

Compound Code	Substitution R	Molecular formula	Molecular weight (g/mol)	Melting points (°C)	R_f^* value
QAS-1	4-F	$C_{25}H_{16}N_3O_2F$	409	241.34	0.60
QAS-2	4-NO_2	$C_{25}H_{16}N_4O_4$	436	241.55	0.53
QAS-3	3-Cl-4-F	$C_{25}H_{15}N_3O_2ClF$	443	248.77	0.51
QAS-4	4-OCH_3	$C_{26}H_{19}N_3O_3$	421	335.60	0.61
QAS-5	2-Br	$C_{25}H_{16}N_3O_2Br$	470	251.98	0.59

*0.7:0.3v/v-chloroform-methanol

In the present work, the agar well diffusion method (Parekh et al., 2005) was used for the studied for *in vitro* antimicrobial activity of the synthesized Schiff bases against selected bacterial and fungal strains.

RESULTS AND DISCUSSION

The physical parameters of all the synthesized compounds are given in Table 1 along with their side substitutions.

Spectral data

QAS-1:
IR (cm^{-1}): 2972.57 (C-H stretching), 1712.28 (α, β-unsaturated carbonyl), 1605.92, 1543.23 (C-C stretching in ring), 1483.29 (C-H stretching alkane), 1343.38 (C-O stretching), 1204.29, 1116.94, 1072.02 (C-N stretching), 972.18, 956.69 (C-H bending), 817.38 (C-H rock aromatic), 685.32, 643.28 (substituted benzene ring).
^{1}H NMR (DMSO-d_6, δ ppm)*:* 7.1744-7.1901 (2H, doublet, -CH-), 7.4089-7.4625 (4H, multiplet, -CH-), 7.5065-7.5274 (1H, doublet, -CH-), 7.5416-7.5916 (2H, triplet, -CH-, J= 20), 7.7357-7.7423 (2H, doublet, -CH-), 8.2009-8.2187 (2H, triplet, -CH-), 8.4501 (1H, singlet, -CH-), 8.5678 (1H, singlet, -CH-), 9.1032 (1H, singlet,-CH-).
^{13}C NMR (DMSO-d_6, δ ppm)*:* 113.97, 117.37, 120.24, 121.99, 123.06, 123.87, 123.99, 124.56, 126.87, 127.28, 128.39, 129.83, 130.28, 131.56, 133.78, 136.38, 140.37, 142.48, 147.98, 149.23, 153.57, 161.28, 162.56.
***Mass (m/ʒ)*:** 409.

QAS-2:
IR (cm^{-1}): 3137.45 (C-H stretching aromatic), 2985.37, 2879.29 (C-H stretching alkanes), 1727.36 (C=O stretching), 1689.37 (α, β-unsaturated carbonyl), 1644.47 (C-C stretching in ring), 1571.36, 1534.87 (-NO_2 stretching), 1494.92 (C-H stretching alkane), 1364.20, 1332.20 (C-N stretching), 1242.39 (C-N stretching aromatic), 1005.54 (C-H stretching aromatic), 976.12, 919.12 (C-H bending), 804.92 (C-H rock vibration).
^{1}H NMR (DMSO-d_6, δ ppm): 7.1955-7.2136 (2H, doublet, -CH-), 7.4344-7.4659 (4H, multiplet, -CH-), 7.5234 (1H, singlet, -CH-), 7.5651-7.6027 (2H, triplet, -CH-), 7.6958-7.7479 (1H, triplet, -CH-), 7.7901-7.9178 (1H, doublet, -CH), 8.0411-8.0678 (2H, doublet, -CH-), 8.4591 (1H, singlet, -CH-), 8.5714 (1H, singlet, -CH-), 9.1879 (1H, singlet,-CH-).
^{13}C NMR (DMSO-d_6, δ ppm)*:* 113.28, 117.39, 119.46, 120.29, 121.29, 123.46, 126.37, 127.65, 128.28, 129.92, 130.29, 132.92, 139.29, 141.33, 146.39, 146.72, 153.46, 160.02, 161.34.
Mass (m/ʒ): 436.

QAS-3:
IR (cm^{-1}): 3124.37 (C-H stretching aromatic), 2987.93, 2873.28 (C-H stretching alkanes), 1725.38 (C=O stretching), 1684.79 (α, β-unsaturated carbonyl), 1643.34, 1527.28 (C-C stretching in ring), 1499.34 (C-H stretching alkane), 1364.48, 1332.58 (C-N stretching), 1242.29 (C-N stretching aromatic), 1095.54 (C-F stretching), 976.12, 919.12 (C-H bending), 824.39 (C-F stretching), 783.63 (C-Cl stretching).
^{1}H NMR (DMSO-d_6, δ ppm): 7.3578-7.3712 (1H, doublet, -CH-), 7.4141-7.4563 (4H, multiplet, -CH-), 7.4984-7.5101 (1H, doublet, -CH-), 7.5461-7.5811 (2H, triplet, -CH), 7.64237-7.6688 (1H, triplet, -CH-), 7.8913 (1H, singlet), 8.0199-8.0415 (2H, doublet, -CH), 8.1114 (1H, singlet, -CH-), 8.5545 (1H, singlet, -CH-), 8.9987 (1H, singlet,-CH).
^{13}C NMR (DMSO-d_6, δ ppm): 114.02, 116.26, 118.67, 119.13, 120.45, 121.08, 122.89, 125.29, 127.45, 128.73, 129.34, 129.89, 132.23, 139.67, 141.33, 142.36,146.23, 146.78, 153.46, 157.34, 161.84.
Mass (m/ʒ): 443.

QAS-4:
IR (cm^{-1}): 2973.26 (C-H stretching), 1713.83 (α, β-unsaturated carbonyl), 1700.23 (C-O stretching ether), 1609.27, 1543.84 (C-C stretching in ring), 1448.34 (C-H stretching alkane), 1345.73 (C-O stretching), 1202.28, 1113.38, 1072.42 (C-N stretching), 972.45, 957.56 (C-H bending), 817.48 (C-H rock aromatic).
^{1}H NMR (DMSO-d_6, δ ppm): 3.3612 (3H, singlet, -)CH3), 7.1159-7.1291 (2H, doublet, -CH-), 7.4011-7.4377 (4H, multiplet, -CH-), 7.4819 (1H, singlet, -CH-), 7.5409-7.5784 (2H, triplet, -CH-), 7.6442-7.6789 (1H, triplet, -CH-), 7.7537-7.7670 (1H, doublet, -CH), 7.9912-8.0410 (2H, doublet, -CH-), 8.4501 (1H, singlet, -CH-), 8.5643 (1H, singlet, -CH-), 9.1797 (1H, singlet,-CH-).

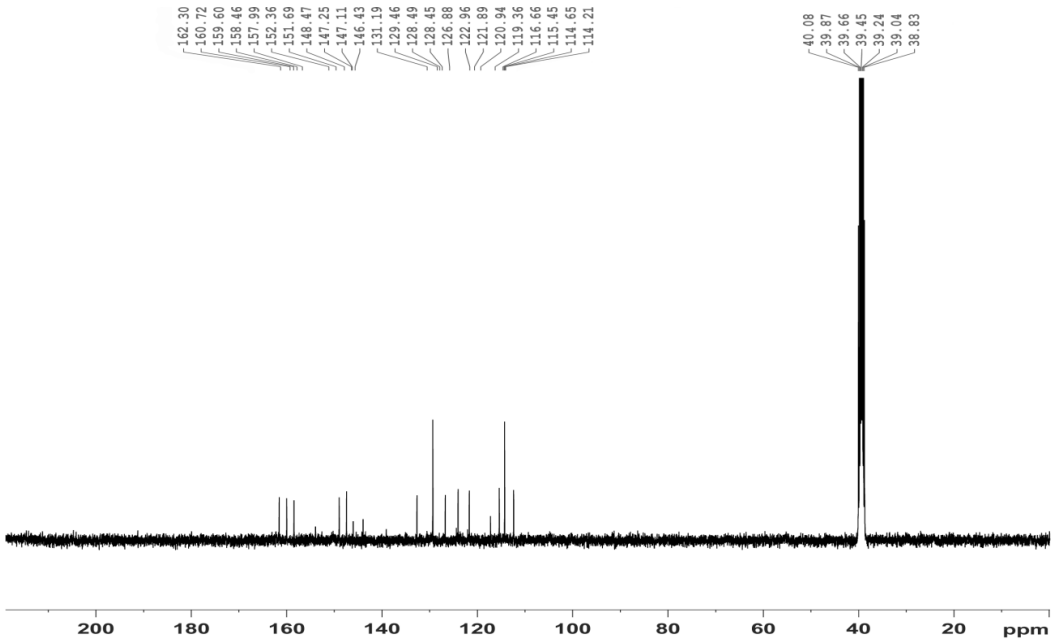


Figure 4. ^{13}C NMR spectrum of QAS-5.

^{13}C NMR (DMSO-d_6, δ ppm): 55.36, 112.47, 116.48, 119.12, 120.67, 121.27, 122.92, 125.28, 126.45, 127.42, 128.13, 129.29, 129.19, 132.23, 139.37, 140.39, 141.48, 146.49, 153.30, 160.02.
Mass (m/ʒ): 421.

QAS-5:
IR (cm^{-1}): 2970.38 (C-H stretching), 1712.79 (α, β-unsaturated carbonyl), 1604.77, 1543.05 (C-C stretching in ring), 1481.33 (C-H stretching alkane), 1342.46 (C-O stretching), 1203.58 (C-N stretching), 1118.71, 1072.42 (C-N stretching aromatic), 972.12, 956.69 (C-H bending), 817.82, 748.38 (C-H rock aromatic), 686.66 (C-Br stretching).
^{1}H NMR (DMSO-d_6, δ ppm): 7.1836-7.2051 (2H, doublet, -CH-), 7.4223-7.4517 (4H, multiplet, -CH-), 7.5178 (1H, multiplet, -CH-), 7.5584-7.5980 (2H, triplet, -CH-), 8.0262-8.0456 (1H, doublet, -CH-), 8.4537 (1H, singlet, -CH-), 8.5666 (1H, singlet, -CH-), 9.1810 (1H, singlet,-CH-).
^{13}C NMR (DMSO-d_6, δ ppm): 114.21, 114.65, 115.45, 116.66, 119.36, 120.94, 121.89, 122.96, 126.88, 128.45, 128.49, 129.46, 131.19, 146.43, 147.11, 147.25, 148.47, 151.69, 152.36, 157.99, 158.46, 159.60, 160.72, 162.30.
Mass (m/ʒ): 470.

IR spectra

The IR spectrum of QAS-5 is given in Figure 2. These Figure shows peak around 2929-2978 cm^{-1} is of CH stretching of aromatic ring. The carbonyl stretching in –COO- group is observed around 1708-1730 cm^{-1}. The C-C stretching for aromatic carbons are obtained around 1606-1703 cm^{-1} and 1549-1695 cm^{-1} whereas alkane C-H bending is observed around 1469-1490 cm^{-1}. The peaks are observed around 1300-1334 cm^{-1} due to C-O stretching of ester group and/or ether group. The –C=N– stretching observed around 1250-1050 cm^{-1}. The peak for C-Br stretching is observed around 670-690 cm^{-1}.

^{1}H NMR spectra

The ^{1}H NMR spectrum of QAS-5 (as in Figure 3) shows residual peak of DMSO at 2.5097 δppm. The aromatic protons showed peaks between 7.1836 to 8.0456 δppm with their appropriate multiplicity. The peaks of two proton of two -N=C-H are observed around 8.4537 δppm and 8.5666 δppm. A peak for -C=C-H appears at 9.1810 δppm as singlet.

All the ^{1}H NMR splitting of peak suggests that compounds are synthesized successfully.

^{13}C NMR spectra

Figure 4 shows the ^{13}C NMR spectrum of compound QAS-5. The aromatic carbons of phenyl rings are shown between 114.21 to 162.30 δppm with their appropriate multiplicity.

Mass spectra

Figure 5 shows the mass spectrum of compound QAS-5. From mass fragmentations, the structures of synthesized compounds are confirmed.

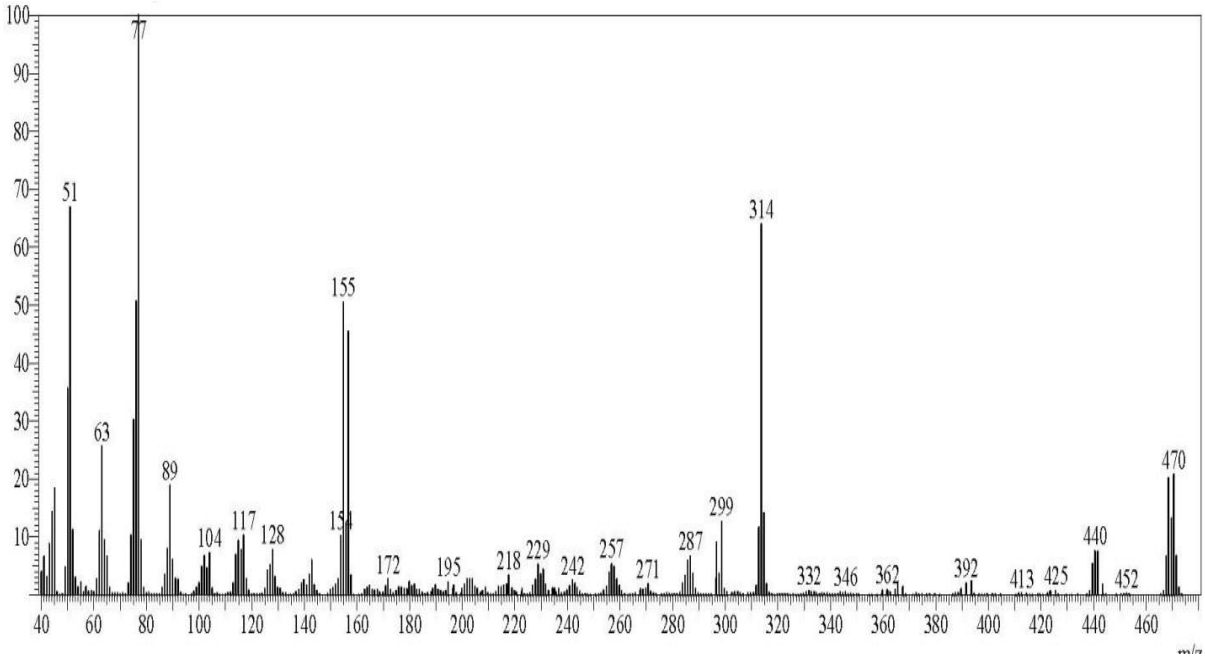


Figure 5. Mass spectrum of QAS-5.

Table 2. The % yield and reaction time for the synthesis of Schiff bases by conventional and microwave irradiation methods.

Compound Code	% Yield		Reaction Time	
	Microwave	Conventional	Microwave (minutes)	Conventional (hours)
QAS-1	81	62	15	8
QAS-2	60	52	20	11
QAS-3	71	63	15	9
QAS-4	65	57	20	11
QAS-5	86	65	15	8

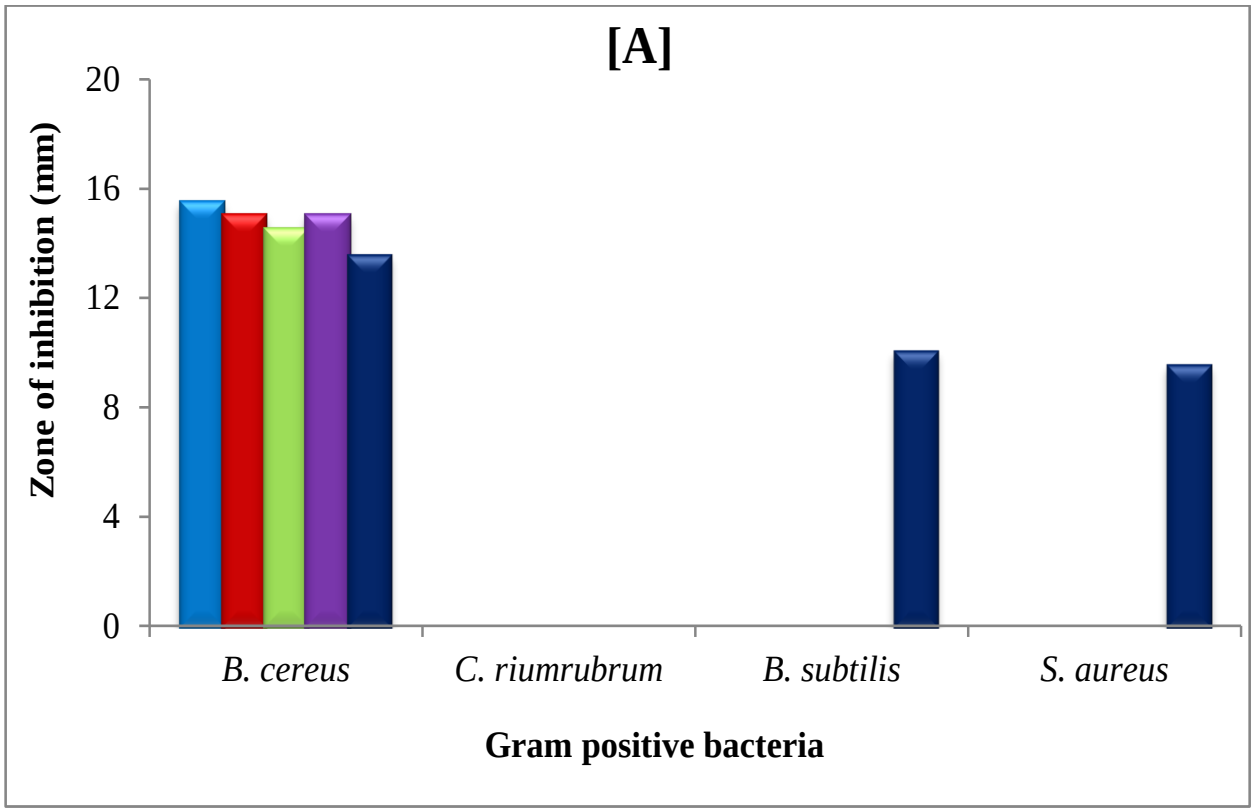
Table 2 shows comparison of % yield and reaction time for the synthesis of Schiff bases carried out by two different methods. It is evident from Table 2 that % yields of Schiff bases increased significantly using microwave irradiation method. In conventional method, reaction time is in hours whereas in microwave irradiation method, it is reduced into minutes. Thus, microwave irradiation method is more favourable for the synthesis of Schiff bases.

Figure 6 shows the zone of inhibition for the studied compounds against some selected Gram positive bacteria in DMF and DMSO. It is observed that against *B. cereus*, all the studied compounds exhibited inhibition in DMF and QAS-1 showed maximum inhibition. Whereas in DMSO, only QAS-5 showed inhibition against this bacterial strain. None of compounds showed inhibition against *C. rubrum* in both the solvents. In DMF, only QAS-5 showed inhibition against *B. subtilis* and *S. aureus* and almost up to same extent. Whereas in DMSO, against *B. subtilis* and *S. aureus,* none of the studied the compounds found to be effective.

The above studies indicate that, inhibition depends on solvent, structure of compound and strain. In present work, all the studied compounds have the same central moiety but different substitution groups as listed in Table 1. QAS-1 contains 4-fluoro substitution which is highly effective against *B. cereus* in DMF. However in DMSO, 2-bromo (as in QAS-5) substitution was found to be effective against this bacterial strain. Further, only 2-bromo substitution showed inhibition against *B. subtilis* and *S. aureus* in DMF. However in DMSO, all the substitutions present in the studied compounds are found to be ineffective against all studied Gram positive bacteria except against *B. cereus.*

Thus, against Gram positive bacteria, DMF is good solvent for the studied compounds.

Figure 7 shows the zone of inhibition against Gram negative bacteria in both DMF and DMSO. In DMF, against *K. pneumoniae* all the studied compounds



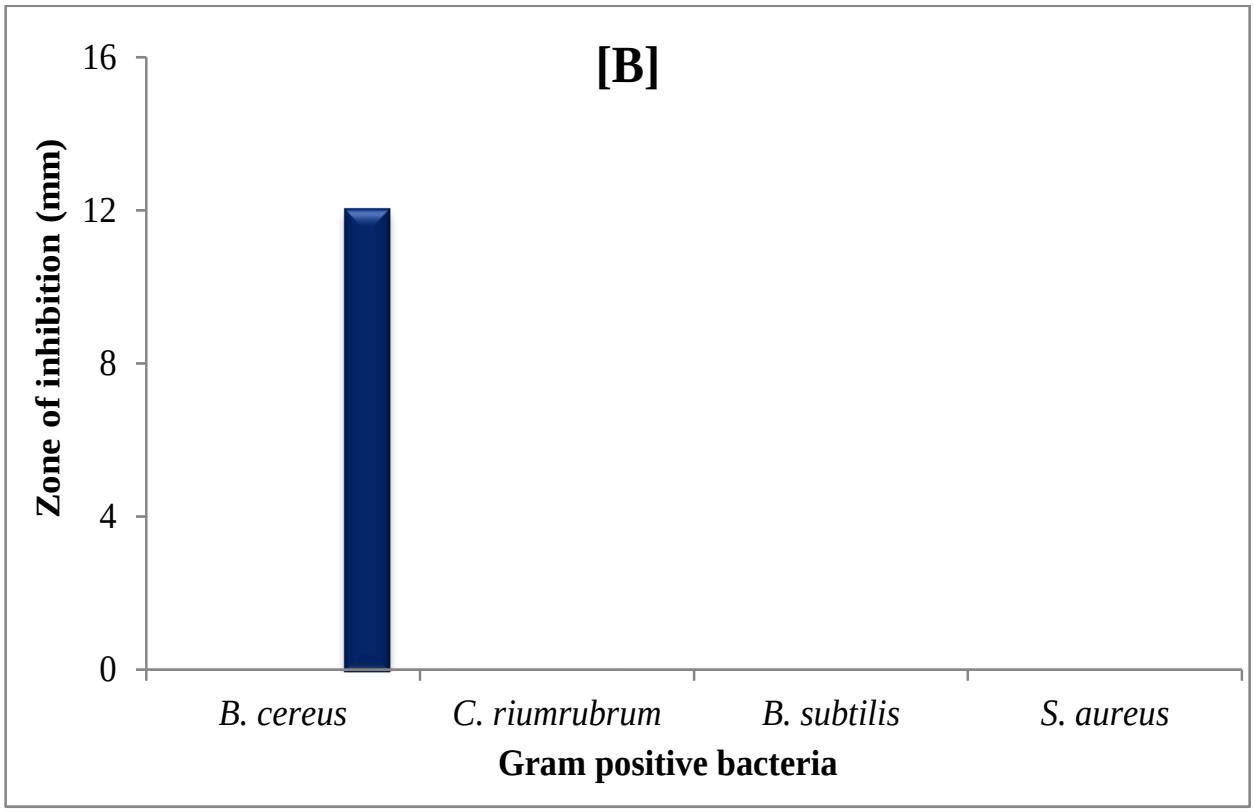


Figure 6. Antibacterial activity of synthesized compounds against Gram positive bacteria in [A] DMF and [B] DMSO.
[QAS-1, (■); QAS-2, (■); QAS-3, (■); QAS-4, (■); QAS-5, (■)].

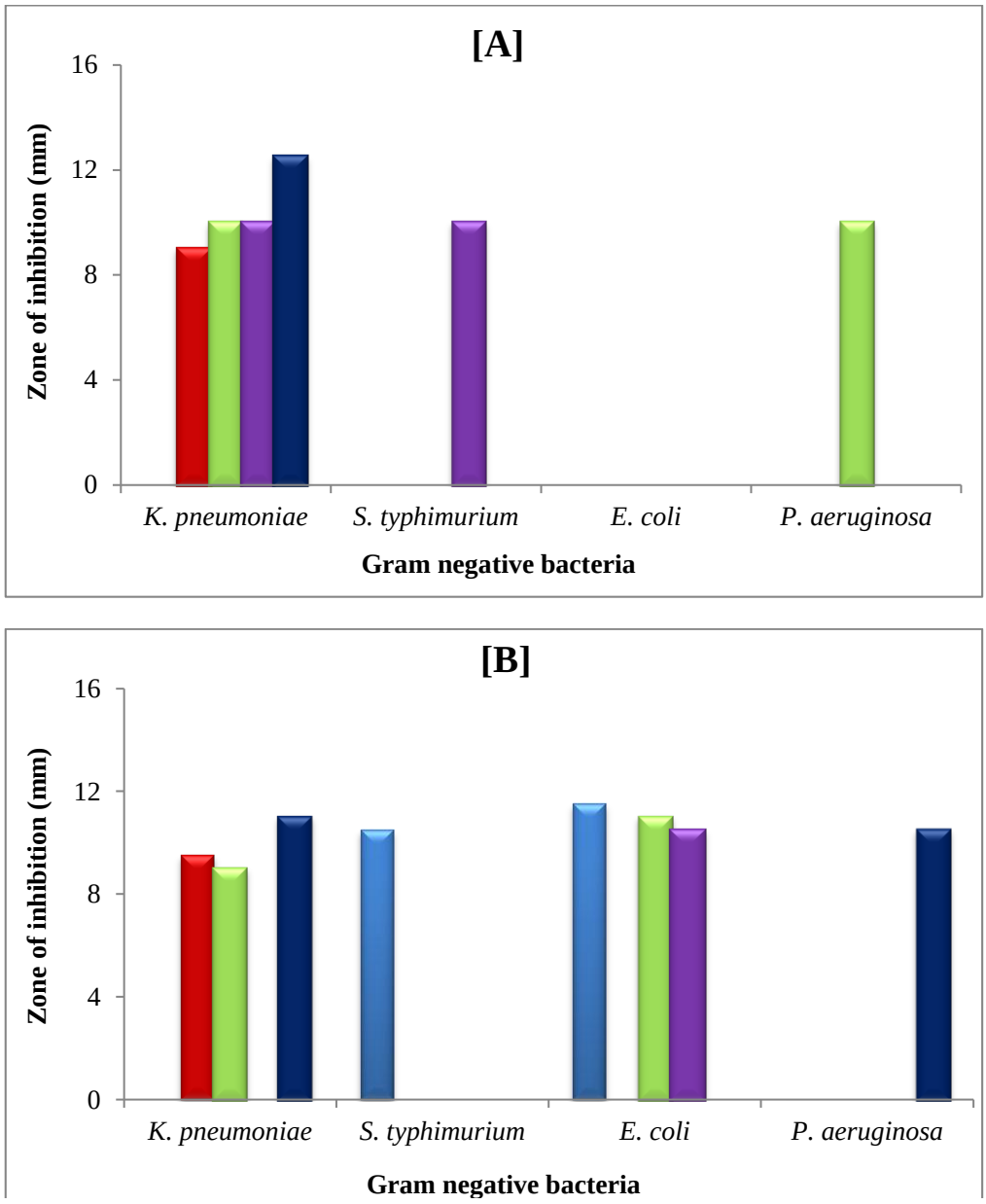


Figure 7. Antibacterial activity of synthesized compounds against Gram negative bacteria in [A] DMF and [B] DMSO.
[QAS-1, (■); QAS-2, (■); QAS-3, (■); QAS-4, (■); QAS-5, (■)]

showed inhibition except 4-fluoro (as in QAS-1) substitution and 2-bromo group (as in QAS-5) showed maximum inhibition. Further, 3-chloro-4-fluoro group (as in QAS-3) and 4-methoxy group (as in QAS-4) showed almost same extent to inhibition against this bacterial strain.

Against *S. typhimurium*, only 4-methoxy (as in QAS-4) group showed inhibition in DMF whereas in DMSO, 4-fluoro group was effective. Against *E. coli*, none of the studied compounds showed inhibition in DMF whereas in DMSO 4-fluoro group (as in QAS-1), 3-chloro-4-fluoro group (as in QAS-3) and 4-methoxy group (as in QAS-4) showed inhibition. Against *P. aeruginosa*, in DMF 3-chloro-4-fluoro group (as in QAS-3) and in DMSO 2-bromo (as in QAS-5) group showed inhibition.

Hence, the synthesized compounds showed better activity against Gram negative bacteria than Gram positive bacteria.

In DMF, none of compounds showed inhibition against any of selected fungal strains. However in DMSO, only 4-methoxy (as in QAS-2) group showed inhibition against *C. albicans* as shown in Figure 8.

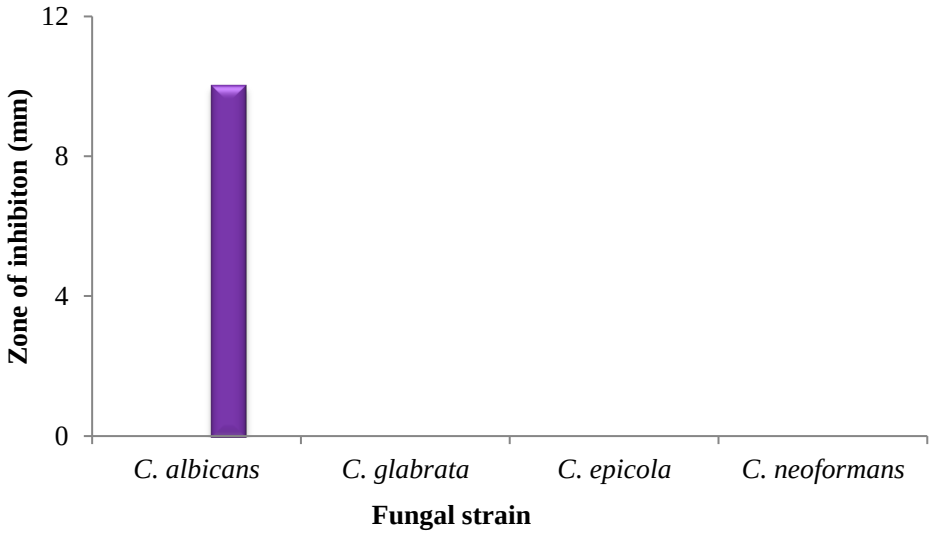


Figure 8. Antifungal activity of synthesized compounds in DMSO. [QAS-1, (■); QAS-2, (■); QAS-3, (■); QAS-4, (■); QAS-5, (■)]

Conclusion

Some novel Schiff bases are synthesized by conventional and microwave irradiation methods. It is observed that synthesis of Schiff bases carried out by microwave irradiation has many advantages such as reduce in reaction time, energy saving with high efficiency, improved yield. In microwave, reaction time is decreases from hours to minutes.

The inhibition depends on three S; solvent, substitution of compounds and strains. For Gram positive bacteria, DMF is good solvent whereas for Gram negative bacteria, DMSO is good solvent. The selected fungal strains are quite resistant in both DMF and DMSO. Overall, compounds having halogen groups are more effective against selected bacterial strains. However, all selected fungal strains showed resistant against studied compounds in both DMF and DMSO.

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