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Synthesis, characterization and *in vitro* antimicrobial screening studies of some pyridyl-coumarin compounds

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Summary

In vitro antimicrobial screening of some pyridyl-coumarin compounds were done against some bacterial and fungal strains in DMF and DMSO. These pyridyl-coumarin compounds were synthesized in the laboratory and their structure was confirmed by different spectroscopic techniques such as IR, ^{1}H NMR, ^{13}C NMR and mass. Some of these compounds exhibited excellent antibacterial activity in both the solvents.

Keywords: Pyridyl-coumarin compounds, Gram positive bacteria, Gram negative bacteria, fungal strains, DMF, DMSO.

Resumen

Síntesis, caracterización y evaluación antimicrobiana *in vitro* de algunos derivados de piridil-coumarina

La actividad antimicrobiana *in vitro* de algunos compuestos derivados de piridil-coumarina se evaluó frente a algunas cepas bacterianas y fúngicas en DMF y DMSO. Las piridil-cumarinas se sintetizaron en el laboratorio y sus estructuras se confirmaron por diferentes técnicas espectroscópicas, tales como IR, ^{1}H NMR, ^{13}C NMR y masas. Algunos de los compuestos que se obtuvieron presentaron buena actividad antibacteriana en ambos solventes.

Palabras clave: Derivados de piridil-cumarina, bacterias Gram positivas, bacterias Gram negativas, cepas fúngicas, DMF, DMSO.

Introduction

The infections causes by various microbes are dramatically increased during recent years [1]. Further, bacteria are becoming resistant to antimicrobial agents [2] so the effect of antimicrobial drugs available in the market is somewhat in doubt in future. These available antimicrobial drugs also have several drawbacks such asside effects, toxicity, low effectiveness and environmental issues [3, 4]. Therefore, there is always need to develop new antimicrobials drugs for the treatment of infectious diseases [5].

Nitrogen and oxygen containing heterocyclic compounds like pyridine, coumarin etc., are always an attraction for researchers because of its efficiency towards various pharmacological usages [6, 7]. Literature survey shows that large array of coumarin derivatives possess a variety of biological activities such as antihistaminic [8], anticancer [9], antifungal [10], analgesic [11], anti-tubercular [12], antioxidant [13], antimicrobial [14], anti HIV [15], etc. They are also used as herbicides [16], neuroimaging agent [17], fluorescent whitening agent [18], organic sensitizers in dye sensitized solar cells [19], etc.

Owing to these interesting applications of pyridyl-coumarine derivatives, in the present work, some new pyridyl-coumarinecompounds have been synthesized. The structure of these compounds was confirmed by different spectroscopic techniques. Further, *in vitro* screening of these compounds was carried out against bacterial as well as fungal strains in *N,N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO).

Experimental and materials

Materials

The solvents, DMF (LOBA Chemie Pvt. Ltd. & CAS No.- 68-12-2) and DMSO (LOBA Chemie Pvt. Ltd. & CAS No. 67-68-5) 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 [20].

Synthesis

- **Synthesis of 2-benzylidenemalanonitrile derivatives (Int-1):**

Equimolar mixture of different substituted benzaldehydes (Spectrochem Pvt. Ltd. & CAS No. 100-52-7) and malanonitrile (LOBA Chemie Pvt. Ltd. & CAS No. 109-77-3) in methanol (Allied Chemical Chemie Pvt. Ltd. & CAS No.- 67-56-1) was stirred at room temperature (RT) in presence of catalytic amount of piperidine (Sigma Aldrich & CAS No. 110-89-4). The reaction progress was checked by analytical thin layer

chromatography (TLC) (Performed on aluminum coated plates Gel $60F_{254}$ (E. Merck)) using (0.5:0.5 v/v-hexane: ethyl acetate) as mobile phase. After completion of reaction, the obtained solid was filtered, washed with cold methanol and was dried under vacuum. The obtained crude product was used in next step without further purification.

- **Synthesis of pyridyl coumarin derivatives:**

Equimolar mixture of 2-benzylidenemalanonitrile derivatives (Int-1), 3-acetylcoumarin and thiophenol (Sigma Aldrich & CAS No. 108-98-5) in ethanol was refluxed in presence of tri ethylamine (TEA) (Sigma Aldrich & CAS No. 121-44-8) used as a catalyst. The progress of reaction was checked by TLC using (0.9: 0.1 v/v-chloroform: methanol) as a 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 reaction scheme is given in Figure 1. Following five pyridyl-coumarin derivatives were synthesized.

QMS-1: 4-(4-fluorophenyl)-6-(2-oxo-2*H*-chromen-3-yl)-2-(phenylsulfanyl)pyridine-3-carbo nitrile

QMS-2: 4-(4-bromophenyl)-6-(2-oxo-2*H*-chromen-3-yl)-2-(phenylsulfanyl)pyridine-3-carbo nitrile

QMS-3: 4-(2-chlorophenyl)-6-(2-oxo-2*H*-chromen-3-yl)-2-(phenylsulfanyl)pyridine-3-carbo nitrile

QMS-4: 4-(4-(dimethylamino)phenyl)-6-(2-oxo-2*H*-chromen-3-yl)-2-(phenylsulfanyl) pyridine -3-carbonitrile

QMS-5: 4-(2-hydroxyphenyl)-6-(2-oxo-2*H*-chromen-3-yl)-2-(phenylsulfanyl)pyridine-3-carbo nitrile

All the synthesized pyridyl-coumarin derivatives were crystallized from ethanol before use. The purity of these synthesized compounds was checked by GC-MS (SHIMADZU Model-QP2010) and was found to be greater than 99.98 %.

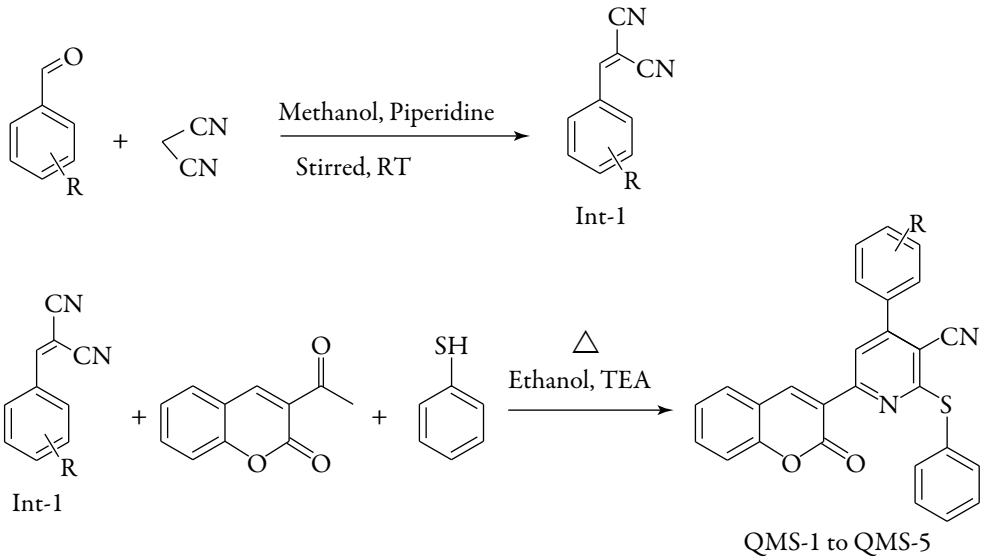

Figure 1. Reaction scheme for the synthesis of pyridyl-coumarine compounds.

Spectroscopy study

The structure of the synthesized compounds was confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The IR spectra were taken on Fourier 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 MHzfrequency. 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.

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

The melting points of compounds were measured by Differential Scanning Calorimeter (SHIMADZU Model-DSC-60) under nitrogen atmosphere (flow rate 100 ml/min) and at 10 °C/min heating rate.

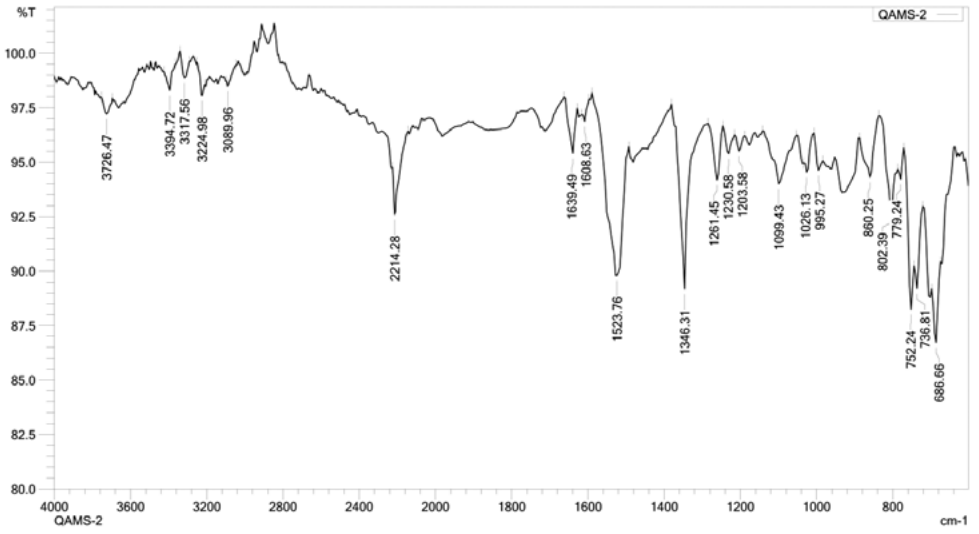

Figure 2. IR spectrum of QMS-1

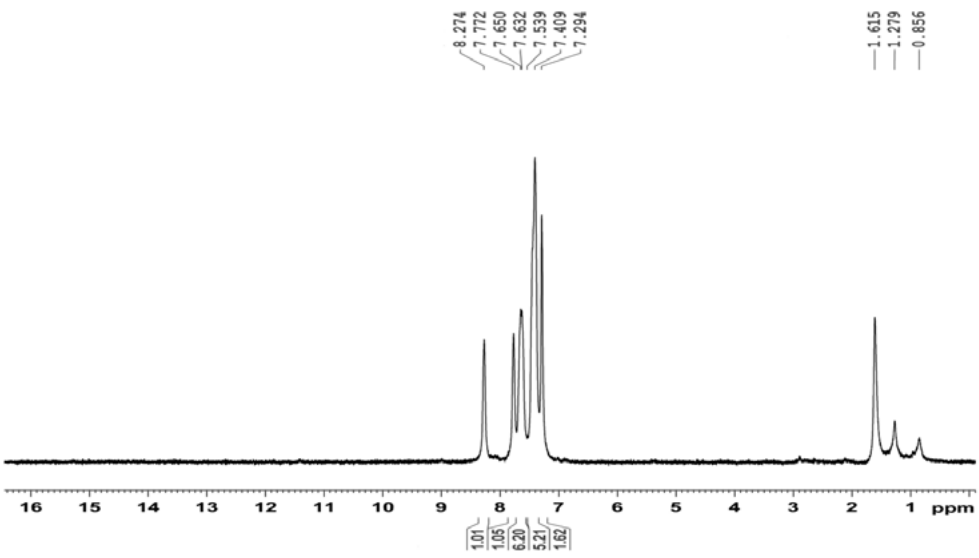

Figure 3. ^{1}H NMR spectrum of QMS-1.

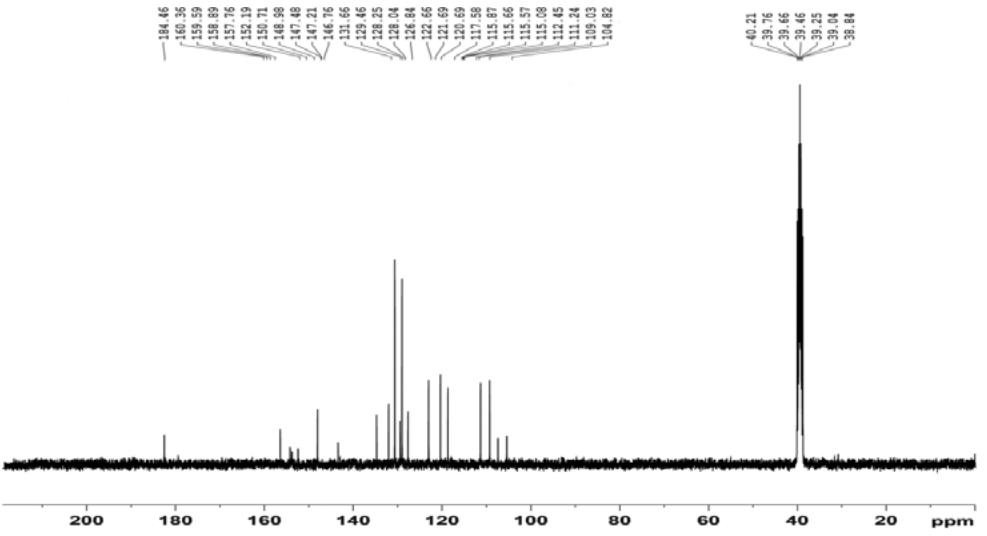

Figure 4. ^{13}C NMR spectrum of QMS-1.

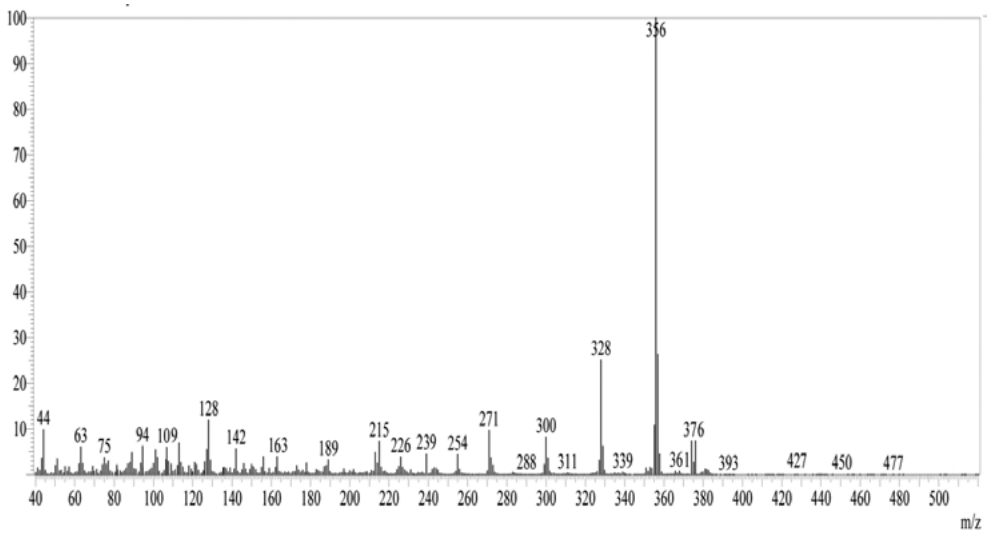

Figure 5. Mass spectrum of QMS-1.

Microorganisms tested

The studied microorganisms were obtained from National Chemical Laboratory, Pune, India and were maintained at 4 °C. The selected Gram positive bacteria for the present study were *Bacillus cereus* ATCC11778 (BC), *Corynebacterium rubrum* ATCC14898 (CR), *Bacillus subtilis* ATCC6633 (BS) and *Staphylococcus aureus* ATCC29737 (SA). The Gram negative bacteria were *Klebsiella pneumoniae* NCIM2719(KP), *Staphylococcus typhimurium* ATCC23564 (ST), *Escherichia coli* NCIM2931 (EC), *Pseudomonas aeruginosa* ATCC9027 (PA). The selected fungal strains were *Candida albicans* ATCC2091 (CA), *Candida glabrata* NCIM3448 (CG), *Candida epicola* NCIM3367 (CE) and *Cryptococcus neoformans* NCIM3542 (CN).

The agar well diffusion method [21] was used to study *in vitro* antimicrobial study of the synthesized compounds. For each compound in each solvent for a particular strain, the experiment was repeated three times.The average of these three values is graphically represented in Figures 6 to 8 along with uncertainty values.

Results and Discussion

Table 1 shows the physical constant of synthesized compounds along with their side chain substitutions.

Table 1. Physical properties of pyridyl-coumarine compounds

Compound Code	Substitution R	Molecular formula	Molecular Weight (g/mol)	Yield (%)	R_f* value	Melting Points (°C)
QMS-1	4-F	$C_{27}H_{15}FN_2O_2S$	450	65	0.68	298.14
QMS-2	4-Br	$C_{27}H_{15}BrN_2O_2S$	511	62	0.62	227.04
QMS-3	2-Cl	$C_{27}H_{15}ClN_2O_2S$	466	59	0.53	26047
QMS-4	4-$N(CH_3)_2$	$C_{29}H_{21}N_3O_2S$	475	47	0.49	241.51
QMS-5	2-OH	$C_{27}H_{16}N_2O_3S$	448	61	0.53	301.09

*0.9:0.1 v/v-chloroform: methanol

Spectral data

QMS-1:

IR (cm^{-1}): 3394.72, 3317.56, 3224.98 (-OH stretching, H-bonded and/or –NH-stretching), 2934.67 (-CH- stretching), 2214.28 (-CN stretching), 1639.49, 1608.63

(C=Ostretching), 1523.76 (-CH- bending), 1346.31 (-CH- rock), 1261.45, 1230.58, 1203.58 (C-O stretching), 1099.43 (C-O stretching), 1026.13 (C-N stretching), 955.27, 806.25, 786.96 (substituted benzene).

^{1}H NMR (DMSO-d_6, 400 MHz) (δ ppm): 7.2942-7.3183 (2H, doublet, -CH- aromatic, J= 9.64 Hz), 7409-7.539 (5H, multiplet, -CH- aromatic), 7.6324-7.6550 (6H, multiplet, -CH- aromatic), 7.7726 (1H, singlet, -CH- aromatic), 8.2743 (1H, -CH- aromatic).

^{13}C NMR (DMSO-d_6, 400 MHz) (δ ppm): 104.82, 109.03, 111.24, 112.45, 115.08, 115.57, 115.66, 115.87, 117.58, 120.69, 121.69, 122.66, 126.84, 128.04, 128.25, 129.40, 131.66, 146.76, 147.21, 147.48, 148.98, 150.71, 152.59, 160.36, 184.46.

Mass (m/≅): 450.

QMS-2:

IR (cm^{-1}): 3352.67, 3339.37, 3228.29 (-OH stretching, H-bonded and/or –NH- stretching), 2978.09, 2885.51 (C-H stretching alkane), 2299.15, 2260.57, 2214.28 (-CN stretching), 1643.55 (C=Ostretching), 1592.61, 1481.33, 1404.18 (-CH- bending), 1369.46, 1346.31, 1327.03 (-CH- rock),1261.45, 1203.58 (C-O stretching), 1138.00, 1118.71, 1099.43 (C-C stretching), 1026.13 (C-N stretching),752.24, 671.23 (substituted benzene).

^{1}H NMR (DMSO-d_6, 400 MHz) (δ ppm): 6.9637-6.9783 (2H, doublet, -CH- aromatic,), 7.3734-7.5493 (3H, multiplet, -CH- aromatic), 7.5538-7.6132 (2H, doublet, -CH - aromatic), 7.6263-7.7743 (6H, multiplet –CH- aromatic), 8.0958 (1H, singlet, -CH- aromatic), 8.2769 (1H, singlet, -CH- aromatic).

^{13}C NMR (DMSO-d_6, 400 MHz) (δ ppm): 104.38, 109.63, 113.68, 112.96, 115.21, 115.54, 115.98, 127.36, 120.48, 121.13, 122.67, 126.38, 128.09, 129.48, 146.28, 147.79, 147.73, 148.29, 150.68, 153.26, 157.69, 158.26, 159.18, 160.09, 185.56.

Mass (m/≅): 511.

QMS-3:

IR (cm^{-1}): 3356.28, 3356.09, 3223.67 (-OH stretching, H-bonded and/or –NH- stretching), 2981.95, 2881.65 (C-H stretching alkane), 2349.30, 2299.15, 2214.28 (-CN stretching), 1631.78, 1604.77 (C=Ostretching), 1550.77, 1523.76, 1504.48 (N-H bending), 1481.33, 1442.75 (-CH- bending), 1369.46 (-CH- rock), 1296.16, 1222.87 (C-O stretching), 1157.29, 1099.43, 1026.13 (C-N stretching),779.24, 686.66 (substituted benzene).

^{1}H NMR (DMSO-d_6, 400 MHz) (δ ppm): 7.2942-7.3372 (2H, doublet, -CH- aromatic), 7.4932-7.3721 (5H, multiplet, -CH- aromatic), 7.6348-7.6529 (6H, multiplet, -CH- aromatic), 7.2834 (1H, singlet, -CH- aromatic), 8.2758 (1H, -CH- aromatic).

^{13}C NMR (DMSO-d_6, 400 MHz) (δ ppm): 104.48, 109.49, 113.29, 112.60, 115.02, 115.35, 115.89, 127.39, 120.67, 121.59, 122.27, 126.29, 127.46, 128.27, 129.58, 146.37, 147.68, 147.28, 148.48, 150.79, 153.26, 157.47, 158.79, 159.39, 160.29, 185.49.

Mass (m/≅): 466.

QMS-4:

IR (cm^{-1}): 3378.98, 3312.67, 3221.45 (-OH stretching, H-bonded and/or –NH-stretching), 2978.09 (C-H stretching alkane), 2349.30, 2299.15, 2210.42 (-CN stretching), 1708.93, 1639.49 (C=Ostretching), 1546.91, 1523.76, 1442.75 (-CH- bending), 1273.02, 1203.58, 1118.71, 1099.43 (C-O stretching), 1080.14, 1026.13 (C-N stretching), 756.10, 686.66, 671.23 (substituted benzene).

^{1}H NMR (DMSO-d_6, 400 MHz) (δ ppm): 3.4657 (3H, singlet -CH3), 3.5783 (3H, singlet -CH3), 7.2958-7.3349 (2H, doublet, -CH- aromatic), 7.4939-7.3749 (5H, multiplet, -CH- aromatic), 7.6359-7.6527 (6H, multiplet, -CH- aromatic), 7.2583 (1H, singlet, -CH- aromatic), 8.2402 (1H, -CH- aromatic).

^{13}C NMR (DMSO-d_6, 400 MHz) (δ ppm): 23.67, 24.38,104.84, 109.63, 113.28, 112.47, 115.02, 115.35, 115.78, 127.36, 120.48, 121.59, 122.62, 126.29, 128.27, 129.90, 146.37, 147.68, 147.28, 148.69, 150.39, 153.28, 157.90, 158.38, 159.18, 160.29, 185.49.

Mass (m/≅): 475.

QMS-5:

IR (cm^{-1}): 3378.65, 3324.56, 3222.78 (-OH stretching, H-bonded and/or –NH-stretching), 2978.09, 2885.51 (C-H stretching alkane), 2384.02, 2349.30, 2299.15, 2214.28 (-CN stretching), 1708.93 (C=Ostretching), 1512.19 (N-H bending), 1442.75 (-CH- bending), 1369.46, 1346.31 (-CH- rock), 1273.02, 1234.44, 1199.72 (C-O stretching), 1118.71, 1068.56, 1026.13 (C-N stretching), 763.81, 740.67, 682.80 (substituted benzene).

^{1}H NMR (DMSO-d_6, 400 MHz) (δ ppm): 7.2948-7.3338 (2H, doublet, -CH- aromatic), 7.4958-7.3782 (5H, multiplet, -CH- aromatic), 7.6359-7.6924 (6H, multiplet, -CH- aromatic), 7.2548 (1H, singlet, -CH- aromatic), 8.2423 (1H, -CH- aromatic).

^{13}C NMR (DMSO-d_6, 400 MHz) (δ ppm): 104.58, 109.39, 113.68, 112.29, 115.89, 115.37, 115.69, 127.39, 120.97, 121.58, 122.69, 126.38, 127.36, 128.79, 129.90, 136.78, 146.36, 147.48, 147.68, 148.12, 150.45, 153.78, 157.90, 158.23, 159.56, 160.78, 185.12.

Mass (m/≅): 448.

IR spectra

The IR spectrum of QMS-1 is given in Figure 2. The peaks observed around 3200-3500 cm^{-1} are due to stretching of –OH (H-bounded) and/or –NH- groups. The peak around 2929-2978 cm^{-1} is of –CH stretching of aromatic ring. The–CN stretching is observed around 2300-2200 cm^{-1}. The peaks for –C=O and C-H stretching are obtained around 1600-1700 cm^{-1} and 1550-1600 cm^{-1} respectively whereas alkane C-H bending peak is observed around 1469-1490 cm^{-1}. The peaks observed around 1300-1334 cm^{-1} are due to C-O stretching of ester group and/or ether group. The –CN stretching is observed around 1250-1050 cm^{-1}.

^{1}H NMR spectra

The ^{1}H NMR spectrum of QMS-1 is shown in Figure 3. For aromatic protons, peaks are between 7.2940 to 7.6500 δ ppm with their appropriate multiplicity. Two singlet peaks of aromatic proton (=CH-) are observed at 7.7120 and 8.2740.

All the ^{1}H NMR peaks suggests that compounds are synthesized successfully.

^{13}C NMR spectra

Figure 4 shows the ^{13}C NMR spectrum of compound QMS-1. The aromatic carbons of phenyl rings are shown between 104.82 to 184.46 δ ppm with their appropriate multiplicity.

Mass spectra

Figure 5 shows the mass spectrum of compound QMS-1. From mass fragmentation, the structures of synthesized compounds are confirmed.

Antimicrobial activity

Figure 6 shows the zone of inhibition for the studied compounds against Gram positive bacteria in DMF and DMSO along with two standard antibiotics. It is observed that against Bacillus cereus, all the studied compounds exhibited inhibition (except QMS-4 in DMSO) in both DMF and DMSO. However, in DMF, QMS-5 showed maximum inhibition and this value is higher than tetracyclin but lower than Chloramphenicol.

However in DMSO, QMS-1 showed maximum inhibition against *Bacillus cereus* but lower than both the antibiotics.

In DMF, QMS-1, QMS-3 and QMS-5 showed inhibition against *Corynebacterium rubrum* whereas in DMSO only QMS-1 was found to be effective against this bacterial strain. Against *Bacillus subtilis* in DMF, all the studied compounds exhibited significant inhibition. However in DMSO, QMS-1, QMS-2 and QMS-3 exhibited inhibition. In DMF, against *Staphylococcus aureus* only QMS-1 showed inhibition whereas in DMSO, none of compounds was found to be effective.

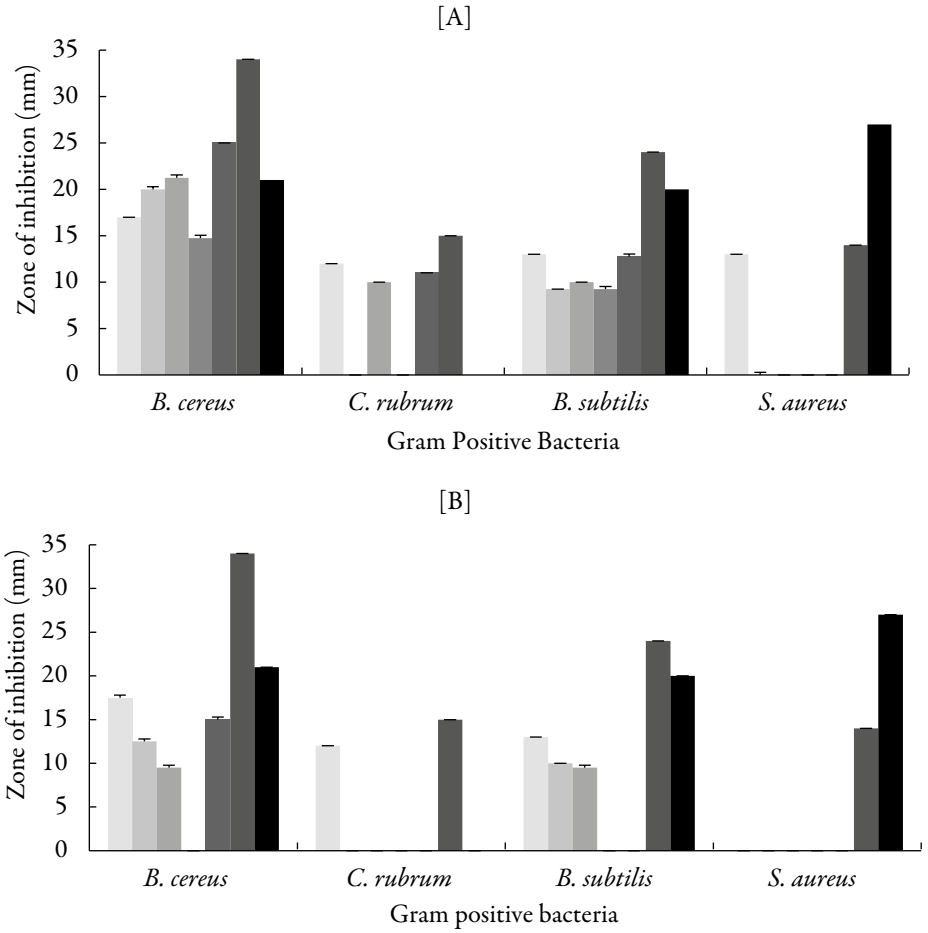

Figure 6. Antibacterial activity of synthesized compounds against Gram positive bacteria in [A] DMF and [B] DMSO. [QMS-1, (□); QMS-2, (□); QMS-3, (□); QMS-4, (□); QMS-5, (□); Chloramphenicol (□); Tetracyclin (■)].

This suggests that inhibition depends on solvent, structure of compound and bacterial strain. In the present work, all the studied compounds have the same central moiety but different substitution groups as listed in Table 1. QMS-5 contains 2-hydroxy group which shows maximum inhibition against *Bacillus cereus* in DMF than other substitutions. However in DMSO, 4-fluoro (as in QMS-1) group showed significant inhibition against this bacterial strain. In DMF, against *Bacillus subtilis* and *Staphylococcus aureus*, again 4-fluoro group (as in QMS-1) is most effective. However, in DMF, against *Bacillus subtilis*, 4-bromo (as in QMS-2) and 4-N,N-dimethylamine (as in QMS-4) groups are also found to be effective almost up to same extent. None of the groups are found to be effective against *Staphylococcus aureus* in DMF and DMSO except QMS-1 containing 4-fluoro group in DMF.

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

Figure 7 shows the zone of inhibition against Gram negative bacteria in both DMF and DMSO. In DMF, against *Klebsiella pneumoniae*, compounds QMS-1 containing 4-fluoro, QMS-4 containing 4-*N,N*-dimethylamine and QMS-5 containing 2-hydroxy groups exhibited significant inhibition then antibiotic chloramphenicol and inhibition is maximum for QMS-1. In DMSO, compounds QMS-1, QMS-2 and QMS-3 showed significant inhibition against *Klebsiella pneumonia* and inhibition of QMS-1 is almost to the same extent as chloramphenicol. Thus, in DMF and DMSO, 4-fluoro group is found to be most effective against *Klebsiella pneumonia*.

Against *Staphylococcus typhimurium*, only QMS-1 and QMS-5 having 4-fluoro and 2-hydroxy groups respectively showed inhibition in DMF whereas in DMSO except QMS-2, other compounds exhibited inhibition. Thus, in DMSO 4-bromo group is not effective against this strain. Against *Escherichia coli* in DMF, only QMS-1 showed inhibition whereas in DMSO, compounds QMS-3 and QMS-5 containing 2-chloro and 2-hydroxy groups respectively showed inhibition. Against *Pseudomonas aeruginosa*, none of the studied compounds are effective in DMF whereas in DMSO, only 4-bromo (as in QMS-2) group showed inhibition and up to same extent with tetracyclin.

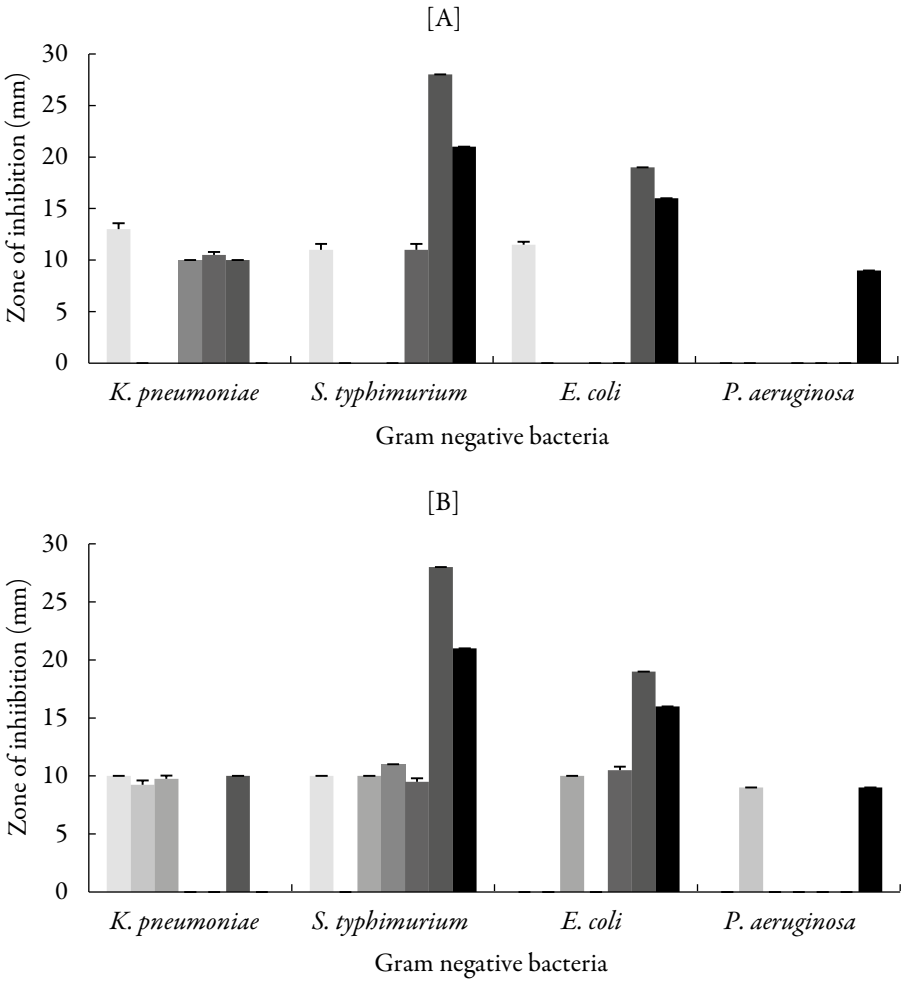

Figure 7. Antibacterial activity of synthesized compounds against Gram negative bacteria in [A] DMF and [B] DMSO. [QMS-1, (▫); QMS-2, (▫); QMS-3, (▫); QMS-4, (▫); QMS-5, (▫); Chloramphenicol (▫); Tetracyclin (▫)].

Hence, the synthesized compounds showed better activity in DMSO against Gram negative bacteria.

Figure 8 shows the zone of inhibition for the studied compounds and two antibiotics such as nystatin and itroconazolagainst selected fungal strain in DMF and DMSO. Against *Candida albicans*, in DMF except QMS-3, other compounds exhibited significant inhibition and QMS-5 containing 2-hydroxy group showed maximum inhibition. However, in DMSO none of the studied compounds are found to be effective

against this fungal strain. In DMF, none of compound was found to inhibit *Candida glabrata* and *Candida epicola*. Whereas in DMSO,only QMS-3 showed some inhibitionagainst *Candida glabrata*. Against *Candida epicola*, there was no inhibition by any of the compound in DMSO. *Against Cryptococcus neoformans* in DMF, only QMS-1 having 4-fluoro group showed inhibition whereas in DMSO, none of the studied compounds was effective.

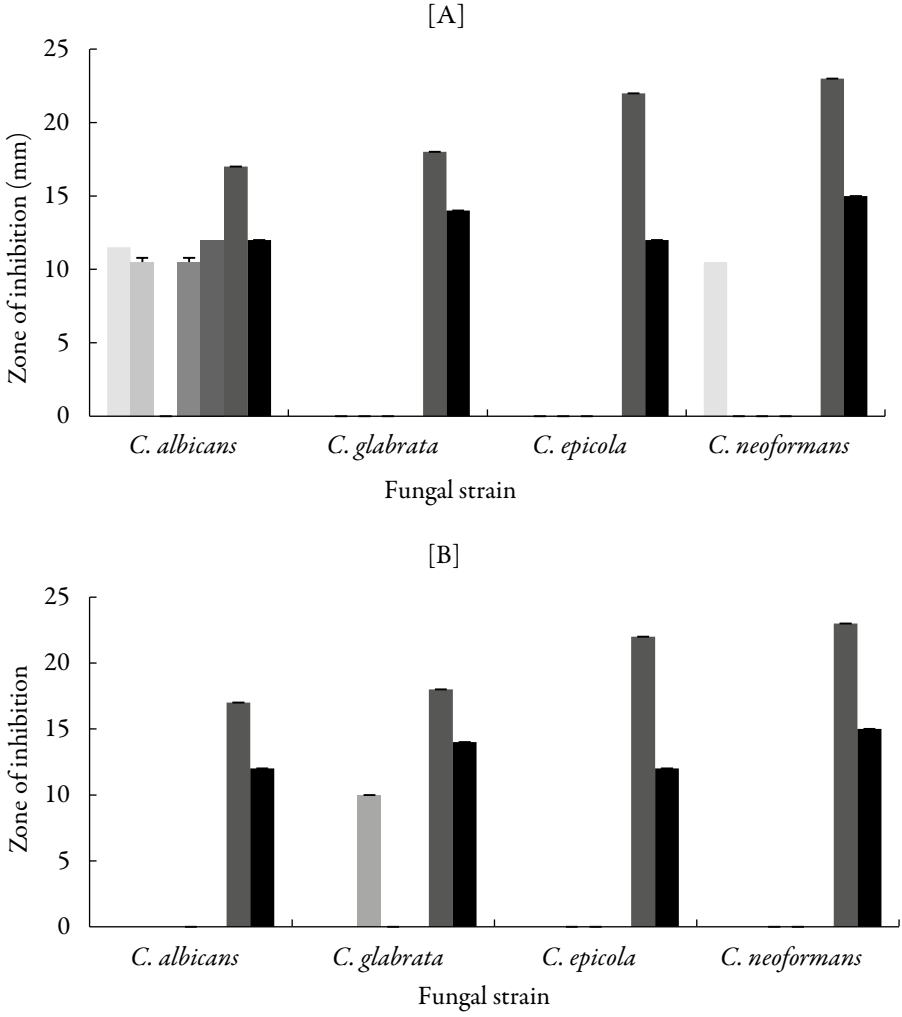

Figure 8. Antifungal activity of synthesized compounds in [A] DMF and [B] DMSO. [QMS-1, (▒); QMS-2, (▒); QMS-3, (▒); QMS-4, (▒); QMS-5, (▒); Nystatin (▒); Itroconazol (▒)].

Overall, *Staphylococcus aureus*, *Candida albicans*, *Candida epicola* and *Cryptococcus neoformans* are most resistant strains.

Conclusions

The inhibition against bacterial and fungal strains depends upon the solvent, structures of compound and strain. For the selected Gram positive bacterial and fungal strains, DMF is better solvent whereas for Gram negative bacteria, DMSO is better solvent. Compounds having halogen groups are more effective against selected microbial strains. *Staphylococcus aureus*, *Candida albicans*, *Candida epicola* and *Cryptococcus neoformans* are the most resistant strains.

Disclosure statement

No potential conflict of interest was reported by the authors.

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