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(RESEARCH ARTICLE)

Synthesis, characterization and *in vitro* antimicrobial activity of cyclic imide: Isoindoline-1, 3-dione derivatives

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Abstract

A series of new cyclic imide: isoindoline-1, 3-dione derivatives were synthesized by condensation of 2-hydrazinyl-2-oxo-N-phenylacetamide and phthalic anhydride. The characterization of synthesized compounds was done by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. All these synthesized compounds were tested for *in vitro* antimicrobial against various bacterial and fungal strains in N, N-dimethyl formamide and Dimethyl sulfoxide. It is observed that almost all the compounds showed moderate antimicrobial activity and N, N-dimethyl formamide is better solvent than dimethyl sulfoxide.

Keywords: Cyclic imide; Isoindoline-1; 3-dione derivatives; N, N-dimethyl formamide; Dimethyl sulfoxide; Gram positive bacteria; Gram negative bacteria; Fungal strains

1. Introduction

Imides are diacyl derivatives of ammonia or primary amine. Among imides, cyclic imides and their N-derivatives contain bisamide linkages with a general structure of [-CO-N(R)-CO-] are the most important representatives of this class. These compounds are structurally related to acid anhydrides. The presence of oxygen and nitrogen atoms as co-ordination sites can attach these ligands with the biological system and cause various pharmacological effects [1, 2]. Due to hydrophobicity and neutral structures, these compounds can easily cross biological membranes in vivo [3-5]. In view of the favourable pharmacokinetic properties, derivatives of cyclic imides have been found to exhibit wide range of biological activities such as antibacterial [6-8], antifungal [9, 10], antiviral [11, 12], analgesic [13, 14], antiangiogenic [15, 16], anti-HIV [17-19], antimalarial [20], anticancer [21, 22], androgen receptor antagonistic [23], anti-inflammatory [24-26], anxiolytic [27, 28], anti-depressive [29], anticonvulsant [30, 31], hypolipidemic [32] and muscle-relaxant activities [33] etc.

A very important cyclic imide moiety; Isoindoline-1, 3-dione commonly known as phthalimide, is the key structural unit of a variety of biologically active molecules which are of pharmaceutical significance. Various drugs such as lenalidomide, pomalidomide, etc., contain isoindoline structure and these drugs have been used for the treatment of multiple myeloma [34, 35]. Various other isoindoline structure containing drugs are also known to be used for the treatment of certain types of diseases [36-38].

Thus, in present work, some new isoindoline-1, 3-dione derivatives have been synthesized. By some spectroscopic techniques such as IR, ^{1}H NMR ^{13}C NMR and mass, their structures were confirmed. The antimicrobial activity of the synthesized compounds was done against some pathogenic gram-positive and gram-negative bacteria and fungi in N,N-dimethyl formamide (DMF) and Dimethyl sulfoxide (DMSO).

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2. Experimental

2.1. Material

Different substituted amines, hydrazine hydrates (99.9%), diethyl oxalate, phthalic anhydride, glacial acetic acid used for the synthesis, was supplied from Spectrochem Pvt. Ltd. (Mumbai, India) and was used without any treatment. The solvents methanol, 1,4-dioxane used for synthesis and DMF, DMSO used for antimicrobial activity of synthesized derivatives were of AR grade supplied by Spectrochem Pvt. Ltd. (Mumbai, India). All the solvents used for activities were purified according to the standard procedure [39].

2.2. Synthesis

2.2.1. Synthesis of ethyl 2-oxo-2-(phenylamino) acetate derivatives (Int-1)

A mixture of substituted amine (1.0 eq) and diethyl oxalate (1.05 eq) in 1,4-dioxane was refluxed for 5-6 hrs. The completion of reaction was confirmed by analytical thin layer chromatography (TLC) (Performed on aluminum coated plates Gel $60F_{254}$ (E. Merck)) using (7:3-Hexane: Ethyl acetate) as mobile phase. After completion of the reaction, reaction mass was cooled and was poured into crushed ice. The resulting solid was filtered, washed with hexane and dried under vacuum.

2.2.2. Synthesis of 2-hydrazinyl-2-oxo-N-phenylacetamide derivatives (Int-2)

A methanolic solution of ethyl 2-oxo-2-(phenylamino) acetate (Int-1) (1.0 eq) and hydrazine hydrate (1.1 eq) was stirred at 0-5˚C for 30 minutes. The progress of reaction was monitored by TLC using 5:5-Hexane: Ethyl acetate as mobile phase. The solid was filtered, washed with cold water and was dried.

2.2.3. Synthesis of isoindoline-1, 3-dione derivatives

Equimolar solution of 2-hydrazinyl-2-oxo-N-phenylacetamide (Int-2) and phthalic anhydride in glacial acetic acid was refluxed for 3-4 hrs. The progress of reaction was monitored by TLC using 6:4-Hexane: Ethyl acetate as mobile phase. After completion of reaction, the reaction mass was poured into crushed ice. The resulting solid was filtered, washed with water and was purified by silica-gel column chromatography. The pure fraction was collected in 60-40% Hexane: Ethyl acetate and solvent was evaporated under vacuum. All the synthesized compounds were recrystallized using THF. Figure 1 shows complete reaction scheme.

Overall, ten derivatives were synthesized, which are as follows:

GMC-1: N^1-(4-bromophenyl)-N^2-(1,3-dioxoisoindolin-2-yl)oxalamide

GMC-2: N^1-(3-chloro-4-fluorophenyl)-N^2-(1,3-dioxoisoindolin-2-yl)oxalamide

GMC-3: N^1-(4-chlorophenyl)-N^2-(1,3-dioxoisoindolin-2-yl)oxalamide

GMC-4: N^1-(1,3-dioxoisoindolin-2-yl)-N^2-(4-fluorophenyl)oxalamide

GMC-5: N^1-(1,3-dioxoisoindolin-2-yl)-N^2-(4-methoxyphenyl)oxalamide

GMC-6: N^1-(1,3-dioxoisoindolin-2-yl)-N^2-(p-tolyl)oxalamide

GMC-7: N^1-(3-chlorophenyl)-N^2-(1,3-dioxoisoindolin-2-yl)oxalamide

GMC-8: N^1-(1,3-dioxoisoindolin-2-yl)-N^2-(3-methoxyphenyl)oxalamide

GMC-9: N^1-(1,3-dioxoisoindolin-2-yl)-N^2-(2-fluorophenyl)oxalamide

GMC-10: N^1-(3,4-dimethylphenyl)-N^2-(1,3-dioxoisoindolin-2-yl)oxalamide.

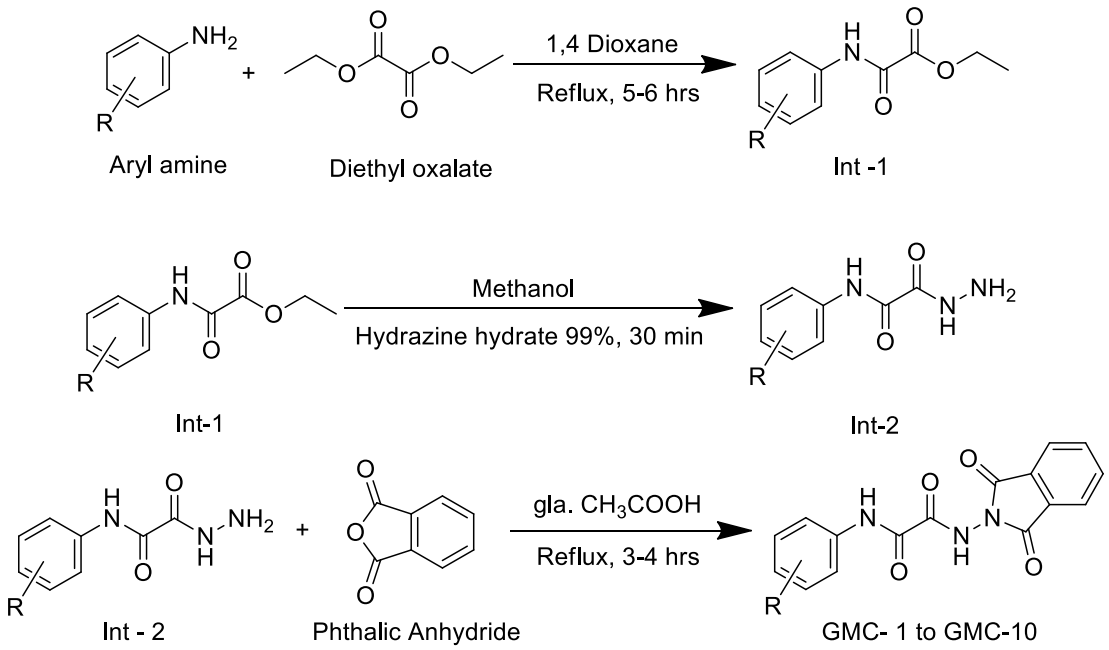

Figure 1 Reaction Scheme

The characterization of these crystallized synthesized compounds was done by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. IR spectra were recorded on Shimadzu furrier transport infrared spectrophotometer (Model No - IR affinity-1S), ^{1}H NMR and ^{13}C 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 TMS as an internal standard. The NMR signals are reported in δ ppm. The mass spectra were determined using direct inlet probe on a Shimadzu GC-MS (Model-QP-2010) mass spectrometer.

Table 1 shows the physical parameters of all the synthesized compounds.

The melting points of compounds were measured by differential scanning calorimeter (Model-Shimadzu-DSC-60) under nitrogen gas atmosphere.

Table 1 Physical parameters of Isoindoline-1, 3-dione derivatives

Compound Code	Substitution R	Molecular Formula	Molecular Weight (gm/mol)	Yield (%)	R_f*value	Melting Points (°C)
GMC-1	-4-Br	$C_{16}H_{10}BrN_3O_4$	388.17	84	0.48	197.3
GMC-2	-3-Cl, 4-F	$C_{16}H_9ClFN_3O_4$	361.71	75	0.49	174.6
GMC-3	-4-Cl	$C_{16}H_{10}ClN_3O_4$	343.72	72	0.48	200.8
GMC-4	-4-F	$C_{16}H_{10}FN_3O_4$	327.27	77	0.46	195.2
GMC-5	-4-OCH_3	$C_{17}H_{13}N_3O_5$	339.30	82	0.39	252.4
GMC-6	-4-CH_3	$C_{17}H_{13}N_3O_4$	323.30	81	0.47	235.9
GMC-7	-3-Cl	$C_{16}H_{10}ClN_3O_4$	343.72	83	0.50	192.5
GMC-8	-3-OCH_3	$C_{17}H_{13}N_3O_5$	339.30	79	0.45	186.7
GMC-9	-2-F	$C_{16}H_{10}FN_3O_4$	327.27	73	0.50	188.6
GMC-10	-3,4-diCH_3	$C_{18}H_{15}N_3O_4$	337.33	86	0.51	207.8

*0.6:0.4 - Hexane:Ethyl acetate

2.3. Antimicrobial activity

2.3.1. Microorganisms tested

The selected microorganisms were obtained from National Chemical Laboratory (NCL), Pune, India. The microorganisms were maintained at 4°C. The Gram positive bacteria were *Bacillus cereus* ATCC11778 (BC), *Bacillus subtilis* ATCC6633(BS), *Staphylococcus aureus* ATCC29737 (SA), *Corynebacterium rubrum* ATCC14898 (CR) and Gram negative *bacteria were Escherichia coli* NCIM2931 (EC), *Pseudomonas aeruginosa* ATCC27853(PA), *Klebsiella pneumoniae* NCIM2719 (KP) and *Salmonella typhimurium* ATCC23564 (ST). The fungal strains were *Candida glabrata* NCIM3448 (CG), *Candida albicans* ATCC2091 (CA), *Cryptococcus neoformans* NCIM3542 (CN) and three clinical isolates of Candida species were C1, C2, C3.

The microorganisms studied are clinically important ones causing several infections and food spoilage. *In vitro* antimicrobial activity of all the synthesized compounds were studied against these pathogenic microbial strains by agar well diffusion method [40].

3. Results and discussion

The IR, ^{1}H NMR, ^{13}C NMR and mass spectra of a compound GMC-6 is shown in Figure 2, 3,4 and 5 respectively.

The spectral data of all the compounds are given below.

3.1. Spectral data

3.1.1. GMC-1

IR (cm^{-1})*:**3149.76 (Ar-C-H str.),1685.79(C=O str. amide), 1587.42(N-H bend.), 1529.55 (N-H in plane amide), 1485.19 (Ar-C=C- str.), 1155.36(-C-N str.), 817.82 (Ar-C-H oop. 1, 4-disubstituted ring), 704.02 (N-H oop. 2° amide), 610.23 (C-Br str.).^{1}H NMR (DMSO-d$_6$, 400 MHz) δ(ppm)*:**7.538-7.560 (2H, d, 8.80 Hz, Ar-CH), 7.616-7.636 (2H, d, 8.00 Hz, Ar-CH), 7.941-8.012 (4H, m, Ar-CH), 11.093 (1H, singlet, -NH-N), 11.812 (1H, singlet, -NH-Ar).***^{13}C NMR (DMSO-d$_6$, 100 MHz) δ(ppm)*:** 116.95, 122.36, 122.65, 123.88, 129.26, 131.48, 135.33, 136.54, 156.65, 159.11, 164.27.***MS: (m/z) =***388.

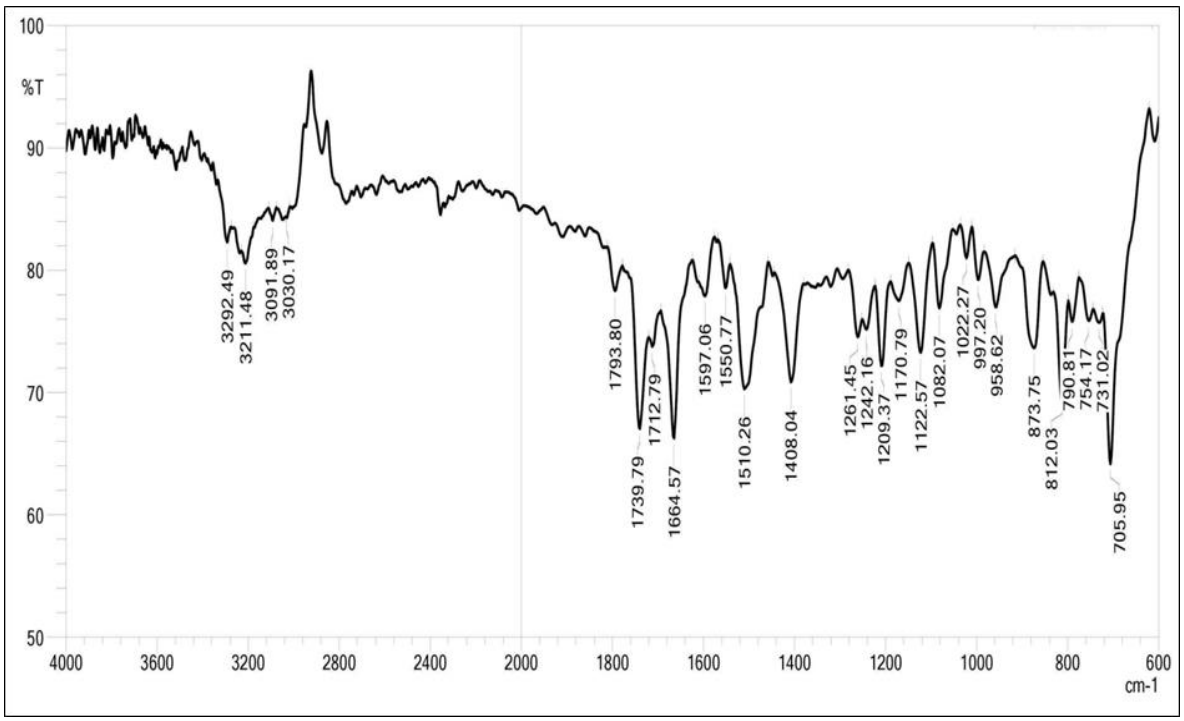

Figure 2 IR spectrum of compound GMC-6

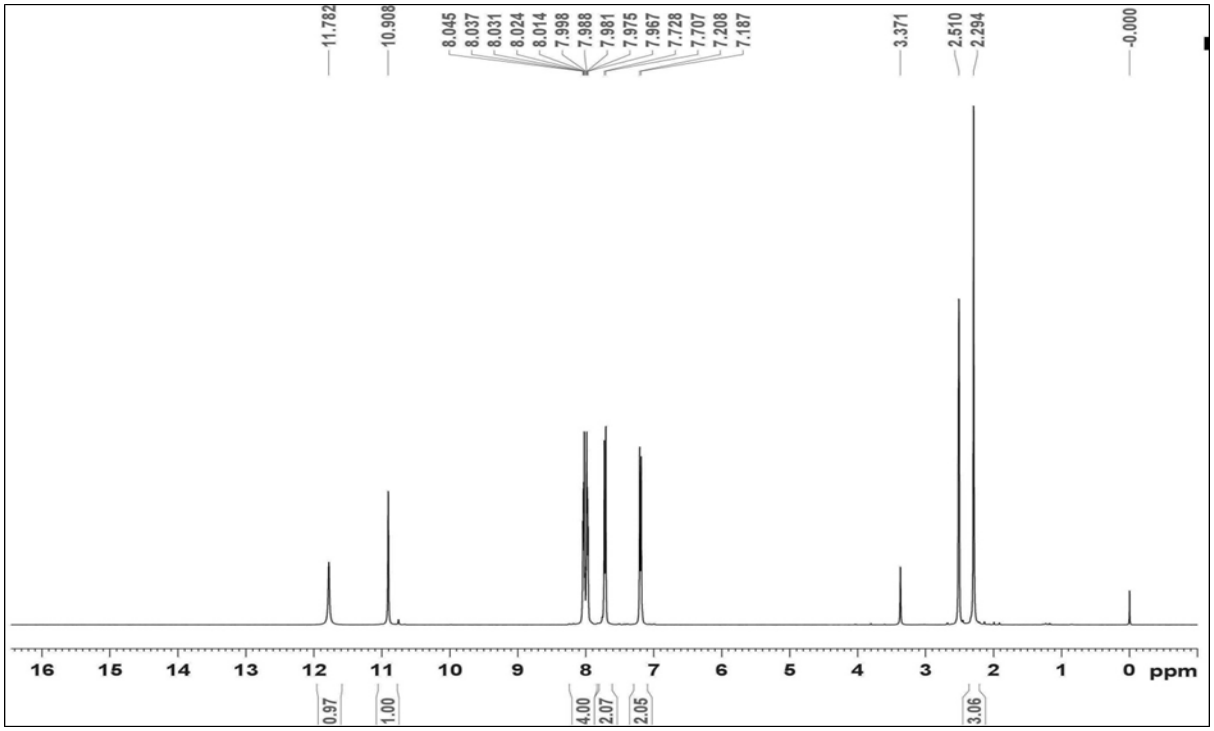

Figure 3 ^{1}H NMR spectrum of compound GMC-6

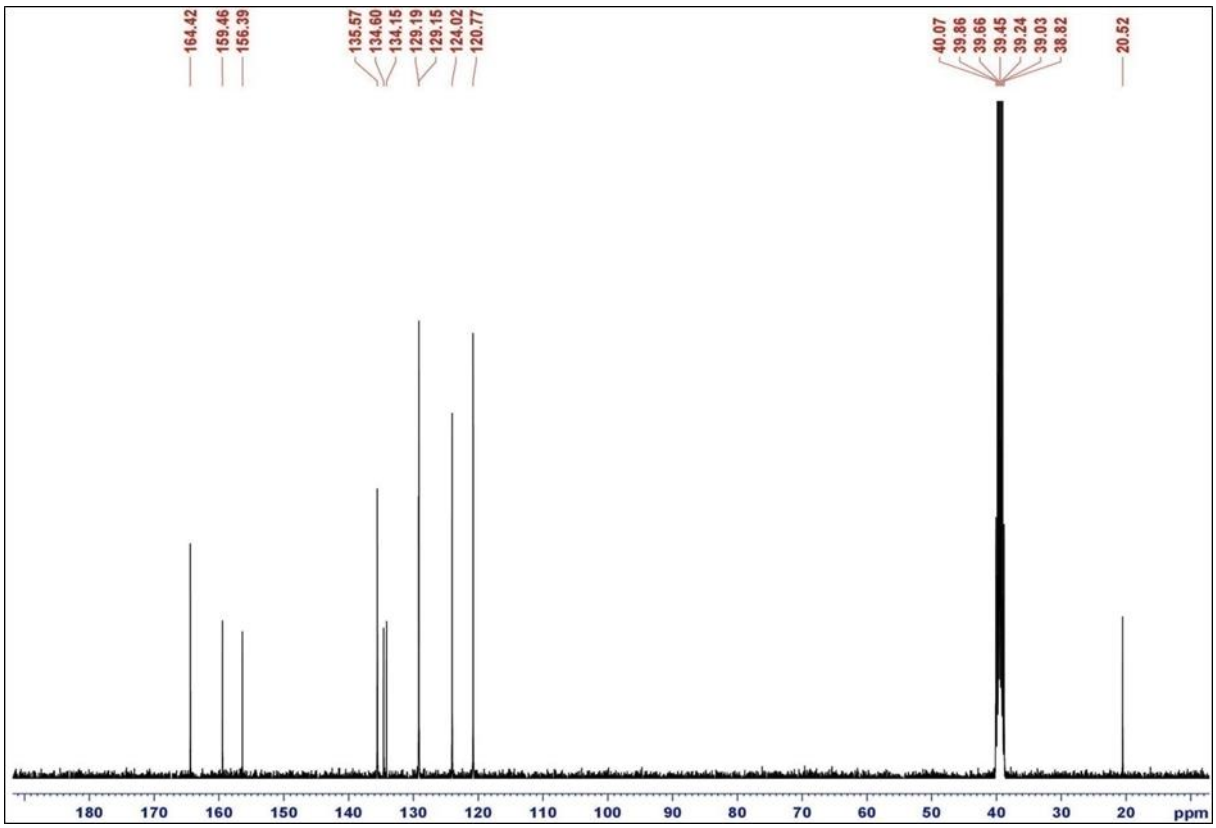

Figure 4 ^{13}C NMR spectrum of compound GMC-6

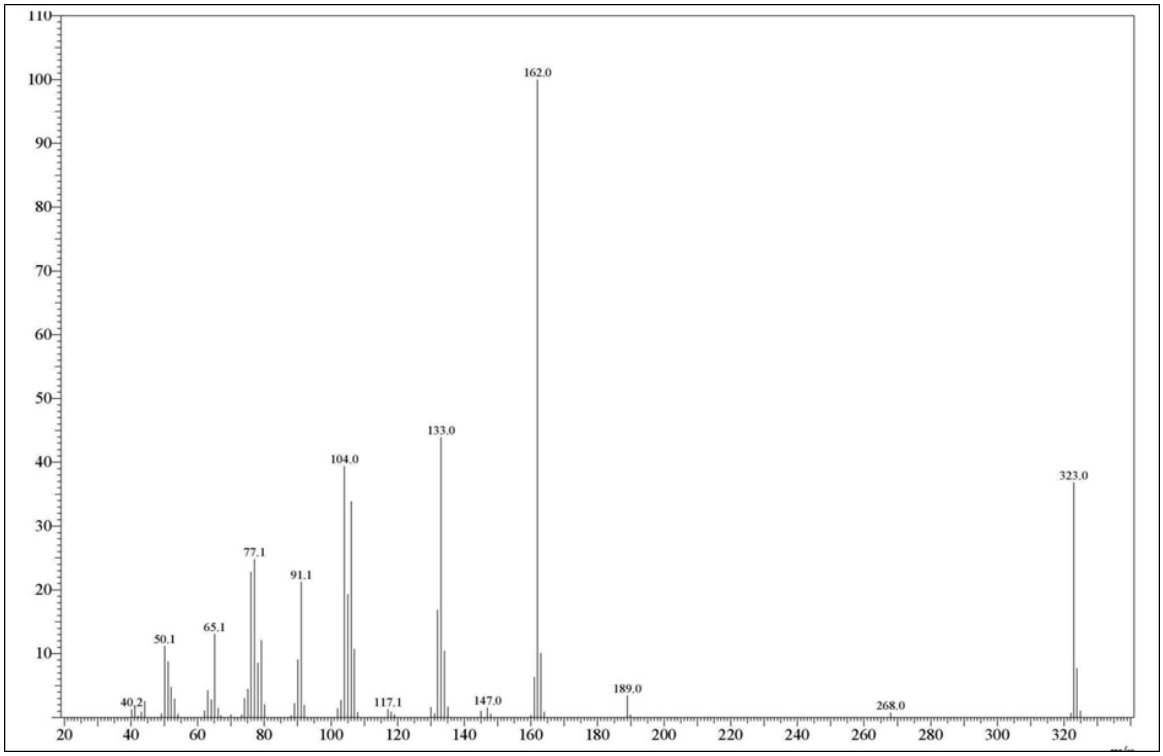

Figure 5 Mass spectrum of compound GMC-6

3.1.2. GMC-2

IR (cm^{-1})*:** 3149.76 (Ar-C-H str.),1683.86(C=O str. amide), 1587.42 (N-H bend.), 1514.12 (N-H in plane amide), 1494.83 (Ar-C=C- str.), 1157.29(-C-N str.), 1074.29 (C-F str.), 711.73 (C-Cl str.).^{1}H NMR (DMSO-d6) δ(ppm)*:**7.581-7.601 (2H, d, 8.00 Hz, Ar-CH), 7.826-8.014 (5H, m, Ar-CH), 11.026 (1H, singlet, -NH-N), 11.824 (1H, singlet, -NH-Ar).***^{13}C NMR (DMSO-d$_6$, 100 MHz) δ(ppm)*:**116.38, 116.59, 116.96, 122.39, 122.45, 122.74, 123.93, 129.26, 131.48, 131.60, 135.45, 136.56, 136.97, 157.02, 159.38, 164.42 ***MS: (m/z) =***361.

3.1.3. GMC- 3

IR (cm^{-1})*:** 3132.70 (Ar-C-H str.), 1658.78 (C=O str. amide), 1587.42 (N-H bend.), 1529.55 (N-H in plane amide), 1485.19 (Ar-C=C- str.), 1056.99 (C-F str.), 817.82 (Ar-C-H oop. 1, 4-disubstituted ring), 711.73 (C-Cl str.).^{1}H NMR (DMSO-d6) δ(ppm)*:** 7.378-7.400 (2H, d, 8.80 Hz, Ar-CH), 7.6654-7.685 (2H, d, 8.00 Hz, Ar-CH), 7.945-8.016 (4H, m, Ar-CH), 11.095 (1H, singlet, -NH-N), 11.816 (1H, singlet, -NH-Ar).***^{13}C NMR (DMSO-d$_6$, 100 MHz) δ(ppm)*:** 121.04, 124.51, 127.88, 128.97, 130.11, 130.72, 135.33, 156.61, 159.09, 164.23.***MS: (m/z) =***343.

3.1.4. GMC-4

IR (cm^{-1})*:** 3120.82 (Ar-C-H str.),1670.35(C=O str. amide), 1597.06(N-H bend.), 1539.20 (N-H in plane amide), 1490.97 (Ar-C=C- str.), 1159.93(-C-N str.), 1082.07 (C-F str.), 810.10 (Ar-C-H oop. 1, 4-disubstituted ring), 707.88 (N-H oop. 2° amide).^{1}H NMR (DMSO-d$_6$) δ(ppm)*:** 7.018-7.040 (2H, d, 8.80 Hz, Ar-CH), 7.845-7.865 (2H, d, 8.00 Hz, Ar-CH), 7.931-8.145 (4H, m, Ar-CH), 11.093 (1H, singlet, -NH-N), 11.824 (1H, singlet, -NH-Ar).***^{13}C NMR (DMSO-d$_6$, 100 MHz) δ(ppm)*:**114.11, 121.09, 123.41, 130.13, 130.72, 134.31, 158.98, 156.63, 159.11, 164.27.***MS*: *(m/z)*** = 327.

3.1.5. GMC-5

IR (cm^{-1})*:** 3082.25 (Ar-C-H str.), 2964.59 (C-H alkane asym. Str. R-O-CH$_3$), 2837.29 (C-H alkane sym. Str. R-O-CH$_3$), 1678.07(C=O str. amide), 1595.13(N-H bend.), 1533.41 (N-H in plane amide), 1469.76 (Ar-C=C- str.), 1265.30 (C-O-C str.), 1155.36(-C-N str.), 813.96 (Ar-C-H oop. 1, 4-disubstituted ring), 707.88 (N-H oop. 2° amide).^{1}H NMR (DMSO-d6) δ(ppm)*:**3.784 (3H, s, -OCH$_3$), 7.677-7.698 (2H, d, 8.40 Hz, Ar-CH), 7.467-7.488 (2H, d, 8.40 Hz, Ar-CH), 7.971-8.055 (4H, m, Ar-CH), 10.987 (1H, singlet, -NH-N), 11.847 (1H, singlet, -NH-Ar).***^{13}C NMR (DMSO-d6, 100 MHz) δ(ppm)*:**55.85, 114.20, 122.50, 125.30, 130.51, 131.10, 131.52, 155.01, 160.80, 161.15, 164.37.***MS: (m/z) =***339.

3.1.6. GMC-6

IR (cm^{-1})*:** 3091.89 (Ar-C-H str.), 2982.61 (C-H alkane asym. Str. R-CH_3), 1664.57(C=O str. amide), 1597.06(N-H bend.), 1550.77 (N-H in plane amide), 1510.26 (Ar-C=C- str.), 1170.79(-C-N str.), 812.03 (Ar-C-H oop. 1, 4-disubstituted ring), 705.95 (N-H oop. 2° amide). ***^{1}H NMR (DMSO-d6) δ(ppm)*:**2.294 (3H, s, -CH_3), 7.187-7.208 (2H, d, 8.40 Hz, Ar-CH), 7.707-7.728 (2H, d, 8.40 Hz, Ar-CH), 7.967-8.045 (4H, m, Ar-CH), 10.908 (1H, singlet, -NH-N), 11.782 (1H, singlet, -NH-Ar). ***^{13}C NMR (DMSO-d_6, 100 MHz) δ(ppm)*:**20.52, 120.77, 124.02, 129.15, 129.19, 134.15, 134.60, 135.57, 156.39, 159.46, 164.42. ***MS: (m/z) =323.

3.1.7. GMC-7

IR (cm^{-1})*:** 3084.18 (Ar-C-H str.), 1676.14 (C=O str. amide), 1591.27 (N-H bend.), 1502.55 (N-H in plane amide), 1413.82 (Ar-C=C- str.), 727.16 (Ar-C-H oop. 1, 3-disubstituted ring), 704.02 (C-Cl str.). ***^{1}H NMR (DMSO-d6) δ(ppm)*:**7.448 (1H, m, Ar-CH), 7.860-7.897 (2H, m, Ar-CH), 7.913 (1H, s, Ar-CH), 7.945-8.016 (4H, m, Ar-CH),10.979 (1H, singlet, -NH-N), 11.797 (1H, singlet, -NH-Ar). ***^{13}C NMR (DMSO-d_6, 100 MHz) δ(ppm)*:**119.97, 120.88, 124.61, 124.75, 128.63, 131.41, 131.63, 132.77,137.63, 156.41, 159.51, 164.47. ***MS: (m/z) =343.

3.1.8. GMC-8

IR (cm^{-1})*:** 3080.32 (Ar-C-H str.), 2974.23 (C-H alkane asym. Str. R-O-CH_3), 2860.43 (C-H alkane sym. Str. R-O-CH_3), 1685.79(C=O str. amide), 1597.06(N-H bend.), 1554.63 (N-H in plane amide), 1483.26 (Ar-C=C- str.), 1278.81 (C-O-C str.), 1163.08(-C-N str.), 742.59 (Ar-C-H oop. 1, 3-disubstituted ring), 707.88 (N-H oop. 2° amide). ***^{1}H NMR (DMSO-d6) δ(ppm)*:**3.823 (3H, singlet, -OCH_3), 7.345 (1H, m, Ar-CH), 7.671-7.676 (2H, m, Ar-CH), 7.875 (1H, s, Ar-CH), 7.945-8.016 (4H, m, Ar-CH),10.918 (1H, singlet, -NH-N), 11.797 (1H, singlet, -NH-Ar). ***^{13}C NMR (DMSO-d_6, 100 MHz) δ(ppm)*:**55.97, 105.45, 108.42, 114.11, 124.41, 128.31, 131.43, 131.73, 137.67, 156.49, 159.01, 159.54, 164.51. ***MS: (m/z) =339.

3.1.9. GMC-9

IR (cm^{-1})*:** 3136.25 (Ar-C-H str.),1680.00(C=O str. amide), 1597.06 (N-H bend.), 1550.77 (N-H in plane amide), 1483.26 (Ar-C=C- str.), 1172.72(-C-N str.), 1082.07 (C-F str.), 759.95 (Ar-C-H oop. 1, 2-disubstituted ring), 702.09 (N-H oop. 2° amide). ***^{1}H NMR (DMSO-d6) δ(ppm)*:**7.711-7.851 (3H, m, Ar-CH), 7.875-7.911 (1H, m, Ar-CH), 7.945-8.016 (4H, m, Ar-CH),10.918 (1H, singlet, -NH-N), 11.797 (1H, singlet, -NH-Ar). ***^{13}C NMR (DMSO-d_6, 100 MHz) δ(ppm)*:**115.53, 123.93, 124.57, 124.63, 124.74, 125.17, 131.42, 131.71, 154.49, 159.17, 159.83, 164.91. ***MS: (m/z) =327.

3.1.10. GMC-10

IR (cm^{-1})*:** 3091.89 (Ar-C-H str.), 2972.31 (C-H alkane asym. Str. R-CH_3), 1658.78(C=O str. amide), 1593.20(N-H bend.), 1498.69 (N-H in plane amide), 1471.67 (Ar-C=C- str.), 1118.71(-C-N str.), 704.02 (N-H oop. 2° amide). ***^{1}H NMR (DMSO-d6) δ(ppm)*:**1.986 (3H, s, -CH_3), 2.092 (3H, s, -CH_3), 6.882-6.901(1H, d, Ar-CH), 7.064-7.087 (2H, m, Ar-CH), 7.945-8.016 (4H, m, Ar-CH),10.918 (1H, singlet, -NH-N), 11.797 (1H, singlet, -NH-Ar). ***^{13}C NMR (DMSO-d_6, 100 MHz) δ(ppm)*:**19.45, 20.37, 118.55, 121.13, 124.61, 128.50, 131.39, 131.67, 133.21, 135.44, 136.22, 159.11, 159.71, 164.79. ***MS: (m/z) =337.

3.2. Antimicrobial activity

Figure 6 represents the zone of inhibition of compounds against Gram positive bacteria. It is observed that in DMF, out of four Gram positive bacterial strains selected for the study, only BC and BS could be affected by the synthesized compounds. Against BC, GMC-3 had no effect al all whereas GMC-4, GMC-5, GMC-6, GMC-7 and GMC-8 exhibited almost equal zone of inhibition. Minimum inhibition was exhibited by GMC-1 and GMC-2. For BS, GMC-1, GMC-8 and GMC-9 showed maximum inhibition whereas GMC-6 had no effect at all. Other compounds also exhibited significant inhibition.

In DMSO, not a single synthesize compound could inhibit BC, SA and CR. Against BS, only GMC-1, GMC-8 and GMC-9 exhibited and maximum inhibition was by GMC-9. Thus, zone on inhibition depends on solvent, bacterial strain as well as on structure of compounds. As evident from Figure 6 that for these synthesized compounds, DMF is better solvent than DMSO.

Table 1 shows that central moiety for all the compounds is same but substitutions are different which gives different zone of inhibition. Thus, in DMF against BC, 4-chloro substitution present in GMC-3 is not effective at all. However, when chloro group is present at 3rd position, it exhibited maximum inhibition. This suggests that position of group also play an important role in inhibition. Other substitutions had significant effect on BC. For BS, 4-methyl group had no effect. 4-bromo (as in GMC-1), 3-methoxy (as in GMC-8) and 2-fluoro (as in GMC-1) had maximum effect. GMC-5 also contains methoxy group but at 4th position but inhibition is less by GMC-5, which again prove the effect of position of group on inhibition.

In DMSO, against BS, only 3-methoxy (as in GMC-8), 2-fluoro (as in GMC-9) and 3, 4-dimethyl (as in GMC-10) groups were effective and 2-fluoro substitution had maximum inhibition.

Thus, in DMF, both SA and CR gram positive bacteria are resistant and BC and BS are susceptible. In DMSO, BC, SA and CR are resistant and only BS is susceptible.

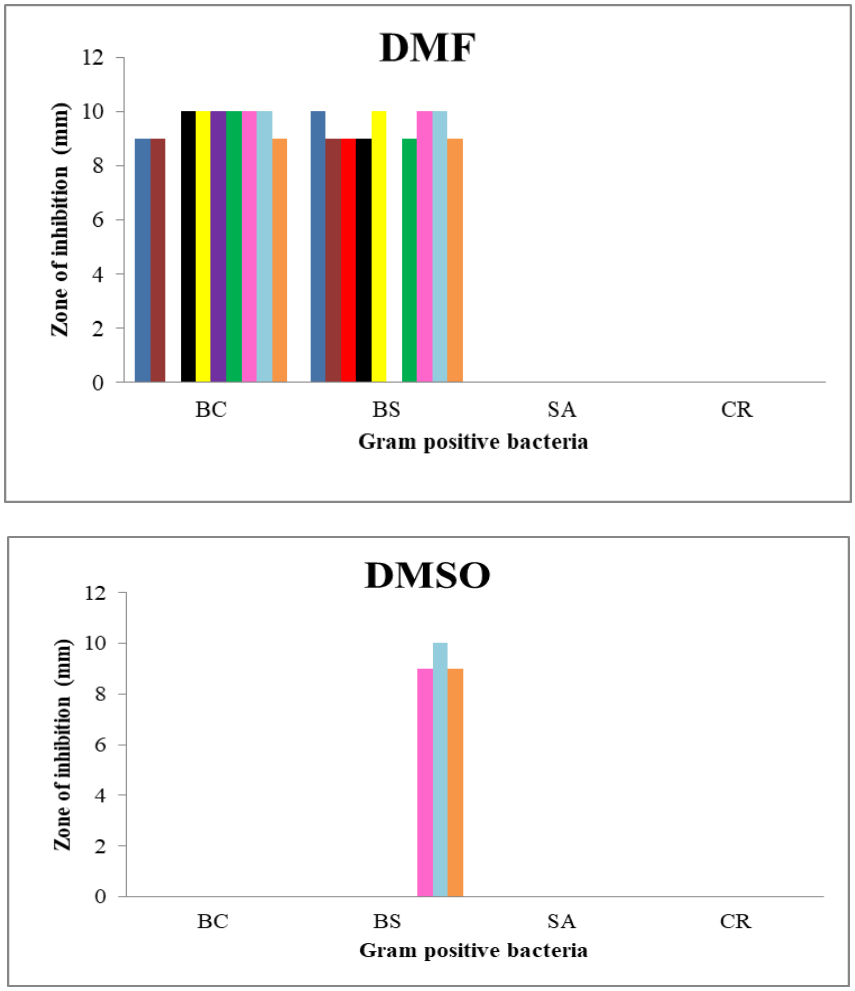

Figure 6 The zone of inhibition of isoindolinone-1,3-dione derivatives against Gram positive bacteria in DMF and DMSO

GMC-1, (■); GMC-2, (■); GMC-3, (■); GMC-4, (■); GMC-5, (■); GMC-6, (■);

GMC-7, (■); GMC-8, (■); GMC-9, (■); GMC-10, (■)

Figure 7 shows the zone of inhibition of compounds against gram negative bacteria in DMF and DMSO. In DMF, against EC, all the compounds were effective except GMC-10. Thus, 3, 4 –dimethyl group is not effective at all. The inhibition exhibited by GMC-2, GMC-7 and GMC-8 are equal and maximum. That is, 3-chloro, 4-fluoro (as in GMC-2), 3-chloro (as in GMC-7), and 3-methoxy (as in GMC-8) groups are most effective. Other groups could also inhibit this strain to some extent. For KP, except GMC-4, GMC-8 and GMC-10, all the compounds exhibited inhibition and almost to the same extent. Thus, for KP, 4-fluoro, 3-methoxy and 3,4-dimethyl groups are not effective at all. For PA, except GMC-3 and GMC-4, all the compounds exhibited inhibition and inhibition is almost same and maximum for GMC-1, GMC-2, GMC-5, GMC-7 and GMC-8. So, 4-chloro and 4-fluoro groups are not effective for PA. None of the compound could inhibit ST. Thus, in DMF, ST is the most resistant bacteria.

In DMSO, only GMC-9 containing 2-flouro group exhibited inhibition against EC, Other compounds had no effect. For other three strains i.e., KP, PA and ST, none of the compound exhibited inhibition.

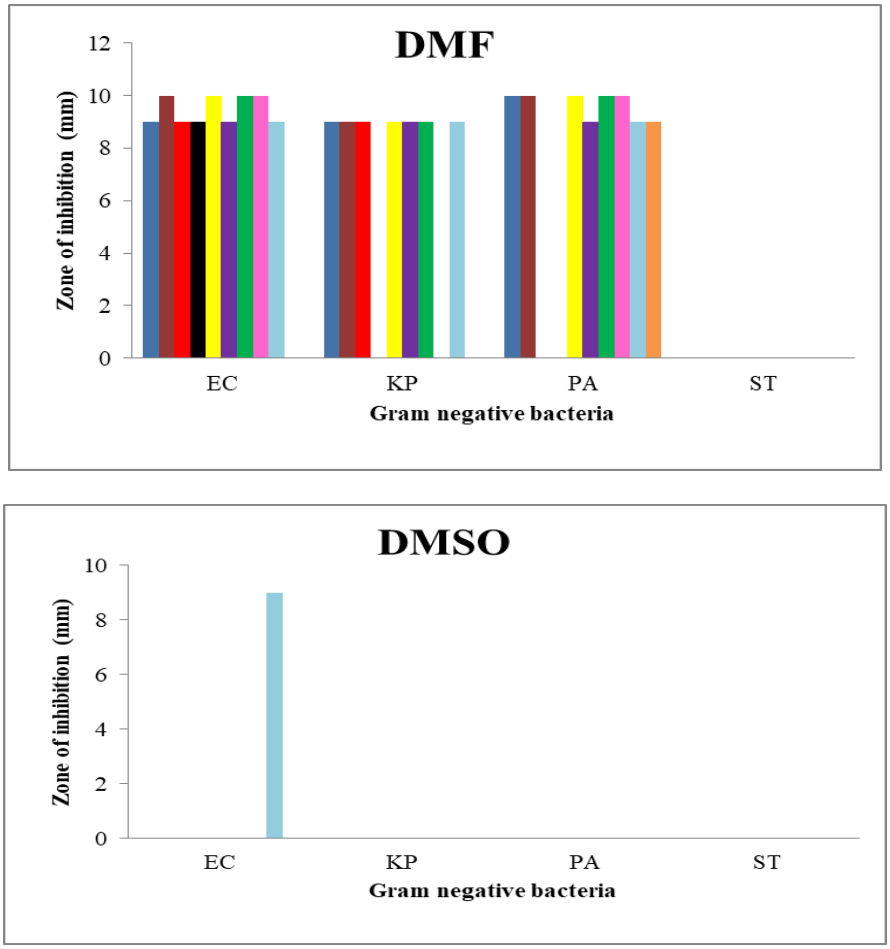

Figure 7 The zone of inhibition of isoindolinone-1, 3-dione derivatives against Gram negative bacteria in DMF and DMSO

GMC-1, (■); GMC-2, (■); GMC-3, (■); GMC-4, (■); GMC-5, (■); GMC-6, (■);

GMC-7, (■); GMC-8, (■); GMC-9, (■); GMC-10, (■)

Figure 8 shows zone of inhibition of compounds against fungal strains and clinical isolates. In DMF, all the compounds exhibited inhibition against all the three fungal strains as well as clinical isolates. Thus, all the substitutions are effective in inhibiting the selected fungal strains. For CA, 3-chloro group present in GMC-7 is most effective. For CG, both 3-chloro group (present in GMC-7) as well as 3-methoxy group (present in GMC-8) are equally effective whereas against CN, various substitution groups are effective. The 3-chloro,4-fluoro (in GMC-2), 4-fluoro (in GMC-4), 4-methoxy (in GMC-5), 4-methyl (in GMC-6), 4-chloro (in GMC-7) and 3, 4-dimethyl (in GMC-10) groups are equally effective.

In DMSO, all the compounds exhibited inhibition against C1 and C2. For C2, except GMC-10, all showed inhibition. However, against CA, only GMC-1 containing 4-bromo and GMC-6 containing 4-methyl groups showed inhibition. Other compounds had no effect at all. For CG, none of the compound was effective at all. Against CN, all the compounds are found to be effective and substitution groups 4-fluoro and 3,4-dimethoxy present in GMC-9 and GMC-10 are most effective. Thus, CG is most resistant whereas CN is most susceptible fungal strain.

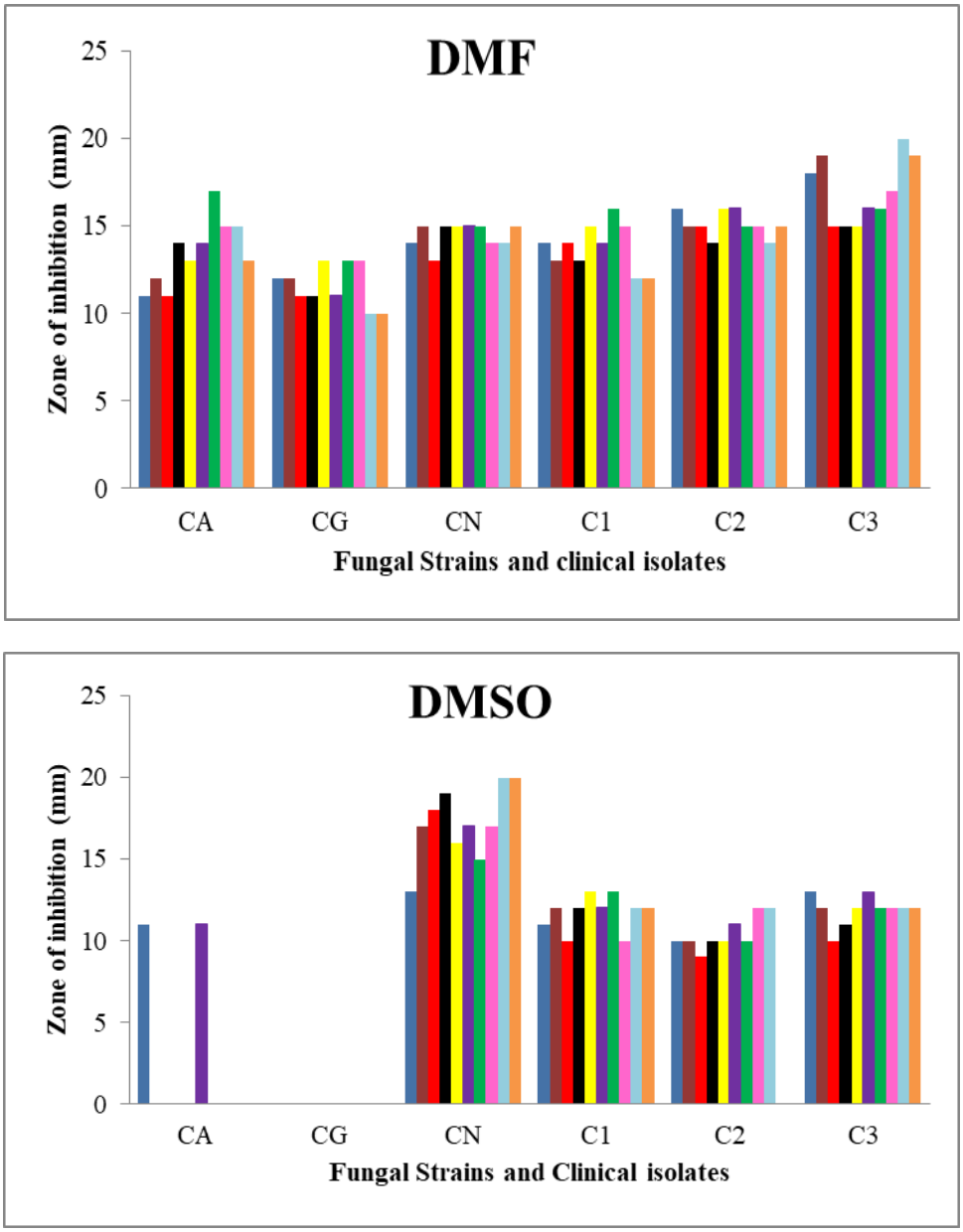

Figure 8 The zone of inhibition of isoindolinone-1,3-dione derivatives against fungal strains and clinical isolates in DMF and DMSO

GMC-1, (■); GMC-2, (■); GMC-3, (■); GMC-4, (■); GMC-5, (■); GMC-6, (■); GMC-7, (■); GMC-8, (■); GMC-9, (■); GMC-10, (■)

Against all the clinical isolates, all the studied compound had inhibition which varies depending upon the type of substitution group and solvent. Figure 8 shows that in both the solvents, compounds had significant inhibition against clinical isolates.

In DMF, against clinical isolate C1. GMC-7 (containing 3-chloro group) is more effective against C1. GMC-9 (containing 2-flouro) and GMC-10 (containing 3, 4 dimethyl groups) compounds are found to be less effective than others. Rest of the compounds possess moderate inhibition. For C2, GMC-1, GMC-5 and GMC-6 showed maximum inhibition. That is, 4-bromo, 4-methoxy and 4-methyl groups are equally effective. GMC-9 (2-F) and GMC-4 (4-F) shows minimum inhibition. Other compounds also affected C2.For C3, GMC-9 containing 2-fluoro group is most effective in DMF. Other substitution groups also exhibited significant effect.

In DMSO, against C1, GMC-9 (containing 2-flouro) and GMC-10 (containing 3, 4 dimethyl groups) compounds are found to be most effective than others. Rest of the compounds possess significant inhibition. For C2, in DMSO, GMC-5 (containing 4-OCH_3 group) and GMC-7 (containing 3-chloro group) exhibited maximum inhibition. GMC-3 (containing 4-chloro group) and GMC-8 (containing 3-OCH_3 group) showed minimum inhibition. Rest of the compounds could also inhibit to some extent.Against GMC-1 and GMC-6 containing 4-bromo and 4-methyl groups are very effective as compared to other groups. Minimum inhibition is exhibited by 3-chloro group present in GMC-3.

4. Conclusion

For all the synthesized compounds against studied bacterial and fungal strains, DMF is found to be better solvent. In both DMF and DMSO, the Gram positive bacteria; SA and CR are most resistant bacteria. In case of Gram negative bacteria, in DMF, ST is most resistant bacteria. In DMSO, all the selected four strains i.e., EC, KP, PA and ST are resistant as only one compound showed inhibition against EC. It is observed against selected Gram positive and Gram negative bacterial strains, mostly compounds containing halogen and methoxy groups are more effective. Further, position of substitution group affects inhibition. The synthesized compounds are found to be more effective against selected fungal strains and clinical isolates. Thus, novel compounds can be synthesized with halogen and methoxy groups which will inhibit these strains.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest.

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