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Research Article

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF SOME NEW 2-THIOXOIMIDAZOLIDIN-4-ONE DERIVATIVES

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ABSTRACT

Derivatives of 2-thioxoimidazolidin-4-one possess a broad spectrum of pharmacological action. A series of 2-thioxoimidazolidin-4-one derivatives were synthesized and were characterized by Mass, IR and ^{1}H NMR spectroscopy. All these synthesized compounds were tested for *in vitro* antimicrobial against four Gram positive bacteria, four Gram negative bacteria and four fungal strains in polar solvent DMSO. Among the screened compounds, RPI-10 containing hydroxyl group as substituent exhibited most potent antimicrobial activity.

Keywords: 2-thioxoimidazolidin-4-one, DMSO, Gram positive bacteria and Gram negative bacteria.

INTRODUCTION

2-thioxoimidazolidin-4-one derivatives belong to heterocyclic compounds which have a wide range of biological and pharmacological properties such as antibacterial[1], antifungal[2], anti thyroidal[3], antiviral[4], anti HIV[5], anti tuberculosis[6] and anticonvulsant[7] activities.

In the present work, some new2-thioxoimidazolidin-4-one derivatives were synthesized from (E)-1-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)thiosemicarbazide.The characterization of synthesized compounds was done by IR, NMR and mass spectral analysis. Theantimicrobial activity of the synthesized compounds was done against some pathogenic Gram positive and Gram negative bacteria and fungi in Dimethyl sulphoxide (DMSO). DMSO is a versatile non-aqueous dipolar aprotic solvent having a dielectric constant of 46.6 (25 °C) and a dipole moment of 3.9 D (25°C). It is a highly polar but aprotic solvent, which can mix very well with any liquid. It is also called a super solvent and exhibits quite interesting properties.

EXPERIMENTAL SECTION

Synthesis

Synthesis of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde

Synthesis of (E)-2-phenyl-1-(1-phenylethylidene)hydrazine:To a methanolic solution of acetophenone(0.01M) and phenyl hydrazine(0.01M), small amount of concentrated hydrochloric acid was added and solution wasstirred at room temperature for about 10 to 15 minutes. The resulting solid was filtered, washed with cold methanol and crystallized.

Vilsmeier-HaackFormylation:Theabove synthesized product(E)-2-phenyl-1-(1-phenylethylidene)hydrazine was added in a mixture of Vilsmeier-Haack reagent(prepared by drop wise addition of 3ml $POCl_3$ in ice cooled 15ml DMF) and the solution was refluxed for 1hr. The completion of reaction was confirmed by analytical thin layer chromatography (TLC).The reaction mixture was poured into crushed ice and was kept overnight. The resulting product was filtered, washed and dried.

Synthesis of 3-((1,3-diphenyl-1H-pyrazol-4-yl)methyleneamino)-2-thioxoimidazolidin-4-one:

Synthesis of (E)-1-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)thiosemicarbazide:Equimolarmixture of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde and thio-semicarbazide in methanol was refluxed for 1hr in presence of concentrated hydrochloric

acid. The resulting solid product was filtered, washed with cold methanol and dried.

Synthesis of 3-((1,3-diphenyl-1H-pyrazol-4-yl)methyleneamino)-2-thioxoimidazolidin-4-one:Equimolar amount of (E)-1-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)thiosemicarbazide and ethyl chloro acetatewere dissolved in chloroform in presence of sodium acetate. The reaction mixture was refluxed for 8hrs. The solid product was filtered and washed with hexane and water respectively to remove impurities. The crude product was recrystallized.

MATERIAL AND METHODS

The melting point of all the synthesized compounds was determined byDifferential Scanning Calorimeter (Shimadzu-DSC-60). The characterization of all these compounds was done by IR, NMR and mass spectral data. The IR spectra were recorded on Shimadzu FT-IR-8400 instrument using KBr pellet method. ^{1}H NMR and was determined in DMSO solution on a Bruker Ac 400 MHz spectrometer.

The Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique.

Antimicrobial activity

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 *Staphylococcusaureus* ATCC29737 (*SA*), *Corynebacteriumrubrum* ATCC14898 (*CR*), *Listeria monocytogenes* ATCC19112 (*LM*),*Bacillus cereus* ATCC11778 *(BC)*;Gram negative bacteriawere*Pseudomonas aeruginosa*ATCC27853(*PA*),*Escherichia coli* NCIM2931 (*EC*), *Klebsiellapneumoniae* NCIM2719 (*KP*), *Salmonella typhimurium* ATCC23564 (*ST*) and fungal strains were *Candida albicans* ATCC2091 (*CA*), *Cryptococcusneoformans* NCIM3542 (*CN*), *Candida glabrata* NCIM3448 (*CG*) and*Candida epicola* NCIM3367 (*CE*).

The microorganisms studied are clinically important ones causing several infections and food spoilage.

In vitro antimicrobial activity of the 2-thioxoimidazolidin-4-one derivatives were studied against pathogenic microbial strains by the agar well diffusion method[8].

RESULTS AND DISCUSSION

In total 10 compounds were synthesized (RPI-1 to RPI-10). Analysis of their IR, NMR and Massspectral data confirmed their molecular structure. The spectral data of all the compounds are given below:

RPI-1:IR (KBr,cm^{-1}): -C=C(str.):1545,-C=S(str.):1172,-C=O(str.):1643,-N-H(sym.):1597,-C-H(str.):2773.**^{1}H-NMR (δ, ppm):** 2.50(s,3H,CH_3),3.91(s,2H,CH_2),7.53(q,1H,CH),7.55(t,1H,NH),7.57(t,1H,Ar-CH),8.41(s,1H,CH hydrazide),11.89(s,1H,SH). **MS: (m/z)** = 421

RPI-2: IR (KBr,cm^{-1}): -C=C(str.):1545,-C=S(str.):1172,-C=O(str.):1643,-N-H(sym.):1597,-C-H(str.):2785.**^{1}H-NMR (δ, ppm):**2.40(s,3H,-CH_3),3.91(s,2H,CH_2),7.33(d,2H,Ar-CH),7.38(t,1H,NH),7.76(d,2H,Ar-CH),7.96(d,2H,Ar-CH),8.41(s,1H,CH hydrazide),11.89(s,1H,SH).**MS: (m/z)** =375

RPI-3: IR (KBr,cm^{-1}): -C=C(str.):1489,-C=S(str.):1157,-C=O(str.):1643,-N-H(sym.):1647,-C-H(str.):2780.**^{1}H-NMR (δ, ppm):** 2.50(s,3H,CH_3),3.91(s,2H,CH_2),7.53(q,1H,CH),7.55(t,1H,NH), 7.57(t,1H,Ar-CH),8.44(s,1H,CH hydrazide),11.91(s,1H,SH).**MS: (m/z)** = 395

RPI-4:IR (KBr,cm^{-1}): -C=C(str.):1452,-C=S(str.):1215,-C=O(str.):1643,-N-H(sym.):1599,-C-H(str.):2780. **^{1}H-NMR (δ, ppm):**3.94(s,2H,-CH_2),6.94(m,2H,Ar-CH),7.29(t,1H,-NH),7.27(t,1H,Ar-CH),7.31(d,1H, Ar-CH), 7.34(t,2H, Ar-CH), 7.43(d,2H, Ar-CH),8.18(s,1H,CH hydrazide), 8.86(s,1H, Ar-CH), 9.83(s, 1H, -OH), 11.80(s,1H,SH).**MS: (m/z)** =377

RPI-5:IR (KBr,cm^{-1}): -C=C(str.):1504,-C=S(str.):1111,-C=O(str.):1645,-N-H(sym.):1597,-C-H(str.):2752.**^{1}H-NMR (δ, ppm):** 3.75(s,3H,-OCH_3),3.95(s,2H,CH_2),7.18(t,1H,-NH),7.20(d,1H, NH), 7.41(t,1H, Ar-CH),7.42(d,2H, Ar-CH),8.41(s,1H,CH hydrazide),11.89(s,1H,SH).**MS: (m/z)** =391

RPI-6:IR(KBr,cm^{-1}):-C=C(str.):1446,-C=S(str.):1215,-C=O(str.):1651,-N-H(sym.):1600,-C-H(str.):2783.**^{1}H-NMR(δ,ppm):**2.50(s,3H,CH_3),3.91(s,2H,CH_2),7.53(q,1H,CH),7.55(t,1H,NH), 7.57(t,1H,Ar-CH),8.41(s,1H, CH hydrazide),11.89(s,1H,SH).**MS: (m/z)** = 441

RPI-7:IR (KBr,cm^{-1}): -C=C(str.):1504,-C=S(str.):1139,-C=O(str.):1631,-N-H(sym.):1601,-C-H(str.):2785.**^{1}H-NMR (δ, ppm):** 2.50(s,3H,CH_3),3.91(s,2H,CH_2),7.53(q,1H,CH),7.55(t,1H,NH), 7.57(t,1H,Ar-CH),8.41(s,1H,CH hydrazide),11.89(s,1H,SH).**MS: (m/z)** = 379

RPI-8:IR (KBr,cm^{-1}): -C=C(str.):1504,-C=S(str.):1101,-C=O(str.):1653,-N-H(sym.):1597,-

C-H(str.):2783.**^{1}H-NMR (δ, ppm):** 2.50(s,3H,CH_3),3.91(s,2H,CH_2),7.53(q,1H,CH),7.55(t,1H,NH), 7.57(t,1H,Ar-CH),8.41(s,1H,CH hydrazide),11.89(s,1H,SH).**MS: (m/z)** = 406

RPI-9:IR (KBr,cm^{-1}): -C=C(str.):1504,-C=S(str.):1111,-C=O(str.):1645,-N-H(sym.):1597,-C-H(str.):2752.**^{1}H-NMR (δ, ppm):** 2.50(s,3H,CH_3),3.91(s,2H,CH_2),7.53(q,1H,CH),7.55(t,1H,NH), 7.57(t,1H,Ar-CH),8.41(s,1H,CH hydrazide),11.89(s,1H,SH).**MS: (m/z)** = 391

RPI-10:IR (KBr,cm^{-1}): -C=C(str.):1502,-C=S(str.):1174,-C=O(str.):1647,-N-H(sym.):1525,-C-H(str.):2731.**^{1}H-NMR (δ, ppm):** 2.50(s,3H,CH_3),3.91(s,2H,CH_2),7.53(q,1H,CH),7.55(t,1H,NH), 7.57(t,1H,Ar-CH),8.41(s,1H,CH hydrazide),11.89(s,1H,SH).**MS: (m/z)** = 377

The antimicrobial activity was measured by the average diameter of the inhibition zones, expressed in mm. Fig. 5 shows antibacterial activity of synthesized 2-thioxoimidazolidin-4-one derivatives against Gram positive and Gram negative bacteria. It is evident from Fig. 5A that none of the synthesized compound showed activity against *C. rurbum*and *L. monocytogenes*but showed varied activity against *B.cereus* and *S.aureus*. *B.cereus* was inhibited by compound RPI-3, RPI-4, RPI-5, RPI-7 and RPI-10 while *S.aureus* was inhibited by RPI-1, RPI-2 and RPI-5. This differential inhibitory activity is because of different substitution. In all the studied compounds, central moiety is 2-thioxoimidazolidin-4-one but substituent groups are different (Table 1) and each group affected differently on different bacteria.RPI-6, RPI-8 and RPI-9 did not show activity against any of these bacteria. This suggests that -Br, -NO_2, -OCH_3groups are not effective against these bacteria.

However, all the ten compounds showed better antibacterial activity towards Gram negative bacteria than Gram positive bacteria. Fig. 5B shows that *P. aeruginosa* was the most resistant Gram negative bacteria.It was not inhibited by any of the synthesized compound. Similar results were reported by Bhalu*et al.* for dihydropyrano[c]chromenes[9]. This is followed by *S. typhimurium* which was inhibited by only compoundsRPI-8, RPI-9 and RPI-10. *K. pneumonia*was the most susceptible Gram negative bacteria. It was inhibited by all of the synthesized compounds except RPI- 8 and RPI-9.*E. coil* was inhibited by RPI-2, RPI-3, RPI-6, RPI-8 and RPI-10.Similar results were reported by Cheng *et al*,for thiazole derivatives[10]and Nasser *et al*.for 2-Thioxo-imidazolidin-4-one derivatives[11].

This once again confirms our earlier conclusion that antibacterial activity depends on the molecular structure of the compounds and solvent and bacterial strain[12-14].

Further, antifungal activity of all the synthesized compounds were studied against four fungal strains but none of the compound exhibited any activity. This may be due to the fact thatfungal cells are more complex organisms as compared to bacterial cell.

CONCLUSION

The synthesized compounds showed better activity towards Gram negative bacteria than Gram positive bacteria. RPI-10 containing hydroxyl group appears to be the most promising compound.However, the studied compounds are not effective against studied fungal strains.

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Table 1: Physical properties of synthesized compounds

Compound Code	Substitution R	M.F.	M.W.	Yield (%)
RPI-1	-3,4-di-OCH_3	$C_{21}H_{19}N_5O_3S$	421	79
RPI-2	-4-CH_3	$C_{20}H_{17}N_5OS$	375	84
RPI-3	-4-Cl	$C_{19}H_{14}ClN_5OS$	395	80
RPI-4	-2-OH	$C_{19}H_{15}N_5O_2S$	377	85
RPI-5	-2-OCH_3	$C_{20}H_{17}N_5O_2S$	391	74
RPI-6	-4-Br	$C_{19}H_{14}BrN_5OS$	441	76
RPI-7	-4-F	$C_{19}H_{14}FN_5OS$	379	82
RPI-8	-3-NO_2	$C_{19}H_{14}N_6O_3S$	406	74
RPI-9	-4-OCH_3	$C_{20}H_{17}N_5O_2S$	391	82
RPI-10	-4-OH	$C_{19}H_{15}N_5O_2S$	377	80

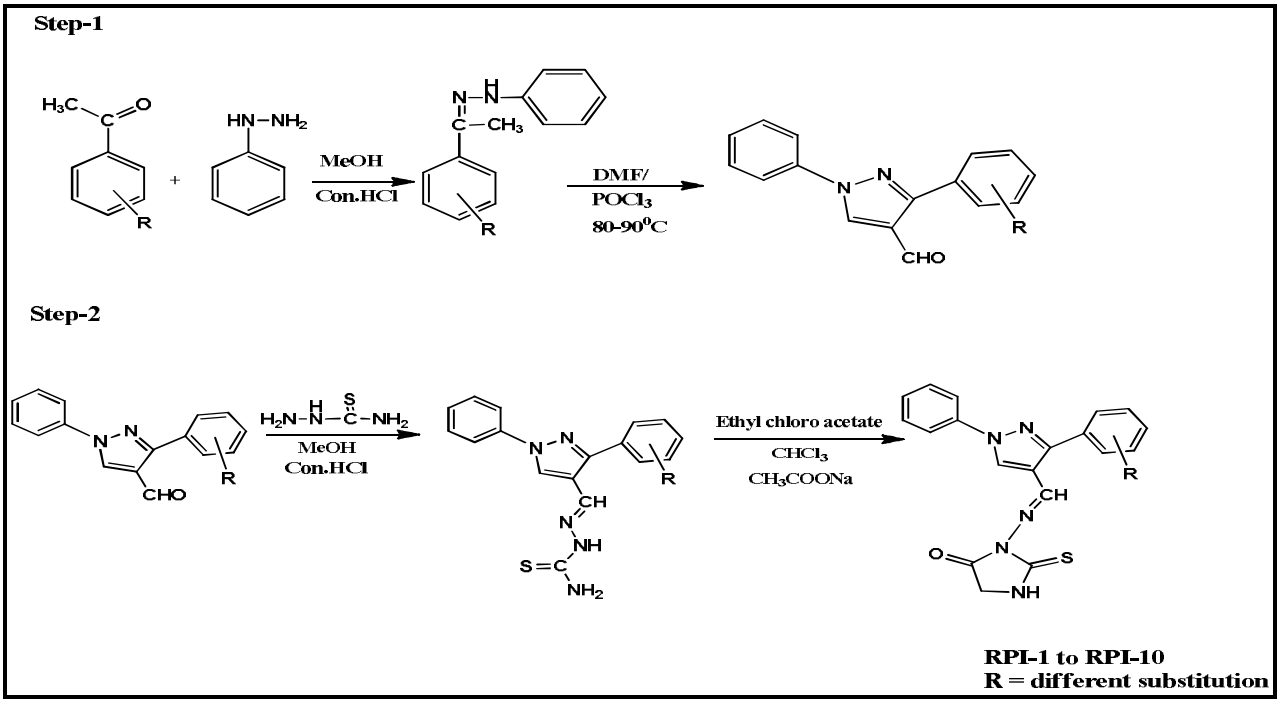

Fig. 1: Synthesis scheme of 2-thioxoimidazolidin-4-one derivatives

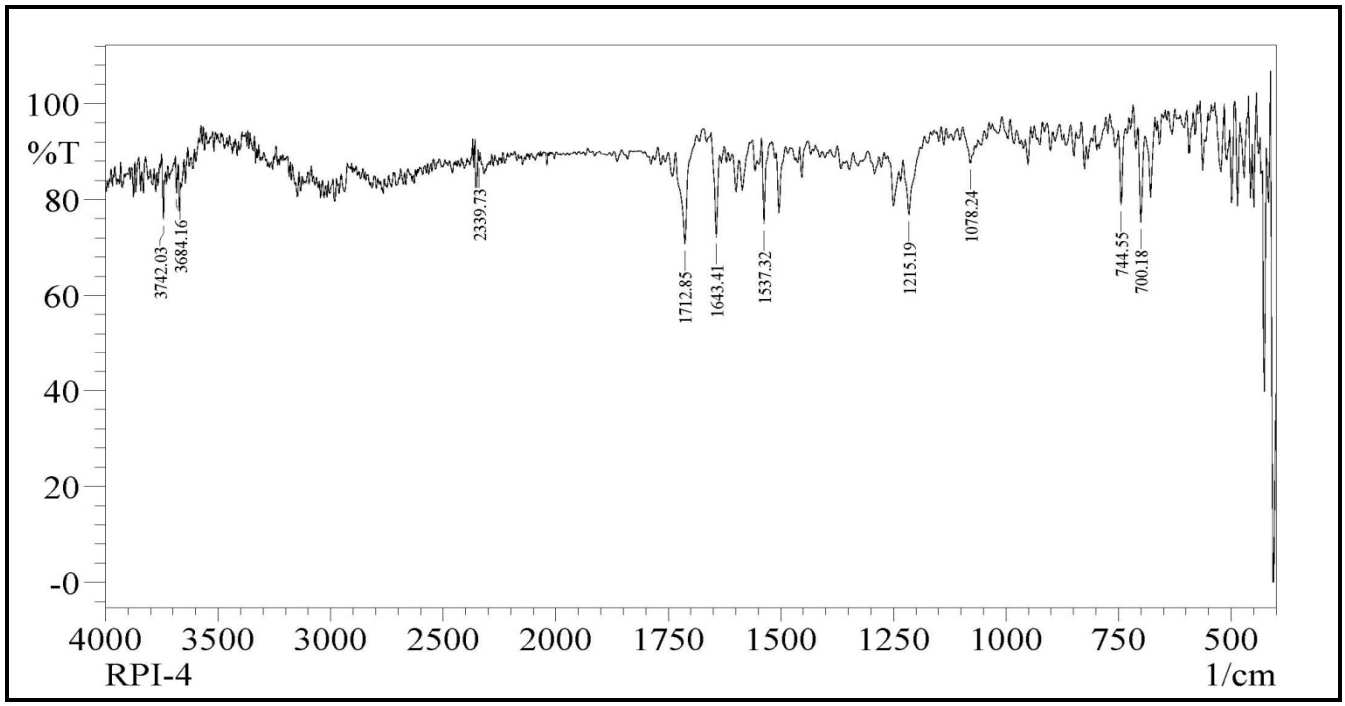

Fig. 2: IR spectra of compound RPI-4

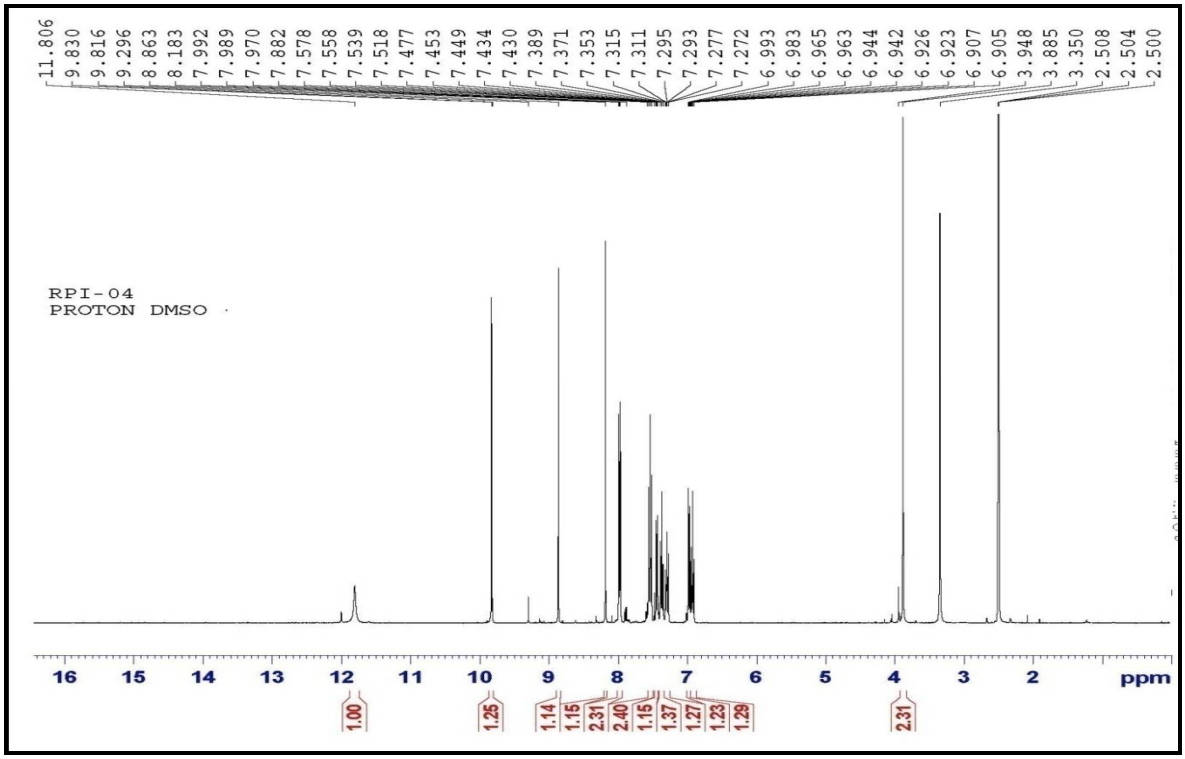

Fig. 3: 1H NMR spectrum of compound RPI-4

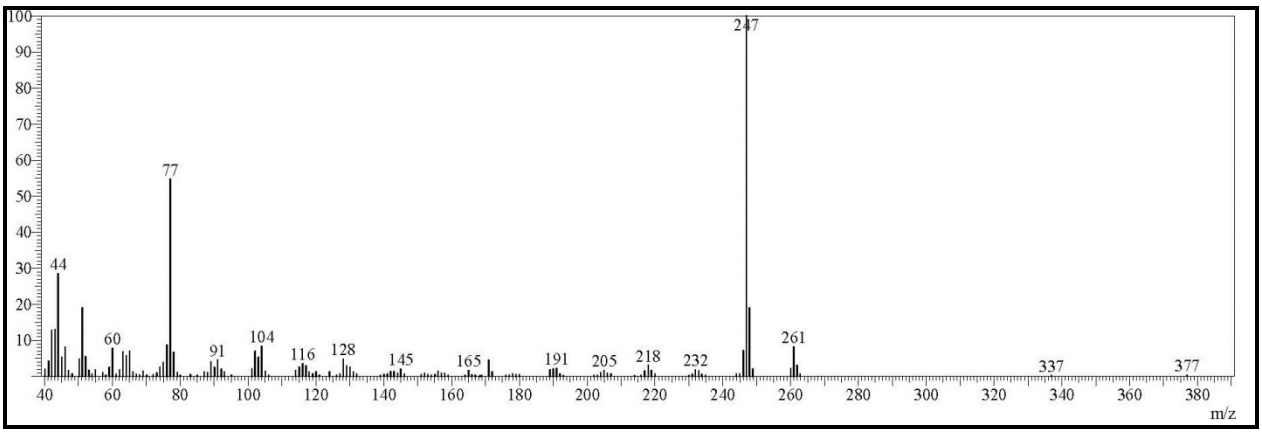

Fig. 4: Mass spectrum of compound RPI-4

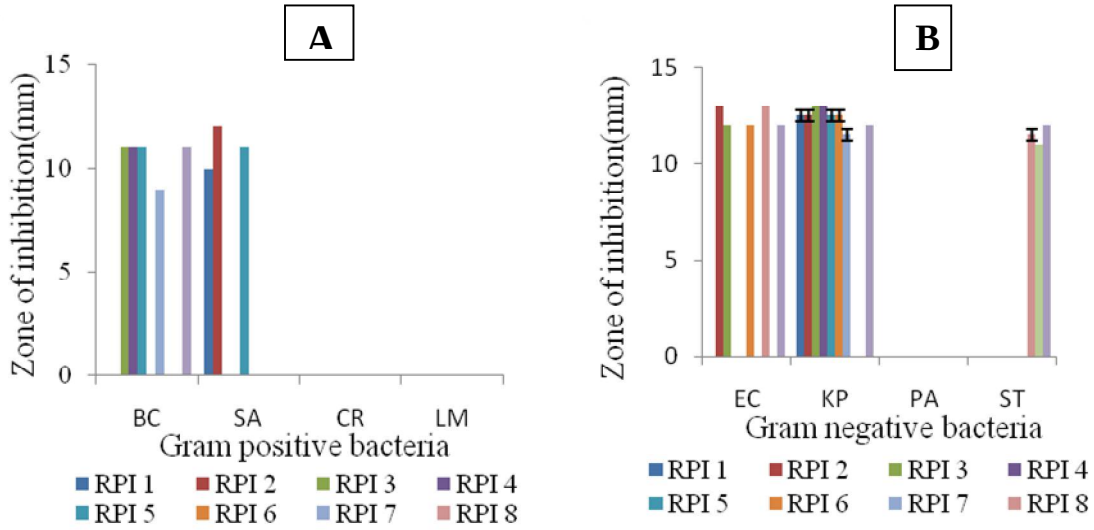

Fig. 5: Antibacterial activity of 2-thioxoimidazolidin-4-one derivatives in DMSO against Gram positive and negative bacteria

REFERENCES

1. Martan J, Enisz J, Hosztafi S and Timer T. Preparation and fungicidal activity of 5-substituted hydantoins and their 2-thio analogs. J Agri food Chem. 1993;41:148-152.
2. Cremlyn RJ, Swinbourne FJ, Shode OO and Lynch J. Cyclisation of benzyls.J Heterocyclic Chem. 1987;24:117-121.
3. MarX JV, Richert DA and Westerfeld WW. Peripheral inhibition of thyroxine by thiohydantoins derived from amino acids. J Med Chem. 1970;13:1179-1181.
4. El-Barbary AA, Khodair AI, Pedersan EB and Nielsen C. S-Glucosylatedhydantoins as new antiviral agents.J Med Chem. 1994;37:73-77.
5. Cherouvrier JR, Carreaux F and Bazureau JP. Reactivity of 2-thiohydantoins towards various electrophilic reagents: Applications to the synthesis of new 2-ylidene-3, 5-dihydro-4H-imidazol-4-ones. Molecules.2004;9:867-875.
6. Arches S, Unser MJ and Froelich E. Some 5-(Oxoalkyl)-2-thiohydantoins and their derivatives. J Am Chem Soc. 1956;78:6182-6185.

7. Cortes S, LIas ZK, Watson D and Kohn H. Effect of structural modification of the hydantoin ring on anticonvulsant activity.J Med Chem. 1985;28:601-606.
8. Baluja S, Chanda S, Chabhadiya R, Kachhadia, Nair R and Solaniki A.A facile synthesis and the antimicrobial activity of some 4-aryltriazoles. J Serb Chem Soc. 2007;72:539-544.
9. Vaghasia Y, Nair R, Soni M, Baluja S and Chanda S. Synthesis, structural determination and antibacterial activity of compounds derived from vanillin and 4-aminoantipyrine.J Serb Chem. Soc. 2004;69:991-998.
10. Cheng K, Xue J and Zhu H. Design, Synthesis and antibacterial activity studies of thiazole derivatives as potent ecKAS III inhibitors. Bioorg Med Chem Letters. 2013;23:4235–4238.
11. Nasser JA, Idhayadhulla A, Kumar SR andSelvin J. Synthesis of some 2-thioxo-imidazolidin-4-one derivatives and its antimicrobial activity. E-J Chem. 2010;7:1320-1325.
12. Bhalu A, Moteriya P, Chanda S and Baluja S. Synthesis, characterization and antimicrobial activity of some new dihydropyrano[c]chromenes.IntLetters ChemPhyAstro. 2014;12:1-6.
13. Parekh J, Inamdhar P, Nair R, Baluja S and Chanda S. Synthesis and antibacterial activity of some Schiff bases derived from 4-aminobenzoic acid. J Serb Chem. Soc.2005;70:1155-1161.
14. Nair R, Shah A, Baluja S, and Chanda S. Synthesis and antibacterial activity of some Schiff base complexes. J Serb Chem Soc. 2006;71:733-744.