



CHEMICAL SYNTHESIS, STRUCTURE DETERMINATION AND EVALUATION OF BIOLOGICAL ACTIVITY OF IMIDAZOLIDINONE DERIVATIVES

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Abstract: A series of novel imidazolidinone derivatives have been obtained starting from 2,4-dinitro phenyl hydrazine and aldehyde. These were converted to corresponding Schiff bases using THF. The resulting Schiff base was treated with α -amino acids to obtain corresponding imidazolidinone derivatives. The newly synthesized compounds showed high antimicrobial activities against some bacterial and fungal strains and anticancer activity.

Keywords: antimicrobial activity, anticancer, tetrahydro furan, *Staphylococcus aureus*, Kirby Bauer Disk Diffusion.

I. INTRODUCTION

INTRODUCTION

Heterocyclic chemistry is a very significant area of organic chemistry accounting for almost one-third of modern publications. In fact two thirds of organic compounds are heterocyclic compounds. A cyclic compound containing all carbon atoms in ring is referred to as a carbocyclic compound. If, at least one atom other than carbon forms a part of the ring system then it is designated as a heterocyclic compound¹. Besides the boundless distribution of heterocycles in natural products, they are also the major components of biological molecules such as DNA and RNA. Heterocycles are present in a wide variety of drugs, most vitamins, many natural products, biomolecules, and biologically active compounds, including antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal agents²⁻⁶. Also, they have been normally found as a key structural unit in synthetic pharmaceuticals. Moreover, they act as organic conductors, semiconductors, molecular wires, photovoltaic cells, and organic light-emitting diodes (OLEDs), light harvesting systems, optical data carriers, chemically controllable switches, and liquid crystalline compounds.

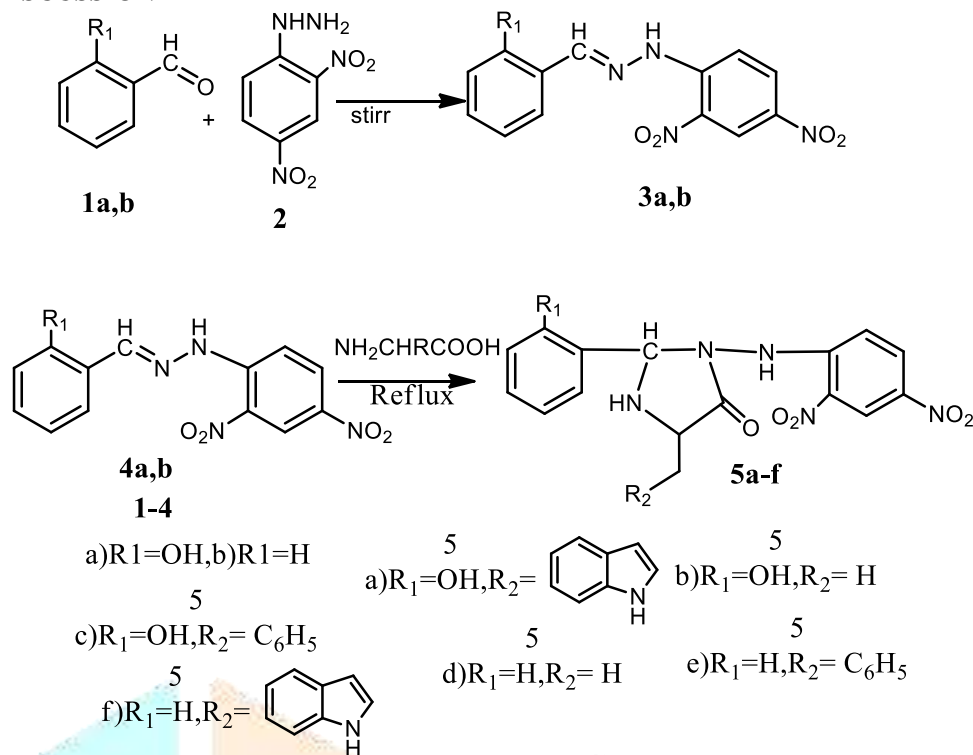
Five membered nitrogen containing heterocyclic compounds such as imidazolidinones¹¹⁻¹³ and imidazolidines¹⁴ possess potent antiviral activities. The imidazolidinone moiety has received considerable attention by medicinal chemists, as many compounds of this scaffold class possess a variety of biological activities.

In addition, organic chemists appreciate them for their use as chiral catalysts. Some of the imidazolidinones have either antiviral,⁷⁻¹⁰ anticancer,¹¹ or anti-inflammatory activities,¹² or act as NK₁ receptor antagonists,¹³ *Leishmania* spp. inhibitors,¹⁴ or β_3 adrenergic receptor agonists.¹⁵

Imidazolidine, a versatile moiety, could be a possible pharmacophore in designing safer anti-inflammatory medicinal agents¹⁶⁻¹⁸. The importance of imidazolidinone moiety for cytotoxicity of 4-phenyl 1-arylsulfonyl imidazolidinones was also reported.

In view of these observations in this work, we thought that it would be interesting to synthesise the newer substituted imidazolidinone derivatives from easily available starting material, like 2,4-dinitro phenyl hydrazine, benzaldehyde and salicylaldehyde compounds with interesting applications in the field of pharmacology.

II. RESULTS AND DISCUSSION



2.1. Synthesis of 2-((2-(2,4-dinitrophenyl)hydrazono)methyl)phenol 4(a)

2,4-dinitro phenyl hydrazine 1g (5mmol) and salicylaldehyde 0.6161g (5mmol) were stirred for 1 hour. The reaction was routinely followed by TLC. After the completion of reaction the excess solvent was removed by slow evaporation method and recrystallised from alcohol. Yield and melting point were noted. Yield: 95%, melting point: 265°C. IR (cm^{-1}) **fig (1)** **3(a)** spectrum of the compound showed absorption peak at 3270(NH), 3388(OH), 1514(NO_2), 1619(C=N), 1334(NO_2).

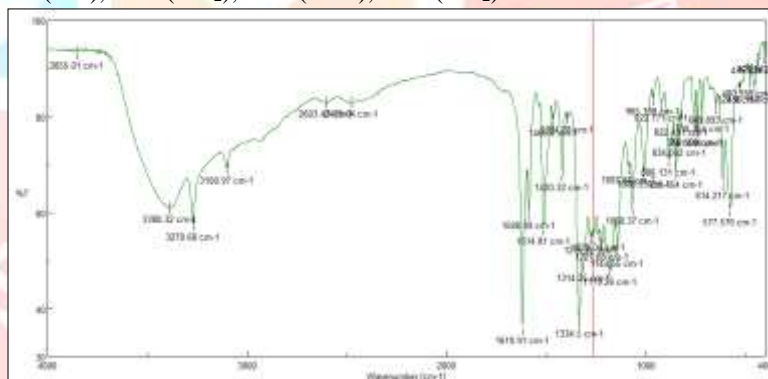


Figure 1 IR spectrum of 2-((2-(2,4-dinitrophenyl)hydrazono)methyl)phenol 4(a)

By following the above procedure **1-benzylidene-2-(2,4-dinitrophenyl)hydrazine** was also obtained. Here 2,4-dinitro phenyl hydrazine 1g (5mmol) and benzaldehyde 0.5151g (5mmol) were stirred for 1 hour. Yield: 83%, melting point: 270°C. IR (cm^{-1}) **fig (2)** spectrum of the compound showed absorption peak at 3278(NH), 1504(NO_2), 1612(C=N), 1319(NO_2).

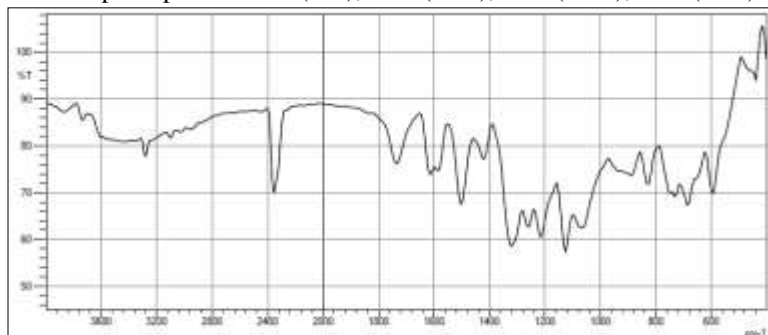


Figure 2. IR spectrum of 1-benzylidene-2-(2,4-dinitrophenyl)hydrazine 4b

2.2. Synthesis of imidazolidinones

The obtained Schiff base was refluxed with the α -amino acids such as alanine, phenyl alanine, tryptophan in THF (10mL) to get corresponding imidazolidinones¹⁹. The reaction progress was monitored by using TLC. The excess solvent was evaporated and the product obtained was recrystallised.

Synthesis of 5-((1H-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl) imidazolidin-4-one. 5(a) 2-((2-(2,4-dinitrophenyl)hydrazono)methyl)phenol: 0.6g(1.98mmol), Tryptophan: 0.408g(1.98mmol), Refluxing time: 14 hour, Yield: 85% , Melting point: >250°C

IR (cm^{-1}) **fig (3)** spectrum of the compound 5(a) showed absorption peak at 3271(NH), 2924(NH), 2854(NH), 1735(C=O), 3101(OH) 1319, 1501(NO_2).

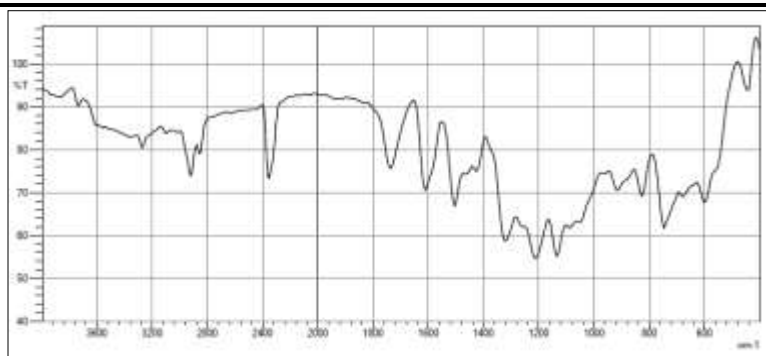


Figure 3. IR spectrum of 5-((1*H*-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl)imidazolidin-4-one 5a

¹H-NMR (DMSO)(ppm) spectrum fig (4) of the compound 5-((1*H*-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl)imidazolidin-4-one (5a) showed absorption at δ 8.3, δ 8.8, δ 8.9 (bs, 1H, NH), δ 6.4-7.3 (m, 5H, Ar-H), δ 11 (OH).

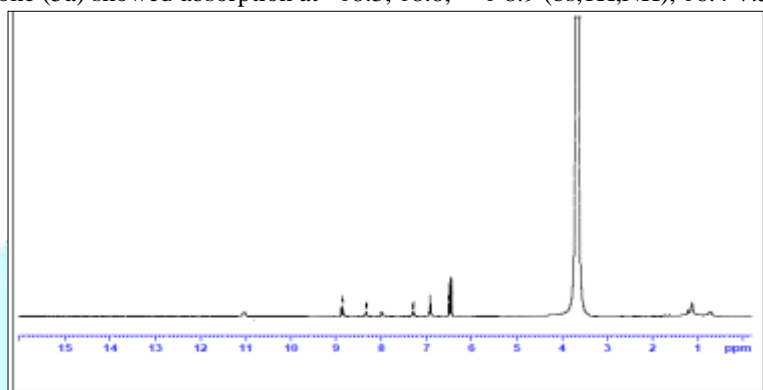


Figure 4. ¹H-NMR spectrum of 5-((1*H*-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl)imidazolidin-4-one 4a

¹³C-NMR (CDCl₃) (ppm) spectrum of the compound 5(a) fig (5) showed absorption at δ 163 (C=O), δ 79 (Aliphatic C), δ 109-157 (Ar-C).

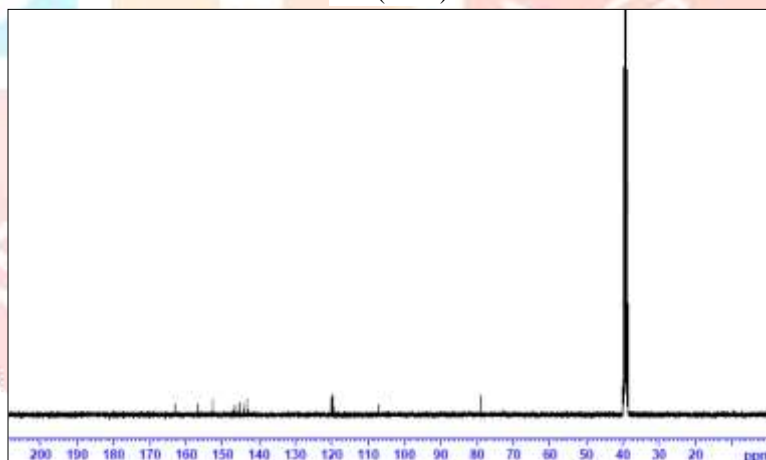


Figure 5. ¹³C-NMR spectrum of 5-((1*H*-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl)imidazolidin-4-one 5a

2.3 Antibacterial susceptibility of (5-((1*H*-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl) imidazolidin-4-one 5(a))

Test organisms	Concentration of the sample in mg					Ciprofloxacin
	10	20	30	40	MIC	5 µg
<i>Escherichia coli</i>	12 mm	12 mm	14 mm	18 mm	10	15mm
<i>Staphylococcus aureus</i>	10mm	10mm	12mm	16 mm	10	20mm
<i>S. typhi</i>	12mm	12mm	14 mm	14mm	10	25mm
<i>K. pneumonia</i>	12mm	12mm	12mm	14 mm	10	20mm

Table1 Antibacterial activity of (5-((1*H*-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl)imidazolidin-4-one5(a))



EC

SA

ST

KP

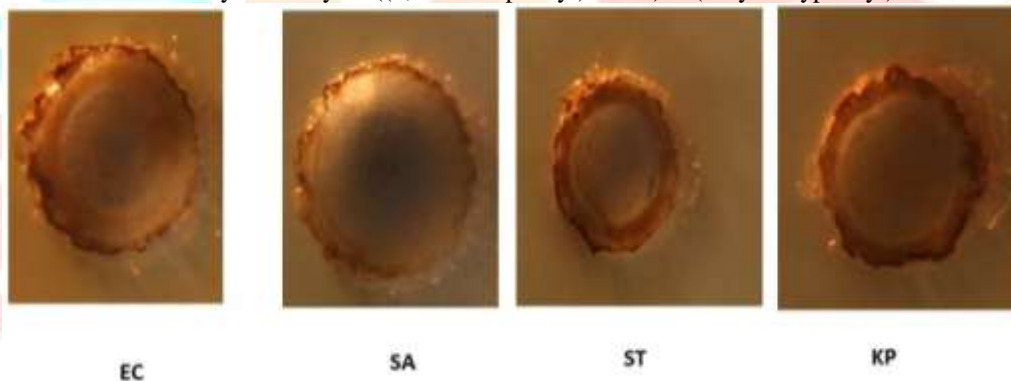
Figure (6) Antibacterial activity of 5-((1H-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl)imidazolidin-4-one 5(a)

From the results it is evidenced that 5-((1H-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl)imidazolidin-4-one 14(a) showed remarkable activity towards all the tested organisms and among these *Escherichia coli* exhibited more value for zone of inhibition infers that the compound is more active against this organism.

2.4. Antibacterial susceptibility of 5-benzyl-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl) imidazolidin-4-one 5c:-

Test organisms	Concentration of the sample in mg					Ciprofloxacin
	10	20	30	40	<u>MIC</u>	5 µg
<i>Escherichia coli</i>	10 mm	10 mm	12 mm	14mm	<u>10</u>	15mm
<i>Staphylococcus aureus</i>	10mm	12mm	12mm	15mm	<u>10</u>	20mm
<i>S. typhi</i>	12mm	14mm	14 mm	16mm	<u>10</u>	25mm
<i>K. pneumonia</i>	12mm	12mm	16mm	18mm	<u>10</u>	20mm

Table 2 Antibacterial activity of-benzyl-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl) imidazolidin-4-one 5c



EC

SA

ST

KP

Figure (7) Antibacterial activity of-benzyl-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl) imidazolidin-4-one 5c

From the Table 2 and figure 7 it is found that-benzyl-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl) imidazolidin-4-one 14I is more active towards *K. pneumonia*.

2.5. Antibacterial susceptibility of 5-((1H-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-phenyl imidazolidin-4-one 5 f

Test organisms	Concentration of the sample in mg					Ciprofloxacin
	10	20	30	40	<u>MIC</u>	5 µg
<i>Escherichia coli</i>	10 mm	10 mm	12 mm	19 mm	<u>10</u>	15mm
<i>Staphylococcus aureus</i>	10mm	10mm	12mm	16 mm	<u>30</u>	20mm
<i>S. typhi</i>	12mm	12mm	14 mm	14mm	<u>10</u>	25mm
<i>K. pneumonia</i>	10mm	12mm	16mm	14 mm	<u>10</u>	20mm

Table 3. Antibacterial activity of 5-((1H-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-phenyl imidazolidin-4-one 5 f

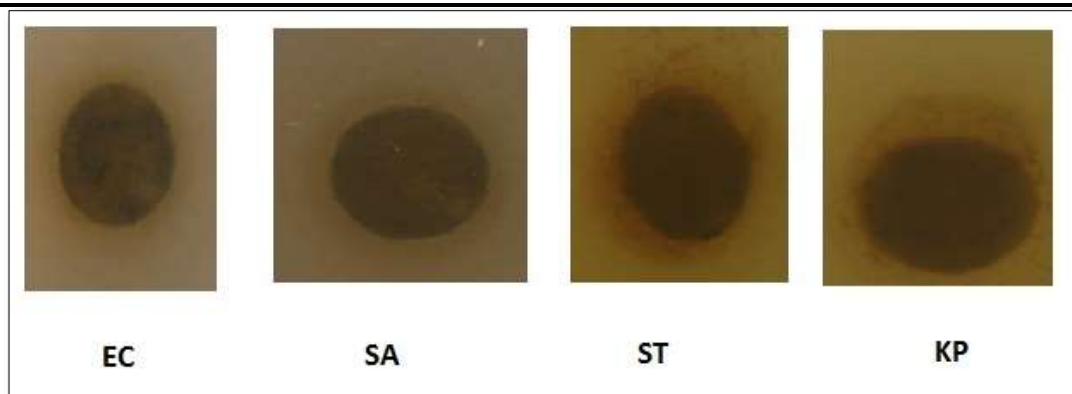


Figure (8) Antibacterial activity of 5-((1H-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-phenyl imidazolidin-4-one 5f

5-((1H-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-phenyl imidazolidin-4-one 5f at 40mg/mL exhibited the highest inhibition against *E.coli* acted as a good inhibitor at 40mg/mL. When comparing these results with the standard drug, the tested compounds were equally or more active than the standard drug and hence the tested compounds might be used as an antibacterial drug in mere future. The compounds showing promising antibacterial activity were evaluated for minimum inhibitory concentration and minimum Inhibitory concentration for all the organism are marked as bold.

2.6. Anticancer studies

Most of the anti-tumor drugs currently used in chemotherapy are toxic to normal cells and cause toxicity for immune cells, so it is important to minimize doses to the least amount possible as well as try to minimize the side effects of these drugs. Cervical cancer one of the most frequently detected cancers in women around the globe and ranks third among all the cancers diagnosed in women. Approximately 0.5 million patients are diagnosed for this lethal type of cancer that is almost 9% of all the new cancer cases diagnosed annually. Although, the currently used treatment options such as chemotherapy, radical hysterectomy and radiotherapy have shown promising outcomes, approximately 0.3 millions deaths still occur due to cervical cancer annually. For the early stage cervical cancers mainly involves office-based ablative therapies. Cold-knife conization or electroconization is performed in most of the patients to exclude invasive disease. Furthermore, surgery followed by chemotherapy is recommended for patients with advanced stage cervical cancer. However the chemotherapeutic agents exhibit adverse effect that compromise the health of the patients and as such Therefore, to there is an urgent need to identify novel molecules that could prove efficient in the treatment of cervical cancer with minimal side effects (3).

The newly synthesized (**5-((1H-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl)imidazolidin-4-one 5a**) were evaluated for their in vitro anticancer activity against MTT assay.

Sample Concentration (µg/ml)	MTT assay 14a % viability	% Inhibition
Control	97.58%	2.42%
50	84.26%	15.74%
100	63.54%	36.46%
150	55.55%	44.45%
200	45.23%	54.77%
250	40.25%	59.75%

Table 4 Anticancer activity of (5-((1h-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl)imidazolidin-4-one 5a
LC 50 =76µg/mL

Our results from Table 4 showed that synthesized product exhibited a moderate to strong growth inhibition activity on the tested cell lines between 50 and 250 µg/mL concentrations in comparison to the reference anticancer drugs. The relationship between surviving fraction and drug concentration was plotted to obtain the survival curve of the two cell lines. The response parameter calculated was the LC50 value, which corresponds to the concentration required for 50% inhibition of cell viability.



Fig 9 Anticancer activity of (5-((1h-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl)imidazolidin-4-one 5a

III. MATERILAS AND METHOD

All the reagents and solvents were received from commercial supplier. Reactions were done in dried glass ware. Melting points were taken in open capillaries by CINTEK melting point apparatus and are uncorrected. The purity of the newly synthesised compounds was checked by thin layer chromatography on silica gel-G coated plates using ethyl acetate and petroleum ether as solvents. Infra red spectra were determined in ATR-IR Affinity instrument and the absorption frequencies quoted in reciprocal centimeters. ^1H NMR and ^{13}C NMR spectra were recorded in AMX-400(400MHz) spectrometer recorded in CDCl_3 and $\text{DMSO}-d_6$ as solvent with TMS as internal standard. The chemical shift were expressed in parts per million (ppm). Tetra methyl silane was used as internal standard.

3.1.Synthesis of 1-benzylidene-2-(2,4-dinitrophenyl)hydrazine (Schiff base) 4b: 2,4dinitro phenyl hydrazine:1g(5mmol), Benzaldehyde: 0.5151g(5mmol), Stirring time: 1 hour ,Yield: 83%, Melting point:270°C. IR (cm^{-1}) **fig 10** spectrum of the compound **4b** showed absorption peak at 3263(NH), 1508(NO_2), 1600 ($\text{C}=\text{N}$), 1319(NO_2).

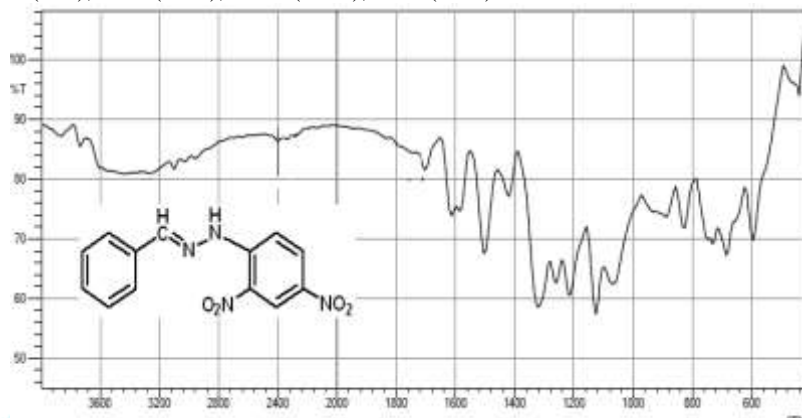


Fig 10 IR spectrum of 1-benzylidene-2-(2,4-dinitrophenyl)hydrazine 4b

3.2. Synthesis of 3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl)-5-methylimidazolidin-4-one 5b: 2-((2-(2,4-dinitrophenyl)hydrazono)methyl)phenol: 0.6g(1.98mmol), Alanine: 0.1768g(1.98mmol), Refluxing time: 20 hour, Yield: 83%, Melting point: 258°C. IR (cm^{-1}) **fig (11)** spectrum of the compound showed absorption peak at 2924(NH), 1504(NO_2), 1735($\text{C}=\text{O}$), 1604($\text{C}=\text{N}$), 1327(NO_2), 3263(OH).

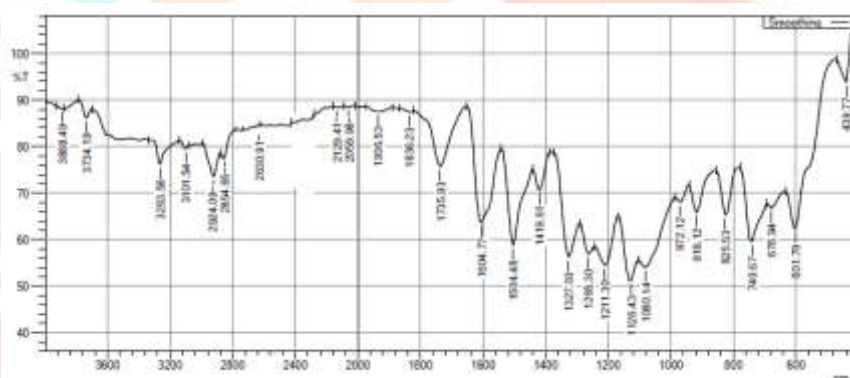


Fig 11 IR spectrum of 3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl)-5-methylimidazolidin-4-one 5b

3.3. Synthesis of 5-benzyl-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl) imidazolidin-4-one5c:

2-((2-(2,4-dinitrophenyl)hydrazono)methyl)phenol: 0.6g(1.98mmol), Phenylalanine: 0.330g(1.98mmol), Refluxing time: 28 hour, Yield: 84%, Melting poin: 240°C. IR (cm^{-1}) **fig (12)** spectrum of the compound showed absorption peak at 3101(NH), 1504(NO_2), 1735($\text{C}=\text{O}$), 1612($\text{C}=\text{N}$), 1327(NO_2), 3263(OH).

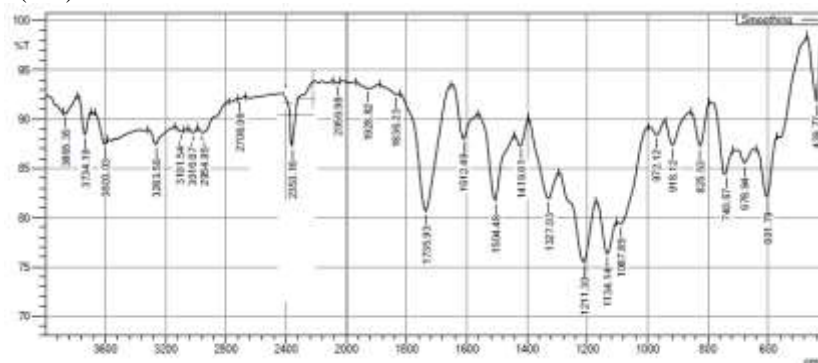


Fig 12 IR spectrum of 5-benzyl-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl) imidazolidin-4-one5c

3.4. ynthesis of 3-((2,4-dinitrophenyl)amino)-5-methyl-2-phenylimidazolidin-4-one 5d: 1-benzylidene-2-(2,4-dinitrophenyl)hydrazine: 1g(3.4965mmol), Alanine: 0.3112g(3.4965mmol), Refluxing time: 19 hour, Yield: 80%, Melting point: 250°C. IR (cm^{-1}) **fig (13)** spectrum of the compound showed absorption peak at 2950(NH), 1500(NO_2), 1750($\text{C}=\text{O}$),1600($\text{C}=\text{N}$), 1227(NO_2).

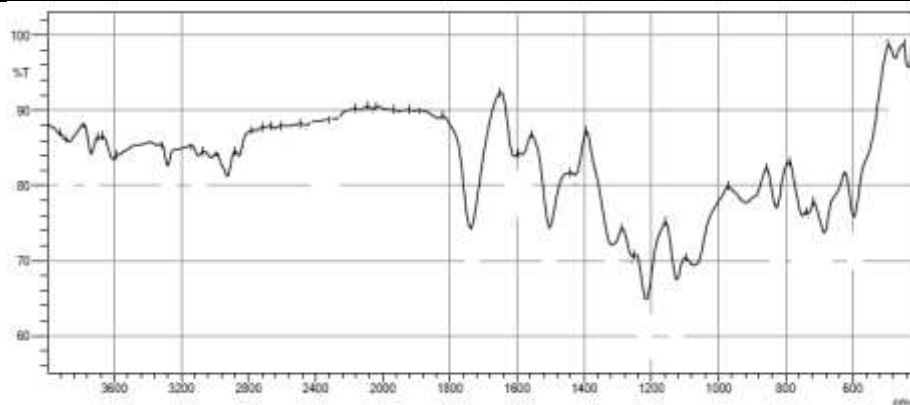


Fig 13 IR spectrum of 3-((2,4-dinitrophenyl)amino)-5-methyl-2-phenylimidazolidin-4-one 5d

3.5. Synthesis of 5-benzyl-3-((2,4-dinitrophenyl)amino)-2-phenylimidazolidin-4-one 5e: 1-benzylidene-2-(2,4-dinitrophenyl)hydrazine: 1g(5mmol), Phenylalanine: 0.3168g(2.0979mmol), Refluxing time: 12 hour, Yield:82%, Melting point: 252°C. **IR (cm⁻¹)** **fig (14)** spectrum of the compound showed absorption peak at 3050(NH), 1210(NO₂), 1640 (C=O),1580(C=N), 1327(NO₂).

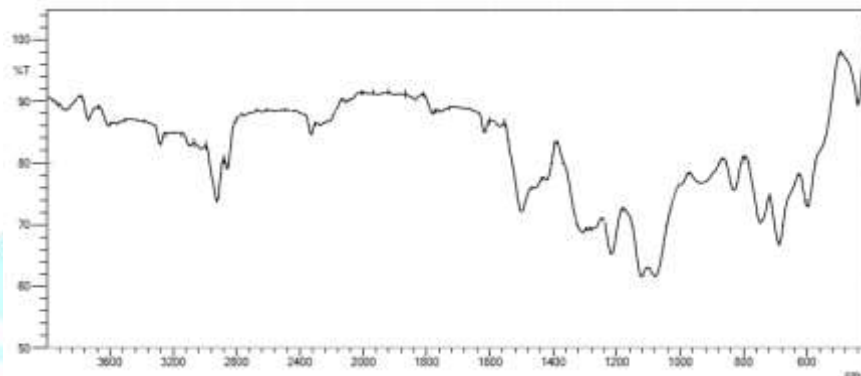


Fig 14 IR spectrum of 5-benzyl-3-((2,4-dinitrophenyl)amino)-2-phenylimidazolidin-4-one 5e

3.6. Synthesis of 5-((1H-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-phenyl imidazolidin-4-one 5f: 1-benzylidene-2-(2,4-dinitrophenyl)hydrazine: 0.6g(2.0979mmol), Tryptophan: 0.4080g(2.0979mmol), Refluxing time: 13 hour, Yield: 82%, Melting point: 258°C. **IR (cm⁻¹)** **fig (15)** spectrum of the compound showed absorption peak at 2944(NH), 1340(NO₂), 1745(C=O),1510(C=N), 1327(NO₂).

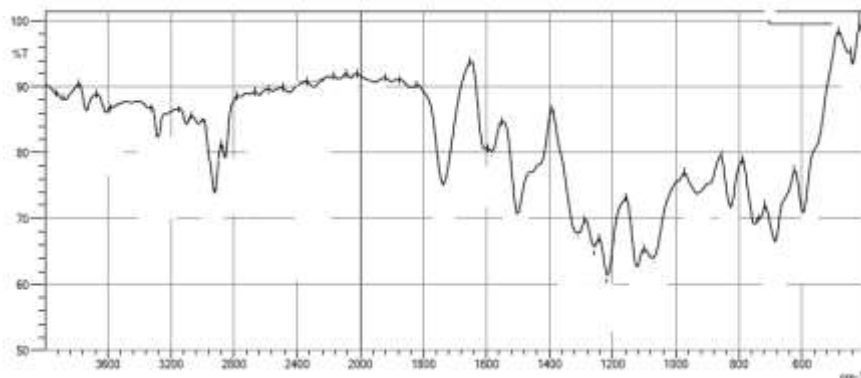


Fig 15 IR spectrum of 5-((1H-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-phenyl imidazolidin-4-one 5f

3.7. Pharmacological activities

Antimicrobial is a general term for natural or synthetic compounds which at certain concentrations inhibit the growth of or kill microorganisms completely. Due to the rapid development of microorganism's resistance to antimicrobial agents, it is necessary to discover compounds both natural and synthetic as new antimicrobial agents to help in the battle against pathogenic microorganisms. Antibacterial activity of **5-((1H-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl)imidazolidin-4-one 5(a)**, **5-benzyl-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl) imidazolidin-4-one 5(c)** and **5-((1H-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-phenyl imidazolidin-4-one 5(f)** were studied against *Escherichia coli*, *Staphylococcus aureus*, *S. typhi* and *K. pneumonia* by using **Kirby Bauer Disk Diffusion Method**. In this method the dried samples were made in to a solution with **DMSO**. In this method the liquid was made up to different concentration as considering the liquid as stock. Overnight bacterial suspension (100μl) adjusted to contain 1x10⁶ CFU/mL of bacteria, spread by a sterile glass rod on Nutrient Agar (NA) medium. The inoculated plates were incubated at 27±20°C for 24 h, and then the inhibition zones were measured in diameter (mm). Antibiotic discs containing 1μg of Ciproflaxin CF1 was used as positive controls and DMSO used as negative control. The **MIC** was calculated using the above said 4 concentrations of the samples.

3.8. Anticancer Studies. MTT assay (HeLa)

For adherent cells, remove the medium and replace it with 100 μL of fresh culture medium. For non-adherent cells, centrifuge the microplate, pellet the cells, carefully remove as much medium as possible and replace it with 100 μL of fresh medium. Add 10 μL of the 12 mm MTT stock solution to each well. Include a negative control of 10 μL of the MTT stock solution added to 100 μL of medium alone. Incubate at 37°C for 4 hours. At high cell densities (>100,000 cells per well) the incubation time can be shortened to 2 hours. Add 100 μL of the SDS-HCl solution to each well and mix thoroughly using the pipette. Incubate the micro plate at 37°C for 4– hours in a

humidified chamber. Longer incubations will decrease the sensitivity of the assay. Mix each sample again using a pipette and read absorbance at 570 nm.

$$\% \text{ Viability} = \text{Corrected OD of sample} / \text{Control OD} \times 100$$

$$\% \text{ Inhibition} = 100 - \% \text{ viability}$$

IV. CONCLUSION

A series of novel imidazolidinone derivatives were prepared from 2,4-dinitro phenyl hydrazine and aldehyde. In the first step 2,4-dinitro phenyl hydrazine and aldehyde were converted to corresponding Schiff bases in the presence of THF. The resulting Schiff base was treated with α -amino acids to obtain corresponding imidazolidinone derivatives. The newly synthesized compound screened for their antimicrobial activity. Further one of the synthesized compounds viz **(5-((1H-indol-3-yl)methyl)-3-((2,4-dinitrophenyl)amino)-2-(2-hydroxyphenyl)imidazolidin-4-one 5a** was analysed for its anticancer behaviour. All the tested drugs showed high antimicrobial activities against some bacterial and fungal strains. Our results of anticancer studies showed that synthesized product exhibited a moderate to strong growth inhibition activity on the tested cell lines between 50 and 250 $\mu\text{g/mL}$ concentrations in comparison to the reference anticancer drugs.

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