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"Design, Synthesis, Characterization, and Biological Evaluation of a Novel 2,6-Dichloro-1-(3-Chloro-4-fluorophenyl)-1,4-dihydropyridine-3,5-dicarbaldehyde Derivative"

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Keyword :- cyclic imides, synthesis , NMR, IR Antibacterial Activity etc.

Abstract

Cyclic imides, characterized by the –CO–N(R)–CO– moiety, are an important class of nitrogen-containing heterocycles known for their membrane permeability and broad pharmacological relevance. These compounds serve as privileged pharmacophores in the design of therapeutic agents, natural product synthesis, and polymer development. Found in bioactive molecules such as migrastatin and julocrotine, cyclic imides exhibit diverse biological activities, including antibacterial, anticancer, anti-inflammatory, and anticonvulsant effects. Despite their significance, traditional synthetic methods often involve harsh conditions and low selectivity, prompting the development of alternative strategies such as microwave-assisted synthesis and solid-phase methods using silica-bound benzoyl chloride. Recent advancements have also explored the efficient synthesis of N-phenyl succinimides and N-phenyl glutarimides from anhydrides and substituted aromatic amines, with further functionalization via the Vilsmeier-Haack reaction. Enzymatic studies have revealed that substituted imides undergo selective hydrolysis, in contrast to their unsubstituted counterparts. These findings highlight the synthetic versatility and biomedical potential of cyclic imides, reinforcing their importance in modern chemical and pharmaceutical research.

Introduction

Cyclic imides, characterized by the general structure –CO–N(R)–CO–, are a significant class of nitrogen-containing heterocycles. These compounds are capable of crossing biological membranes due to their neutral and hydrophobic nature, making them valuable in pharmaceutical and chemical research [1]. Notably, cyclic imines, closely related nitrogen heterocycles, are commonly found in a variety of pharmacologically active alkaloids [2].

Cyclic imides are considered privileged pharmacophores and play a crucial role in the synthesis of natural products, therapeutic agents, and polymers. Natural products such as migrastatin, lamprolobine, julocrotine, and cladoniamide all contain the imide moiety [3]. Due to their structural simplicity and broad range of biological properties—including antibacterial, antifungal, anticancer, anti-inflammatory, anticonvulsant, apoptosis-inducing, and androgen receptor-antagonist activities—cyclic imides and their derivatives have attracted considerable research interest [16]. A variety of cyclic imides can be synthesized through reactions of amino-substituted benzene sulfonamides with different acid anhydrides such as succinic, maleic, tetra hydrophthalic , pyrazine-2,3-dicarboxylic, and substituted phthalic anhydrides [12]. Among them, unsubstituted cyclic imides possess noteworthy biological activities; however, their synthesis via conventional methods often requires harsh conditions, leading to increased by-product formation [4]. Consequently, alternative techniques, including microwave-assisted synthesis, have been developed to obtain these structures more efficiently.

The use of silica-bound benzoyl chloride in solid-phase synthesis has provided an effective approach for the cyclodehydration of N-aryl imidic acids, leading to the formation of N-substituted succinimides and glutarimides [5]. These derivatives serve as essential intermediates in the synthesis of drugs, dyes, and polymers [17]. However, sustainable and straightforward methods for the preparation of cyclic imides from readily available starting materials remain limited. Enzymatic studies have shown that cyclic imides with bulky substituents—such as 2-methylsuccinimide, 2-phenylsuccinimide, and phthalimide—are hydrolyzed to half-amides by imidase enzymes. In contrast, simple, unsubstituted cyclic imides like succinimide and glutarimide are not enzymatically hydrolyzed [18].

Due to their vast application potential, the design and synthesis of new N-phenyl succinimides and N-phenyl glutarimides have become a research priority. Several efficient synthetic routes have been developed, including reactions of succinic or glutaric anhydride with substituted aromatic amines to yield cyclic imides such as 1-(N-methylpyridin-2-yl) pyrrolidine-2,5/6-dione [8].A particularly effective method involves the use of succinic anhydride, glutaric anhydride, 2,6-dichloro-4-trifluoromethylaniline, and acetyl chloride in benzene, followed by formylation via the Vilsmeier-Haack (VH) reaction [14]. This reaction—employing N,N-dimethylformamide (DMF) and phosphorus oxychloride ($POCl_3$)—is a cornerstone in organic synthesis, known for introducing formyl.

Aim of the Present Work:

cyclic imides have been extensively studied by various researchers. However, no reports have been found on the synthesis and characterization of 2,6-dichloro-1-(3-chloro-4-fluorophenyl)-1,4-dihydropyridine-3,5-dicarbaldehyde derived from glutarimide. Therefore, the present work focuses on the synthesis of this novel compound via the reaction of glutarimides with Vilsmeier–Haack reagent. The synthesized compound has been characterized using IR and ^{1}H NMR spectroscopy to confirm its structure.

Experimental method : -

Step 1: Synthesis of 1-(3-chloro-4-fluorophenyl) piperidine-2,6-dione

Materials Required: Glutaric anhydride , Benzene , 3-Chloro-4-fluoroaniline (0.01 mol, 1.45 g)

Acetyl chloride (6.42 mL), Methanol or ethanol (for recrystallization)

Procedure: 1. Formation of Intermediate:

In a round-bottom flask, glutaric anhydride is dissolved in benzene and heated under reflux with constant stirring for 15–20 minutes until a clear solution is obtained.

2. Amide Formation:

To the clear solution, a benzene solution of 3-chloro-4-fluoroaniline (0.01 mol, 1.45 g in 5 mL benzene) is added dropwise with constant stirring. The mixture is stirred for an additional 15–20 minutes until a homogeneous solution forms.

3. Solvent Removal:

The benzene is evaporated under reduced pressure to yield a whitish amorphous powder identified as 5-((N-substituted phenyl) amino)-5-oxopentanoic acid.

4. Cyclization to Piperidine-2,6-dione:

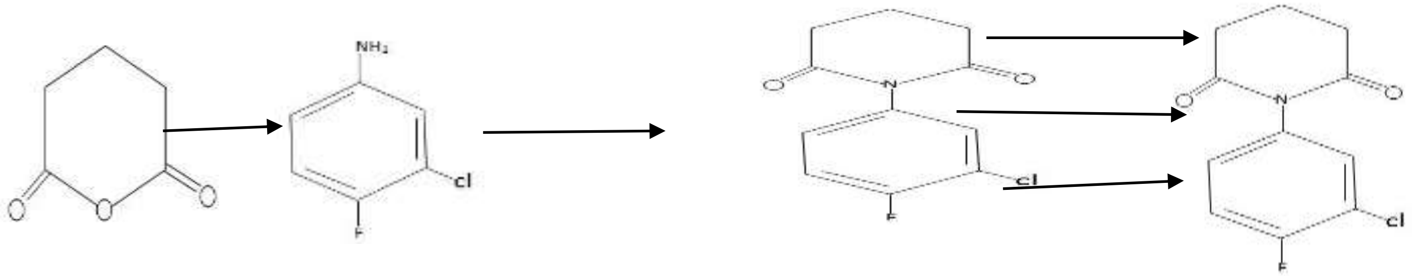
The resulting acid intermediate is then treated with acetyl chloride (6.42 mL) and refluxed for 15–20 minutes. During this step, the evolution of HCl gas confirms the progression of the reaction.

5. Product Isolation:

After completion, the reaction mixture is allowed to cool to room temperature. The resulting solid is filtered and purified by recrystallization from methanol or ethanol.

The 6. Drying:

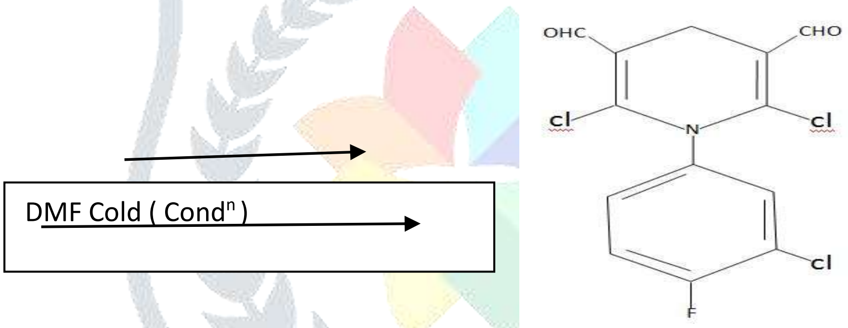
purified product is dried under an infrared (IR) lamp to yield the final compound, 1-(3-chloro-4-fluorophenyl) piperidine-2,6-dione.



glutaric anhydride **3-chloro, 4-fluro aniline** **1-(3-chloro-4- fluorophenyl) piperidine-2,6-dione**

2: Synthesis of 2,6-Dichloro-1-(3-chloro-4-fluorophenyl)-1,4-dihydropyridine-3,5-dicarbaldehyde

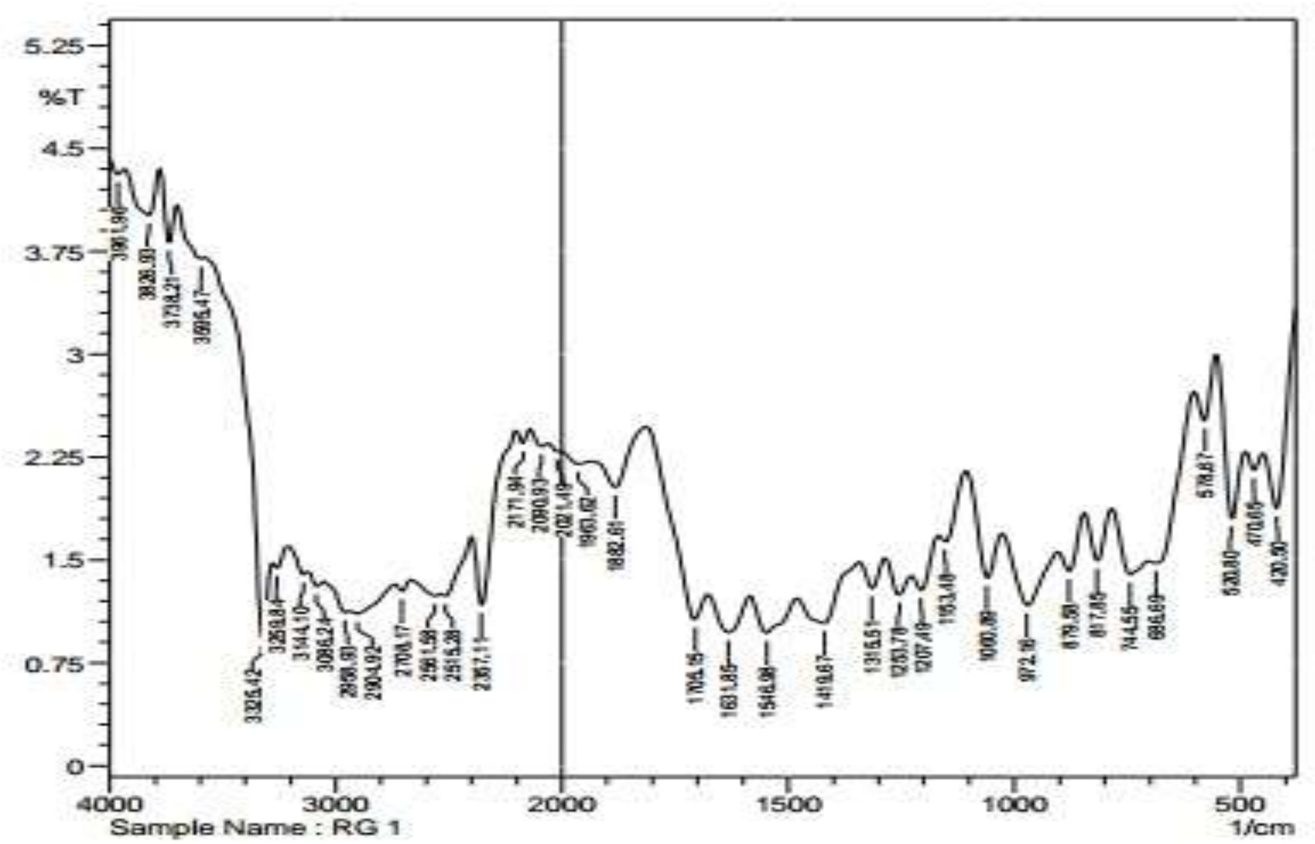
The formylation of the cyclic imide was carried out using the Vilsmeier–Haack reaction. Freshly distilled DMF (0.09 mol) was placed in a reaction flask and cooled to 0–5 °C. To this, $POCl_3$ (0.06 mol) was added dropwise with constant stirring using a magnetic stirrer. After the complete addition, small portions of glutarimide were gradually added to the reaction mixture. The resulting mixture was then heated to 60–70 °C and maintained at this temperature for 6 hours. After the heating period, the reaction mixture was left to stand overnight at room temp The next day, the mixture was slowly poured into crushed ice with constant stirring, resulting in a clear yellow solution. This solution was neutralized using 50% NaOH, and the pH was monitored using pH paper. Upon reaching neutrality, a solid precipitate began to form. The resulting precipitate was collected and recrystallized from ethanol to yield the final product



1-(3-chloro-4-fluorophenyl) piperidine-2,6-dione. **2,6-dichloro-1-(3-chloro-4-fluorophenyl)-1,4**

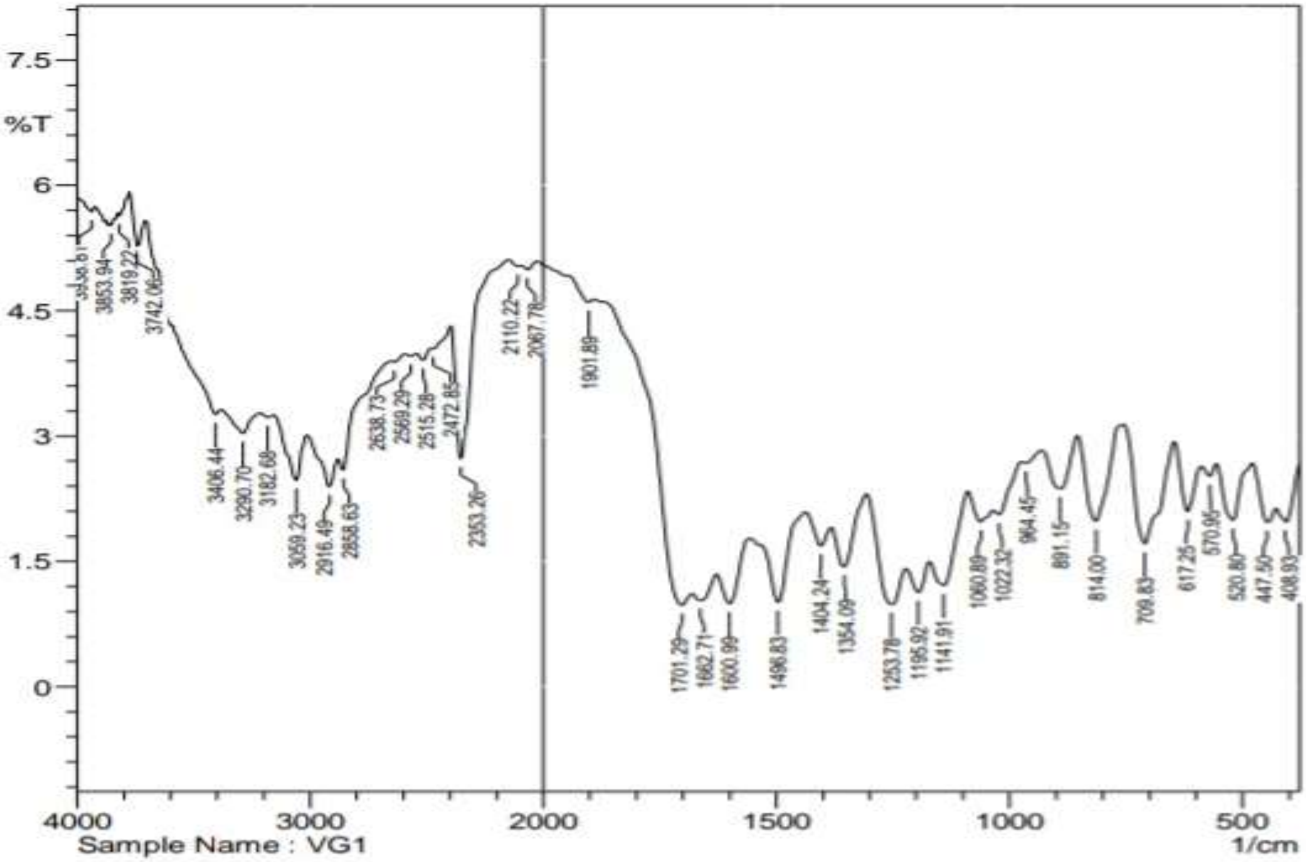
Heat **dihydropyridine-3,5- dicarbaldehyde**

RESULT AND DISCUSSIONS:-



4.1 IR spectra :-

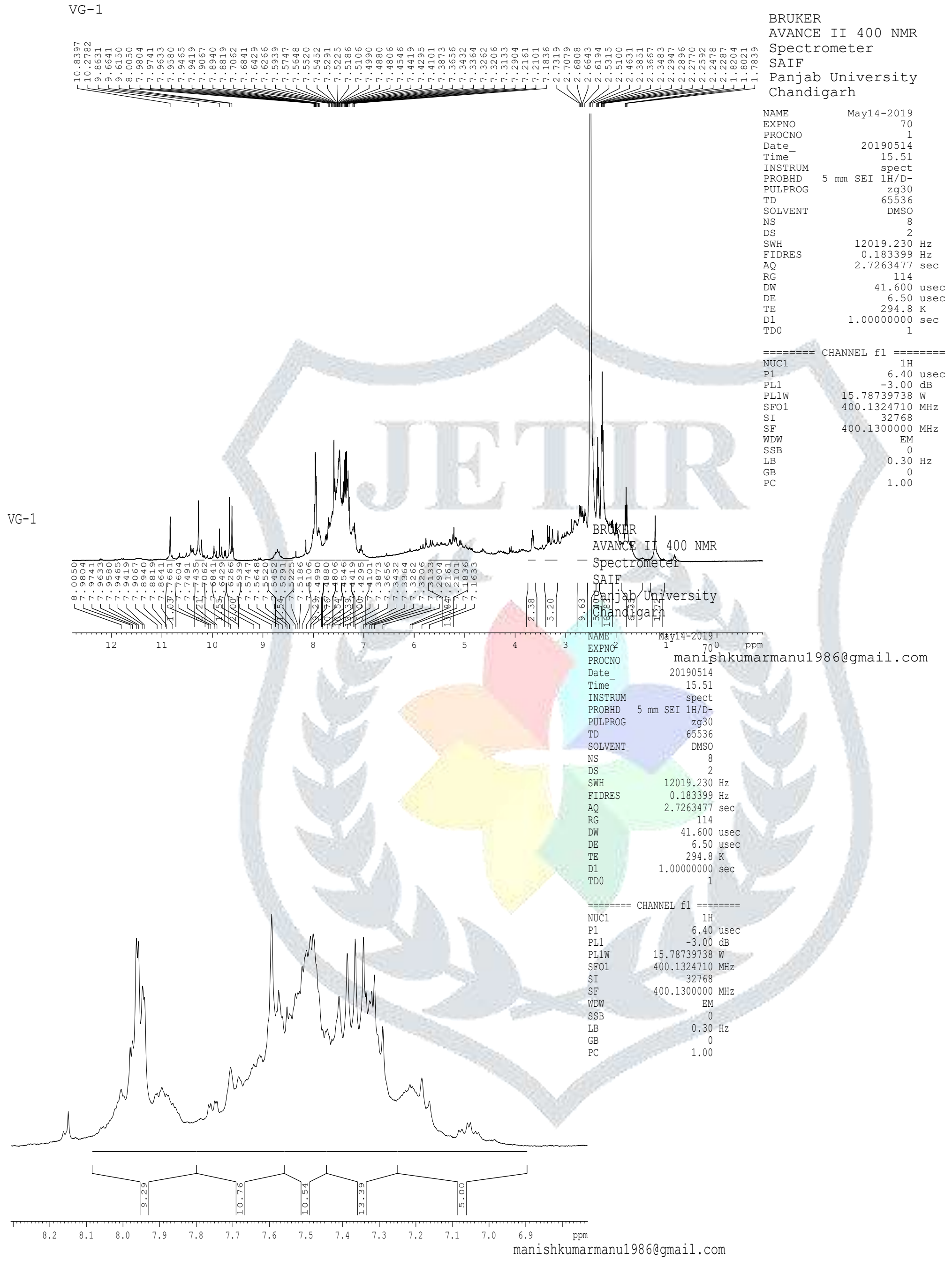
i) FTIR spectra of1-(3-chloro-4- fluorophenyl)piperidine-2,6-dione

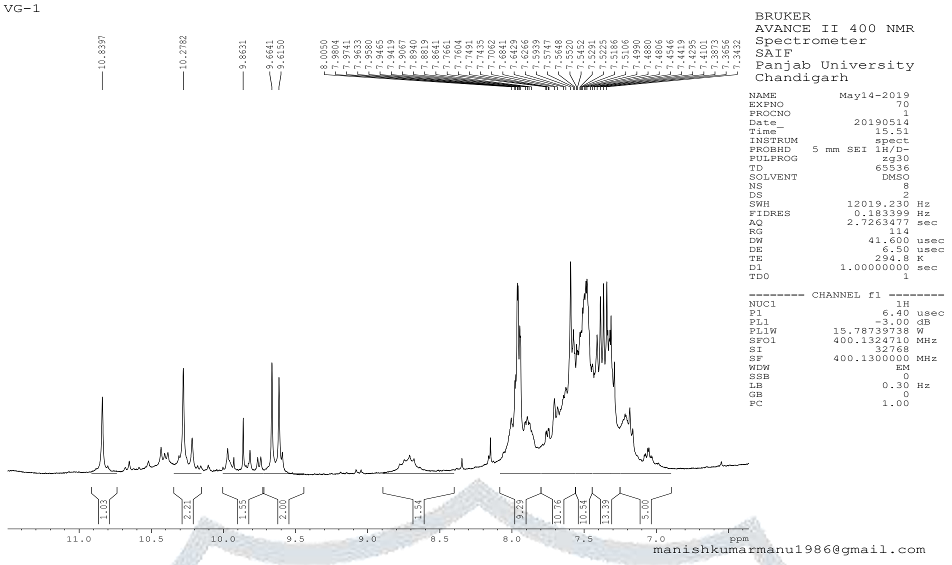


ii) **FTIR spectra of 2,6-dichloro-1-(3-chloro-4-fluorophenyl)-1,4- dihydropyridine- 3,5- dicarbaldehyde**

S.N	**Fuctional group**	**(-CH₂-)**	**(-C=C-)**	**(-C-N-)**	**(C-Cl)**	**(C-F)**	**(C=O) / (CHO)**	**C-H (CHO)**
1.	**1-(3-chloro-4-fluorophenyl)piperidine-2,6-dione**	2904-3016cm^{-1}	1419-1518 cm^{-1}	1253 cm^{-1}	744cm^{-1}	1315cm^{-1}	1631-1705cm^{-1}	-------
2.	**2,6-dichloro-1-(3-chloro-4-fluorophenyl)-1,4-dihydropyridine-3,5-**	3059 cm^{-1}	1404-1600 cm^{-1}	1253cm^{-1}	709cm^{-1}	1354cm^{-1}	1662-1701cm^{-1}	2916 cm^{-1}

	dicarbaldehyde							





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BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

NAME          May14-2019
EXPNO                 70
PROCNO                 1
Date_           20190514
Time               15.51
INSTRUM            spect
PROBHD   5 mm SEI 1H/D-
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                     8
DS                     2
SWH            12019.230 Hz
FIDRES          0.183399 Hz
AQ             2.7263477 sec
RG                   114
DW                41.600 usec
DE                  6.50 usec
TE                 294.8 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                  6.40 usec
PL1                -3.00 dB
PL1W         15.78739738 W
SFO1         400.1324710 MHz
SI                 32768
SF           400.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
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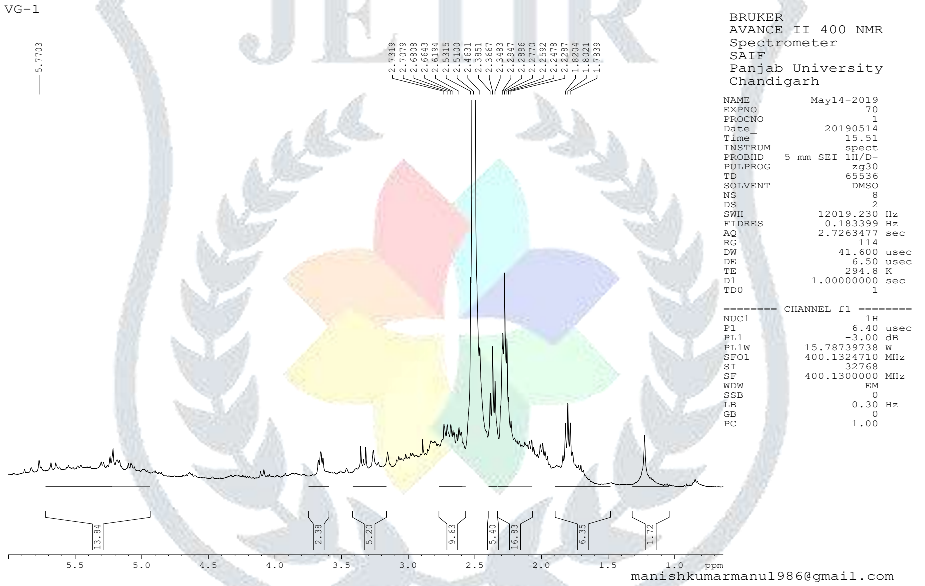

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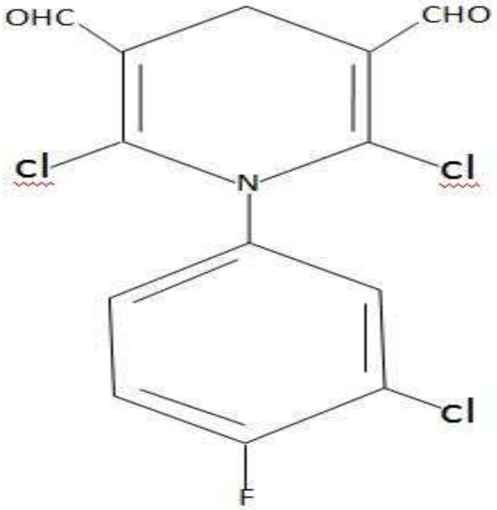
BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

NAME          May14-2019
EXPNO                 70
PROCNO                 1
Date_           20190514
Time               15.51
INSTRUM            spect
PROBHD   5 mm SEI 1H/D-
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                     8
DS                     2
SWH            12019.230 Hz
FIDRES          0.183399 Hz
AQ             2.7263477 sec
RG                   114
DW                41.600 usec
DE                  6.50 usec
TE                 294.8 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                  6.40 usec
PL1                -3.00 dB
PL1W         15.78739738 W
SFO1         400.1324710 MHz
SI                 32768
SF           400.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

^{1}H NMR (400MH$_z$) DMSO,δ ppm :-9.86-10.27 **δ** (S, 2H,-CHO), 7.16 to 8.00**δ**(m –Ar-H),2.51-2.53**δ** (S, 2H,-CH2-).

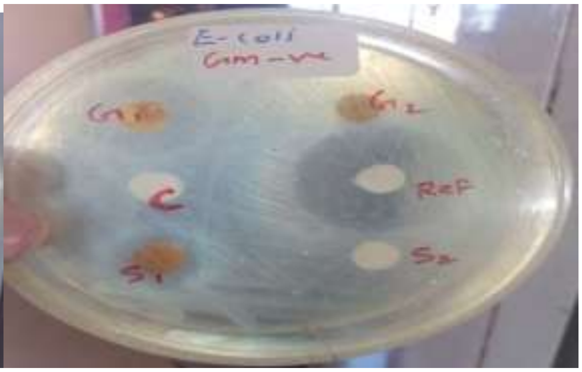


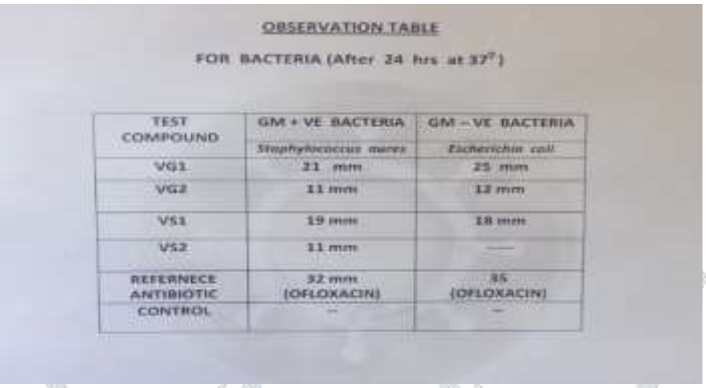
2,6-dichloro-1-(3-chloro-4-fluorophenyl)-1,4- dihydropyridine- 3,5- dicarbaldehyde

Antibacterial Activity:

Biological Activity of Synthesized Halo Vinyl Aldehydes:

The synthesized compound, 2,6-dichloro-1-(3-chloro-4-fluorophenyl)-1,4-dihydropyridine-3,5-dicarbaldehyde, was evaluated for in vitro antimicrobial activity against the bacterial strains Staphylococcus aureus and Escherichia coli. A stock solution of each compound was prepared in DMSO at a concentration of 1000 µg/mL. The antimicrobial assay was performed using 100 µg of the compound per disk. Commercial antibiotic disks containing Ciprofloxacin (10 µg/disk) and moistened with DMSO were used as the standard reference. Nutrient agar medium (Hi-media) was employed for bacterial culture.





OBSERVATION TABLE

FOR BACTERIA (After 24 hrs at 37^{0})

TEST COMPOUND	GM + VE BACTERIA	GM – VE BACTERIA
	Staphylococcus aureus	*Escherichia coli*
VG1	21 mm	25 mm
VG2	11 mm	12 mm
VS1	19 mm	18 mm
VS2	11 mm	——
REFERNECE ANTIBIOTIC	32 mm (OFLOXACIN)	35 (OFLOXACIN)
CONTROL	–	–

Conclusion:

The compound 2,6-dichloro-1-(3-chloro-4-fluorophenyl)-1,4-dihydropyridine-3,5-dicarbaldehyde was successfully synthesized using a conventional chemical method. The structure of the synthesized compound was confirmed through IR and NMR spectroscopy. The IR spectrum exhibited characteristic stretching frequencies, which were compared and correlated with standard values reported in the literature. The NMR spectrum provided chemical shift values consistent with the types of protons present in the compound, supporting the proposed structure. Therefore, based on the IR and NMR spectral data, the successful synthesis and structural confirmation of 2,6-dichloro-1-(3-chloro-4-fluorophenyl)-1,4-dihydropyridine-3,5-dicarbaldehyde can be concluded.

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