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Synthesis, Physiochemical Evaluation and Structural Characterization of Novel Pyrazole Derivatives

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Abstract:
The non-steroidal anti-inflammatory drugs (NSAIDS) are analgesic drugs under clinical usage some of which are highly acidic in nature and suffer from a common drawback of gastro-intestinal toxicity. Pyrazole and it derivatives are considered to be non-acidic analgesics in nature. The purpose of this study is to investigate the physiochemical and structural properties of newly developed Pyrazole derivatives which are non-acidic analgesics. The novel compounds were synthesized with the help of lab produced chalcone and ethanone. The physiochemical characterization was done with the help of melting point determination, thin layer chromatography (TLC) and solubility testing using different solvents of varied polarity. Structural investigation was done with the help of UV spectroscopy and IR spectroscopy. The compounds were found to be pure and semi polar in nature. In IR spectroscopy the compounds showed the peak values of representing groups which is present in the compounds. The study helped us in the better understanding of some of the major properties of pyrozolones (pyrazole derivatives). Further studies are needed to understand the non-acidic analgesicactivity of the compounds and to develop a co-relation between these biological and structural activities.

Keywords: *Pyrazole, Analgesics, Physiochemical evaluation, UV-Visible Spectroscopy, IR Spectroscopy*

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I. Introduction

Pyrazoles are considered to be one of the most active classes of compounds owning awide spectrum of biological activities. Many of the therapeutically useful compounds such as phenybutazone, oxyphenylbutazone, celecoxib, which belong to pyrazoles exhibit anti-inflammatory, anti-pyretic and analgesic properties. Moreover, pyrozole derivatives also constitute an interesting class of organic compound with different clinical, pharmacological and agricultural application. [1]

The success of NSAIDs in treatment of various pain disorders validated inhibition of COX enzyme as a highly suitable target in analgesic therapies.[2] However, the gastrointestinal toxicities associated with the widespread use of NSAIDs proved to be a major problem during long term therapy.[3] Although COX-2 is concerned to be the main isoenzyme related to pain, most NSAIDs in the market today block both forms of COX isoenzymes. Side effects such as gastrointestinal pain have been associated with the NSAID use due to the inhibition of COX-1.

Prolonged use of NSAIDs causes gastrointestinal ulcers and hence, there is a need to develop safer analgesic drugs. Pyrazole are important classes of heterocyclic compound and exhibit a broad spectrum of biological activities such as antimicrobial, anti-inflammatory, COX inhibitor, anti- allergic, analgesic and many more. [4,5] In the course of research devoted to the development of new class pyrazole moieties for the analgesic activities, Synthesis and evaluation of physiochemical and structural activities of pyrazole derivatives was done.

II. Experimental Set-Up

Melting point was determined using open capillary tube by VEEGO Apparatus. Thin layer chromatography was performed using silica gel – G as adsorbent and Chloroform: Acetone (8:2), spots were exposed with the help of iodine vapors. UV- Spectra was performed on UV- SYSTRONICS DOUBLE BEEM SPECTROPHOTOMETER 2203 Smart. The IR spectra was of synthesized compounds were obtained using KBr pellets. [6]

III. Methodology

A. Synthesis of {1- (3,4-dimethoxyphenyl)-3-(4-chlorophenyl)}-prop-2-ene-1-one (Chalcone):

3,4 dimethoxy acetophenone (1.8g, mmol) and 4- chlorobenzaldehyde (1.4g, 10 mmol) were dissolved in approximately 15 mL of ethanol. The mixture was stirred for several minutes at 5-10°C. A 10 mL aliquot of a

40% aqueous potassium hydroxide solution was then slowly added drop wise to the reaction flask. The reaction solution was allowed to stir at room temperature for approximately 4 hours. Then obtained precipitate (Chalcone) was collected by suction filtration.

B. Synthesis of 1-[3-(3,4-dimethoxyphenyl)-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-yl] ethanone:

A solution of Chalcone (5mmol) in 30 mL of acetic acid was added drop wise to 0.6 mL of hydrazine hydrate (12.5mmol) and reflux under stirring for 3 hours. The mixture was then poured into ice-water, obtaining the crude Ethanone pyrazole which were recrystallized twice from ethanol. [7]

C. Preparation of SS-1, SS-2, SS-3 and SS-4:

C.1. Synthesis of SS-1 or compound 1: 1{1-(4-Chlorophenyl-prop-2-ene-1-one)-3-(3,4-dimethoxyphenyl)-5-(4-chlorophenyl)}4,5 dihydro-1H-pyrazole-3yl

Equimolar quantities (1mmol) of the 4-Chlorobenzaldehydes and Ethanone Pyrazole derivatives were dissolved in approximately 15 mL of ethanol. The mixture was stirred for several minutes at 5-10°C. A 10 mL portion of a 40% aqueous potassium hydroxide solution was then slowly added drop wise to the reaction flask. The reaction solution was allowed to stir at room temperature for approximately for 4 hours. The precipitate formed was collected by suction filtration.

C.2. Synthesis of SS-2 or compound 2: 1{1-(4-Flurophenyl-prop-2-ene-1-one)-3-(3,4-dimethoxyphenyl)-5-(4-chlorophenyl)}4,5 dihydro-1H-pyrazole

Equimolar quantities (1mmol) of the 4-Fluorobenzaldehydes and ethanone Pyrazole derivatives were dissolved in approximately in 15 mL of ethanol. The mixture was stirred for several minutes at 5-10°C. A 10 mL portion of a 40% aqueous potassium hydroxide solution was then slowly added drop wise to the reaction flask. The reaction solution was allowed to stir at room temperature for approximately 4 hours. The precipitate formed was then collected by suction filtration.

C.3. Synthesis of SS-3 or compound 3: 1{1-(4-Clorophenyl-prop-2-ene-1-one)-5-(4-Chlorophenyl)}4,5dihydro-1H-pyrazole-3-yl

The chalcone used for the preparation of this structure used1.46 mL, 10mmol of 4-ethyle acetophenone instead of 3, 4- dimethoxyacetophenone.Equimolar quantities (1mmol) of the 4-Fluorobenzaldehyde and ethanone Pyrazole derivatives were dissolved in approximately 15 mL of ethanol. The mixture was stirred for several minutes at 5-10 °C. A 10ml portion of a 40% aqueous potassium hydroxide solution was then slowly added drop wise to the reaction flask[8]. The reaction solution was stirred at room temperature for approximately for 4 hours. Most commonly, a precipitate formed was then collected by suction filtration.

C.4. Synthesis of SS-4 or compound 4: 1{1-(4-Nitro-phenyl-prop-2-ene-1-one)-3-(3,4-dimethoxyphenyl)-5-(4-chlorophenyl)}4,5 dihydro-1H-pyrazole-3-yl

Equimolar quantities (10 mmol) of the 3-nitrobenzaldehydes and Ethanone Pyrazole derivatives were dissolved in approximately 15 ml of ethanol. The mixture was stirred for several minutes at 5-10°C. A 10 ml portion of a 40% aqueous potassium hydroxide solution was then slowly added drop wise to the reaction flask. The reaction solution was stirred at room temperature for approximately 4 hours. Most commonly, a precipitate formed was then collected by suction filtration. [9]

The list of the compounds along with th**ei**r % yields is mentioned in Table 1.

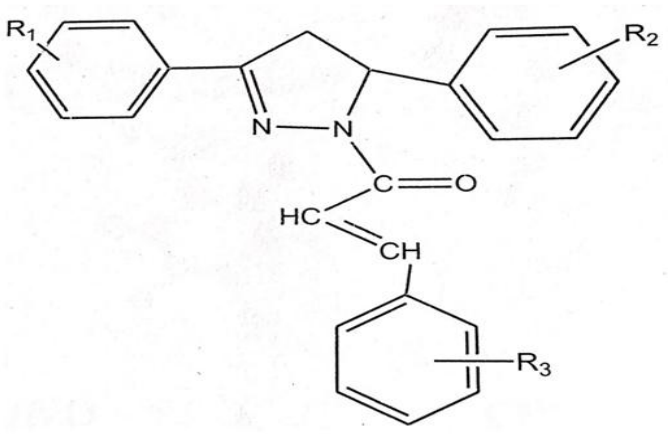

Table 1: List of synthesized compounds with their % yield.

S.No.	Compounds code	R_1	R_2	R_3	%yield
1	SS-1	3,4 $(CH_3O)_2$	4-Cl	4-Cl	65.12%
2	SS-2	3,4 $(CH_3O)_2$	4-Cl	4-Fl	55.24%
3	SS-3	4-C_2H_5	4-Cl	4-Cl	59.09%
4	SS-4	3,4 $(CH_3O)_2$	4-Cl	3-NO_2	50.15%

I. PHYSIOCHEMICAL EVALUATION:

The following tests were performed to check the quality of synthesized compounds. Physiochemical characterization of synthesized compounds was done by using following various parameters.

A. Melting point study:

Melting point of synthesized compounds was determined in open capillary tube by VEEGO apparatus.[10] Practically obtained melting point indicates the purity of synthesized compounds. The melting points of synthesized compounds are reported in table 2.

Table 1: Melting point of synthesized compounds

S. No.	Synthesized Compounds	Melting Point (°C)
1	SS-1	122-123°C
2	SS-2	126-128°C
3	SS-3	96-98°C
4	SS-4	118-120°C

B. Thin Layer Chromatography:

The purity of the compounds were verified by TLC using silica gel-G as adsorbent and Chloroform: Acetone (8:2) and spots were observed when exposed to iodine vapors under iodine chamber. Table 3 represents$R_f$of synthesized compounds:

Table 2: R_f value of synthesized compounds

S. No.	Synthesized Compounds	R_f
1	SS-1	0.73
2	SS-2	0.74
3	SS-3	0.62
4	SS-4	0.66

C. Solubility Study:

2mg of synthesized compounds were transferred in 5ml of different pure solvent. Table 4 shows the solubility studies of the synthesized compounds in different solvents.

Table 3: Solubility studies of synthesized compounds in different solvents.

S. No.	Compound	Water	Alcohol	Acetone	Chloroform	Benzene	DMSO
1	SS-1	--	++	+++	++	-	++
2	SS-2	--	++	+++	++	-	++
3	SS-3	--	++	+++	++	--	++
4	SS-4	--	++	+++	++	--	++

+++ Freely soluble + sparingly soluble
++Soluble - -Practically soluble

II. STRUCTURAL EVALUATION:

A. UV spectroscopy:

For determination of λ_{max} of the samples, ethanol was used as solvent. For UV-spectroscopy, UV SYSTRONICS DOUBLE BEEM SPECTROPHOTOMETER: 2203 SMART was used from the sophisticated instrument lab of the institution. The obtained UV spectra of the compounds SS-1 to SS-4 are given in figure 1 to figure4 respectively and their λ_{max} values are given in table 5.

Table 4: λ_{max} of synthesized compounds.

S. No.	Compound code	λ_{max}
1	SS-1	313.4
2	SS-2	312.6
3	SS-3	291.0
4	SS-4	313.0

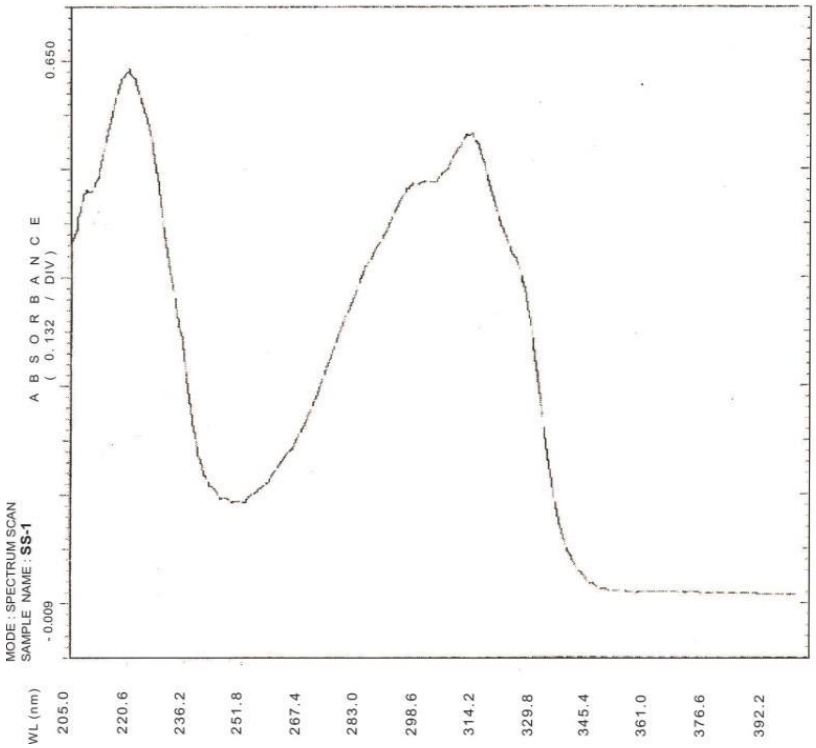

Figure 1: UV- Spectroscopy of compound 1

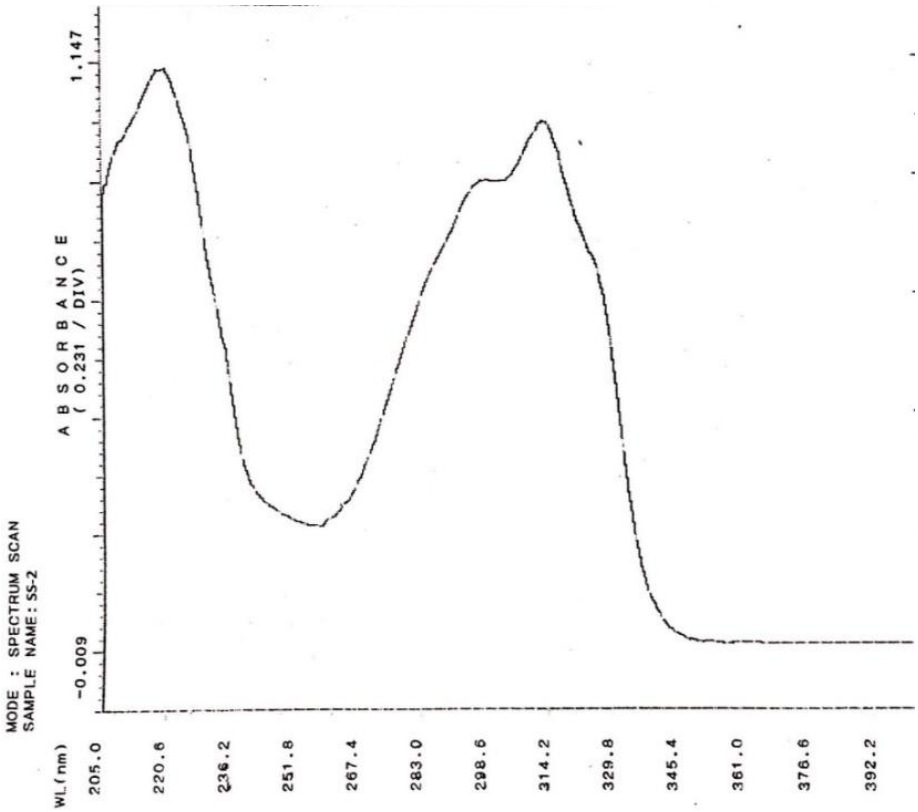

Figure 2: UV- Spectroscopy of compound 2

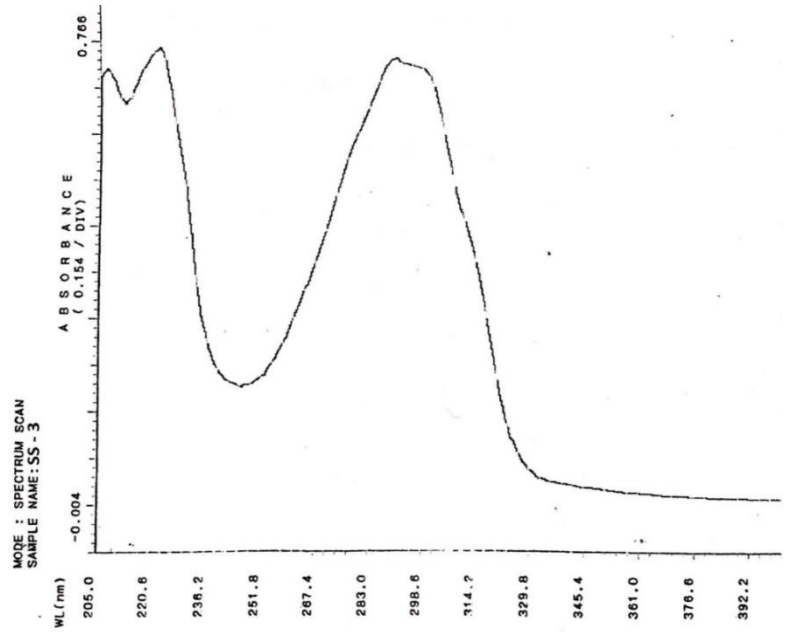

Figure 3: UV-Spectroscopy of compound 3

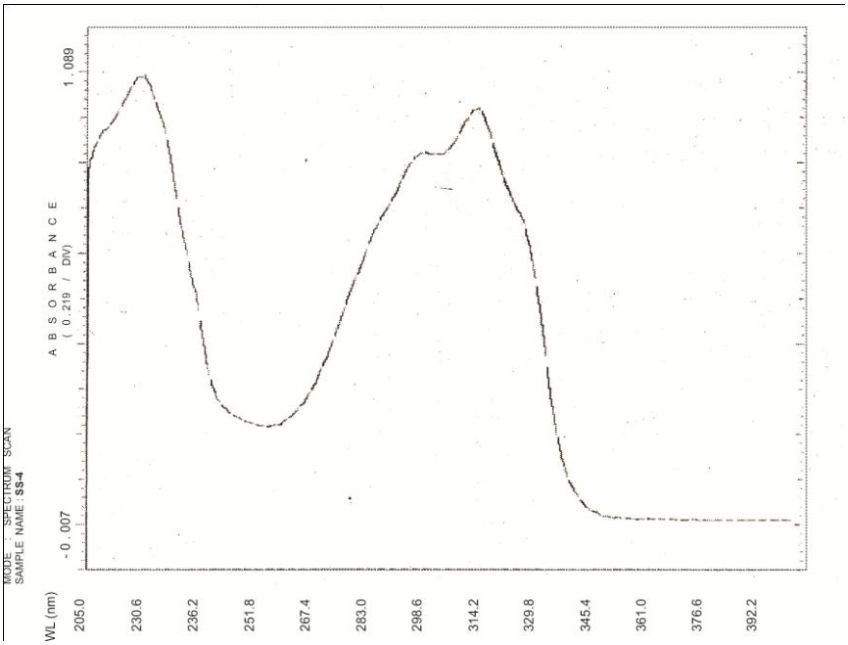

Figure 4: UV-SPectroscopy of compound 4

B. IR Spectroscopy

The IR spectra of synthesized compounds were obtained using KBr pellets.[11] IR specttra of synthesized compounds showed characteristic absorption for the functional groups present in compounds.The IR spectra of compounds SS-1 to SS-4 are given in figure 5 to figure 8 respectively and the interpretation of spectra are given in table 6 to table 9 respectively.

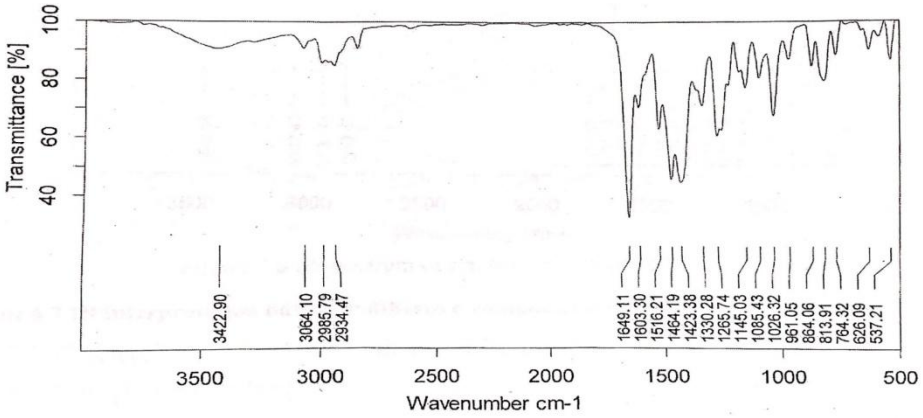

Figure 5: IR- Spectrum of SS-1

Table 5: IR interpretation data of synthesized compound SS-1

S.NO.	IR Peak (cm^{-1})	Inference
1.	3064	C-H stretching (aromatic)
2.	2934	C-H stretching (aliphatic)
3.	1649	C=O stretching (s)
4.	1603	C=C stretching (m)
5.	1423 & 1464	C-H bending (m)
6.	1265	C-O stretching (m)
7.	1026	C-O-C stretching (m)
8.	764	C-Cl stretching (m)

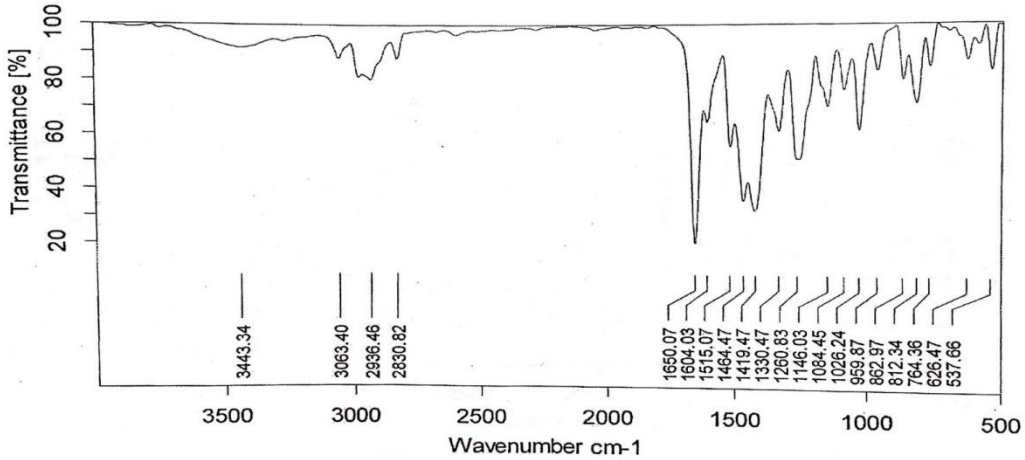

Figure 6: IR- Spectrum of SS-2

Table 6: IR interpretation data of synthesized compound SS-2

S.NO.	IR Peak (cm^{-1})	Inference
1.	3063	C-H stretching (aromatic)
2.	2936	C-H stretching (aliphatic)
3.	1650	C=O stretching (s)
4.	1604	C=C stretching (m)
5.	1419 & 1465	C-H bending (m)
6.	1260	C-O stretching (m)
7.	1146	C-F stretching (m)
8.	764	C-Cl stretching (m)

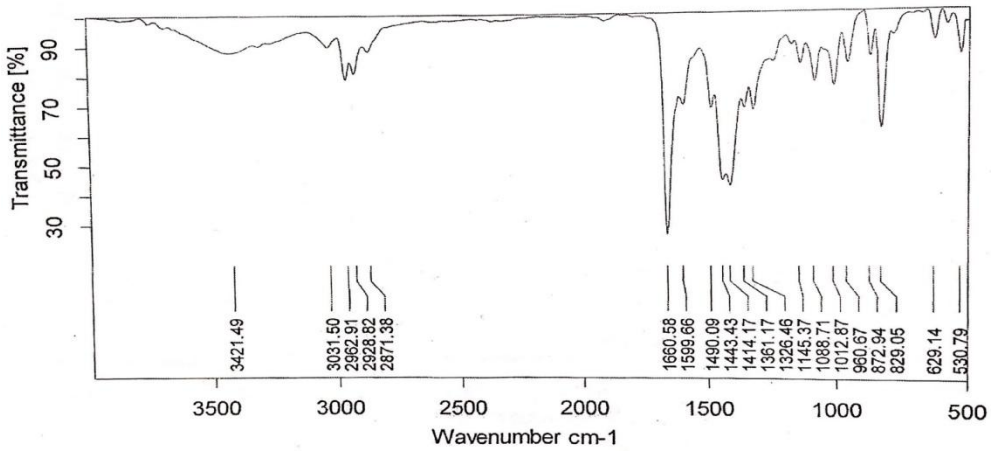

Figure 7: IR- Spectrum of SS-3

Table 7: IR interpretation data of synthesized compound SS-3

S.NO.	IR Peak (cm-1)	Inference
1.	3031	C-H stretching (aromatic)
2.	2962	C-H stretching (aliphatic)
3.	1660	C=O stretching (s)
4.	1599	C=C stretching (m)
5.	1443 & 1414	C-H bending (aromatic)
6.	1145	C-O stretching (m)
7.	1088	C-O-C stretching (m)
8.	629	C-Cl stretching (m)

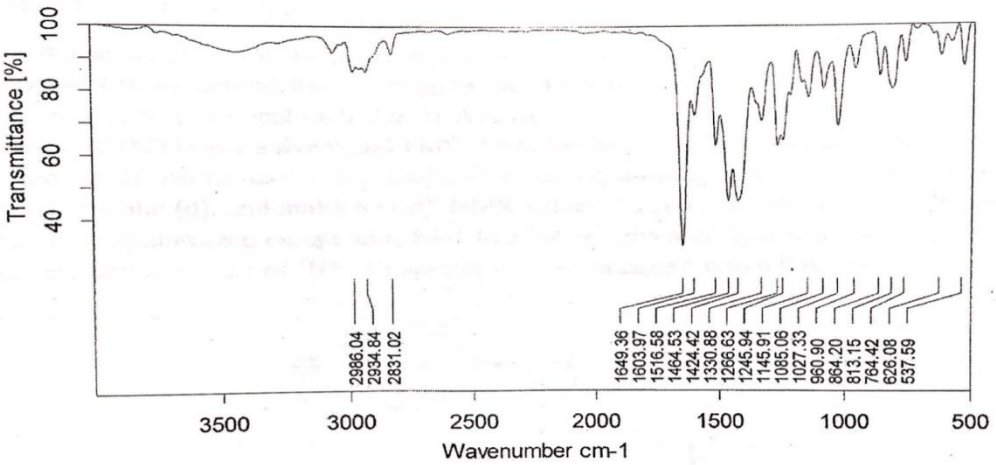

Figure 8: IR- Spectrum of SS-4

Table 8: IR interpretation data of synthesized compound SS-4

S.NO.	IR Peak (cm^{-1})	Inference
1.	2986	C-H stretching (aromatic)
2.	1649	C=O stretching (s)
3.	1603	C= C stretching (m)
4.	1464	NO_2 (aromatic)
5.	1424	C-H bending (m)
6.	1266	C-O stretching (m)
7.	1027	C-O-C stretching (m)
8.	626	C-Cl stretching (m)

IV. Results and Discussion

The research work aimed to synthesize novel pyrazole derivatives compounds with improved biological activities. The synthesis was done with the help of 3 step method. All these synthesized compounds were characterized by melting point, thin layer chromatography, solubility study.

The melting point of all the pyrazole derivatives ranges between 80 to 130°C. The thin layer chromatography was done with the help of silica gel-G as adsorbent and chloroform: acetone (8:2) as solvent system. The R_f value indicates that the compounds are pure. The solubility study shows that the compounds are semi polar in nature.

The obtained spectra of synthesized compounds via the UV Spectrophotometer showed λ_{max} of corresponding compounds. The IR peaks observed were anticipated with the structure. IR spectra of synthesized compound showed characteristic absorption peaks for the functional groups present in the compound. The vibration for C-H stretching (aliphatic) (2986-2936), C=O stretching (1649-1604), C=C stretching, $-NO_2$ (aromatic) (1464-1424), C-O-C stretching (1464-1424), C-F stretching (764-629). The physiochemical and structural data support the laboratory synthesis of compounds. Further in-vivo studies are required for the biological evaluation of the synthesized compounds.

Data Availability: All the data presented in this article to support the findings are available from the corresponding author upon request.

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