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Synthesis of substituted 4-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-1, 5-dimethyl-2-phenyl-1, 2-dihydro-3H-pyrazol-3-one with Green Chemistry approach

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***Abstract**: The rate at which reaction proceeds and how yield does it provide, has always been a question of key importance in the field of research, carried out at both academic and industrial level. With the advent of microwave irradiation technology, it has now become possible to address this difficulty owing to its property to interact directly with molecules of reacting mixture without altering their molecular structure and thus providing a forward thrust to this whole time consuming process. The presented work compares the synthesis of derivatives of 4-aminoantipyrine with microwave irradiation and conventional method. It also addresses and attempts to find out the possession of anti-oxidant activity of the derivatives. The analysis of the synthesized derivatives was carried out using analytical techniques such as HPLC, FTIR.*

***Keywords :** 4-Aminoantipyrine, Microwave irradiation, Anti-oxidant Activity etc.*

I. INTRODUCTION

Microwave is a form of electromagnetic energy which falls at the lower end of the electromagnetic spectrum and is defined in a measurement of frequency as 300 to 300,000 Megahertz [1]. The microwave region of the electromagnetic spectrum lies between infrared and radio frequencies. The basic mechanism of microwave assisted synthesis involves agitation of polar molecules or ions that oscillate under the effect of an oscillating electric or magnetic field [1]. In the presence of an oscillating field, particles try to orient themselves or be in phase with the field. Only materials that absorb microwave radiation are relevant to microwave chemistry. These materials can be categorized according to the three main mechanisms of heating such as dipolar polarization, conduction mechanism, and interfacial polarization [1] .The microwave radiation is used as heating technique in organic synthesis. It has proven to be so efficient that it has gained wide acceptance in the field of organic chemistry. It is a very time saving, efficient and ecofriendly technique.

The potential of this synthetic method with low energy requirements, less waste and minimal use of solvent is what making this an ecofriendly technique [2]. The principles of Green chemistry apply to most of the synthetic routes with microwave irradiation.

The microwave irradiation unlike X-Ray or γ- Ray doesn't alter the molecular structure of the compounds being heated – it provides only thermal activation [3] Microwave-assisted synthesis improves both throughput and turnaround time for medicinal chemists by offering the benefits of drastically reduced reaction times, increased yields, and pure products.

4-Aminoantipyrine [4] has been an important moiety in the field of medicinal chemistry. The derivatives derived from the same along have been showing various pharmacological activities such as anti-inflammatory, anti-oxidant, anti- microbial and anti-fungal properties. Products such as 4-((3-Nitrophenyl)(8-hydroxyquinolinyl)methylamino)-1,5-dimethyl-2-phenylpyrazol-3-one, 4-((4-(Dimethylamino)phenyl)(8-hydroxyquinolinyl)methylamino)-1,5-dimethyl-2-phenylpyrazol-3-one derived from Betty type reaction using 4-aminoantipyrine as main moiety show Anti-inflammatory and Anthelmintic properties. 4-Aminoantipyrine was synthesized and their structure was confirmed (FTIR and elemental analysis). Some of their biological properties were evaluated: antimicrobial and antioxidant (DPPH radical scavenging activity, Fe3+ reducing power).The amides of caffeic and ferulic acid were very efficient antioxidants (DPPH radical scavenging assay: EC50 < 100 μM). The Fe 3+ reducing power for the synthesized substances was similar or superior to that of the positive control (ascorbic acid). [6]

II. MATERIALS AND METHODS

All raw materials used in the synthesis have been obtained from M/S Fluka AG (Bachs, Switzerland) and M/S Sigma-Aldrich chemicals and Co. Inc. (Milwaukee, WI, USA). Microwave synthesis was carried out in Anton Par Monowave-300.Melting points were recorded on a Thermonik Melting point Apparatus (Campbell Electronics, Mumbai, India) and are uncorrected. IR spectra were recorded on IR-Affinity, Shimadzu using DRS system. HPLC chromatograms have been recorded on Thermo Scientific UHPLC plus Ultimate 3000 HPLC

system (Thermo Scientific, USA). Elemental analysis has been carried out on a C, H, and N Elemental Analyzer (Thermo-Finnigan Flash EA 1112, Italy).

1.1. EXPERIMENTAL

1.1.1. SYNTHESIS OF 4-[(E)-BENZYLIDENEAMINO]-1, 5-DIMETHYL-2-PHENYL-1, 2-DIHYDRO-3H-PYRAZOL-3-ONE [3(A-E)] (BY CONVENTIONAL METHOD)

Dissolve 5g. (0.02 moles) of 4-amino-1, 5-dimethyl-2-phenyl-1, 2-dihydro-3H-pyrazol-3-one (1) in minimum quantity of Ethanol. Add equimolar concentration of substituted Benzaldehyde [2(a-e)] 3.054g dissolved in Ethanol. Subject this mixture to reflux on water bath for 18-22 hours. Monitor the progress of the reaction using Thin Layer Chromatography after regular intervals. Solvent System: Ethyl Acetate: n-Hexane (60: 40 v/v). After confirmation using TLC, add sufficient amount of water to the reaction mixture until all the product is precipitated out. Filter out the precipitate. Dry the product and weigh. The Schiff base product obtained is used for further characterization [3(a-e)]

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Dissolve 5g. (0.02 moles) of 4-amino-1, 5-dimethyl-2-phenyl-1, 2-dihydro-3H-pyrazol-3-one (1) in minimum quantity of DMF. Add equimolar concentration of substituted Benzaldehyde [2(a-e)] 3.054g dissolved in DMF. Subject this mixture to microwave irradiation for 15-20 mins. Monitor the progress of the reaction using Thin Layer Chromatography after regular intervals. Solvent System: Ethyl Acetate: n-Hexane (60: 40 v/v). After confirmation using TLC, add sufficient amount of water to the reaction mixture until all the product is precipitated out. Filter out the precipitate. Dry the product and weigh. The Schiff base product obtained is used for further characterization [3(a-e)]

3a:- Yield 81.06%; Yellow amorphous solid. MP; 292°C Found: C, 69.89; H, 5.21, N, 13.57
IR (KBr) cm^{-1} 1008.77 (C-F), 1729 (C=O), 954 (mono substituted 6 membered ring), 837.11 (1, 2, 4, 5 substituted 6 membered ring), 2280 (C-H), 3760-3809 (C-N), 1263 (C-O)

3b:- Yield 79.27%; Yellowish orange amorphous solid. MP; 255°C Found: C, 66.36; H, 4.91, N, 12.89
IR (KBr) cm^{-1} 1008.77 (C-F), 1729 (C=O), 954 (mono substituted 6 membered ring), 837.11 (1, 2, 4, 5 substituted 6 membered ring), 2280 (C-H), 3760-3809 (C-N), 1263 (C-O)

3c:- Yield 83.62%; Brown amorphous solid. MP; 280°C Found: C, 66.86; H, 5.20, N, 12.90
IR (KBr) cm^{-1} 692 (disubstituted 6 membered ring), 837.11 3102-3489 (O-H), 2298 (C-H), 3789-3810 (C-N), 1812 (C=O); 3467-3629 ($O-CH_3$); 1279 (C-O).

3d:- Yield 78.11%; Pale yellow amorphous solid. MP; 265°C Found: C, 67.64; H, 5.63, N, 12.44 IR (KBr) cm^{-1} 3102-3309 (O-H), 3492 ($O-CH_3$), 698 (disubstituted 6 membered ring), 1716 (C=O), 2872.01 (C-H), 3729-3845 (C-N), 1219 (C-O)

3e:- Yield 82.34%; Brown amorphous solid. MP; 249°C Found: C, 66.12; H, 6.03, N, 11.00
IR (KBr) cm^{-1} 1008.77 (C-F), 1729 (C=O), 954 (mono substituted 6 membered ring), 837.11 (1, 2, 4, 5 substituted 6 membered ring), 2280 (C-H), 3760-3809 (C-N), 1263 (C-O); 3467-3629 ($O-CH_3$); 1219 (C-O).

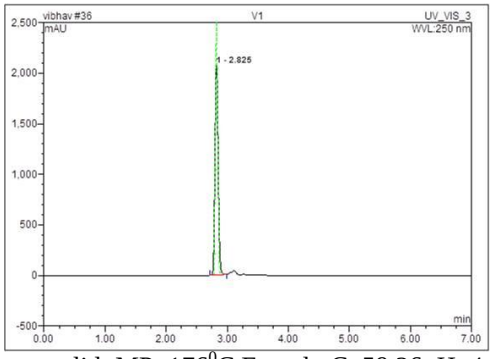
1.1.2. SYNTHESIS OF 4-(3-CHLORO-2-OXO-4-PHENYLAZETIDIN-1-YL)-1, 5-DIMETHYL-2-PHENYL-1, 2-DIHYDRO-3H-PYRAZOL-3-ONE [4(A-E)] (BY CONVENTIONAL METHOD)

Dissolve 0.75g, of the substituted Schiff's bases [3(a-e)] in minimum quantity of Chloroform. Add 1.5 moles of Chloroacetyl Chloride dissolved in Chloroform. Subject this mixture to reflux on a water bath for 22-26 hours. Monitor the progress of the reaction using TLC after regular intervals. Solvent System: Toluene: Ethyl acetate (60: 40 v/v). After confirmation using TLC, allow it to dry by evaporating Toluene completely until solid is left behind. Give the product washing with Ether. Dry the product and weigh.

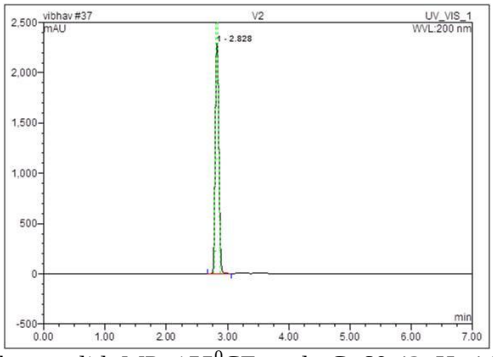
SYNTHESIS OF 4-(3-CHLORO-2-OXO-4-PHENYLAZETIDIN-1-YL)-1, 5-DIMETHYL-2-PHENYL-1, 2-DIHYDRO-3H-PYRAZOL-3-ONE [4(A-E)] (BY MICROWAVE SYNTHESIS)

Dissolve 0.75g, of the substituted Schiff's bases [3(a-e)] in minimum quantity of Toluene. Add 1.5 moles of Chloroacetyl Chloride dissolved in Toluene. Subject this mixture to microwave irradiation for 30-40 mins. Monitor the progress of the reaction using TLC after regular intervals. Solvent System: Toluene: Ethyl acetate (60: 40 v/v). After confirmation using TLC, allow it to dry by evaporating Toluene completely until solid is left behind. Give the product washing with Ether. Dry the product and weigh.

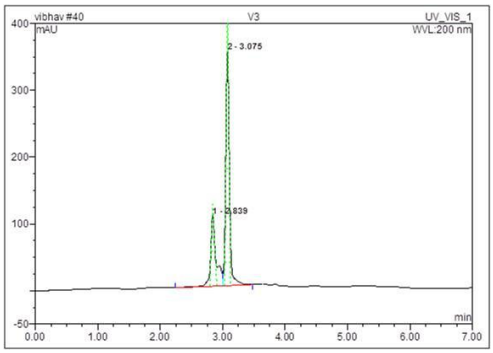
4a:- Yield 82.37%; yellow amorphous solid; MP; 170^0C Found: C, 62.60; H, 4.80; N, 10.49.
IR (KBr) cm^{-1}: 837.11 (C-Cl), 740.67 (mono substituted 6 membered ring), 700.16 (disubstituted 6 membered ring), 1367 (C-H), 1008.77 (C-F), 1049.28 (C-N) λ_{max}; 250nm.
HPLC Experimental Parameters: Instrument make: Thermo Scientific; Instrument model: UHPLC Ultimate-3000; Column specifications: Acclaim™ C-18, 5µ, 4.6 × 250mm; Detector: Photodiode Array detector; Wavelength: 250nm; Mobile phase: Acetonitrile: Methanol (90:10 v/v); Flow rate: 1ml/min; Column temperature: 28ºC; Injection volume: 20µL; Run time: 7mins; RF: 2.825



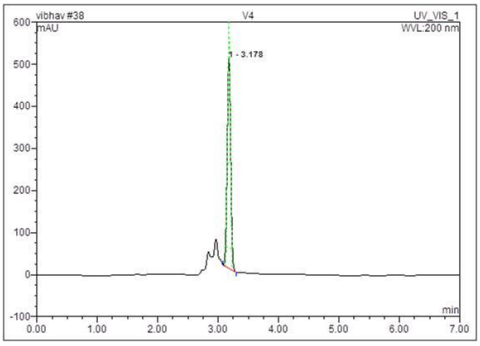
4b:- Yield 84.23%; white amorphous solid; MP; 176^{0}C Found: C; 59.26; H; 4.63 N; 10.84
IR (KBr) cm^{-1}: 837.11 (C-Cl), 1612.49 (5 member hetero-cyclic ring), 740.67 (mono substituted 6 membered ring), 788.89 (metasubstituted 6 membered ring), 2873.94 (C-H), 1068.56 (C-N), 1049.28 (C-O);
HPLC Experimental Parameters: Column specifications: Acclaim™ C-18, 5µ, 4.6 × 250mm; Detector: Photodiode Array detector; Wavelength: 200nm; Mobile phase: Acetonitrile: Methanol (90:10 v/v); Flow rate: 1ml/min; Column temperature: 28ºC; Injection volume: 20µL; Run time: 7mins; RF: 2.828



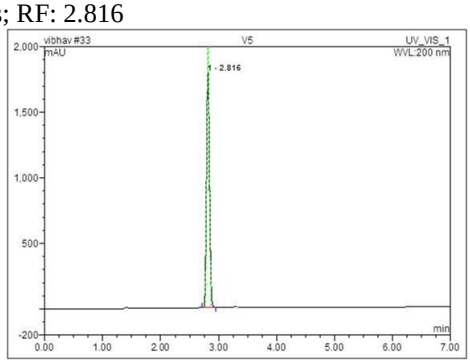
4c:- Yield 88.97%; brown amorphous solid; MP; 155^{0}CFound: C; 60.42; H; 4.90 N; 10.91
IR (KBr) cm^{-1}: 844.28 (C-Cl), 1623 (5 member hetero-cyclic ring), 1716.65 (mono substituted 6 membered ring), 850.61 (1, 3, 5 tri-substituted 6 member ring), 1367 (C-H), 1049.28 (C-N), 1680 (C=O), 3523.95 (O-H);
HPLC Experimental Parameters: Column specifications: Acclaim™ C-18, 5µ, 4.6 × 250mm; Wavelength: 200nm; Mobile phase: Acetonitrile: Methanol (90:10 v/v); Flow rate: 1ml/min; Column temperature: 28ºC; Injection volume: 20µL; Run time: 7mins; RF: 3.075



4d: - Yield 87.44%; yellowish amorphous solid; MP; 165°C Found: C, 56.70; H, 4.43, N, 9.42
IR (KBr) cm^{-1} 840.96 (C-Cl), 765.74 (mono substituted 6 membered ring), 850.61 (1, 3, 5 tri-substituted 6 member ring), 2891.30 (C-H), 1068.56 (C-N), 1068.56 (C-O), 1680 (C=O);
HPLC Experimental Parameters: Column specifications: Acclaim™ C-18, 5µ, 4.6 × 250mm; Wavelength: 200nm; Mobile phase: Acetonitrile: Methanol (90:10 v/v); Flow rate: 1ml/min; Column temperature: 28ºC; Injection volume: 20µL; Run time: 7mins; RF: 3.178



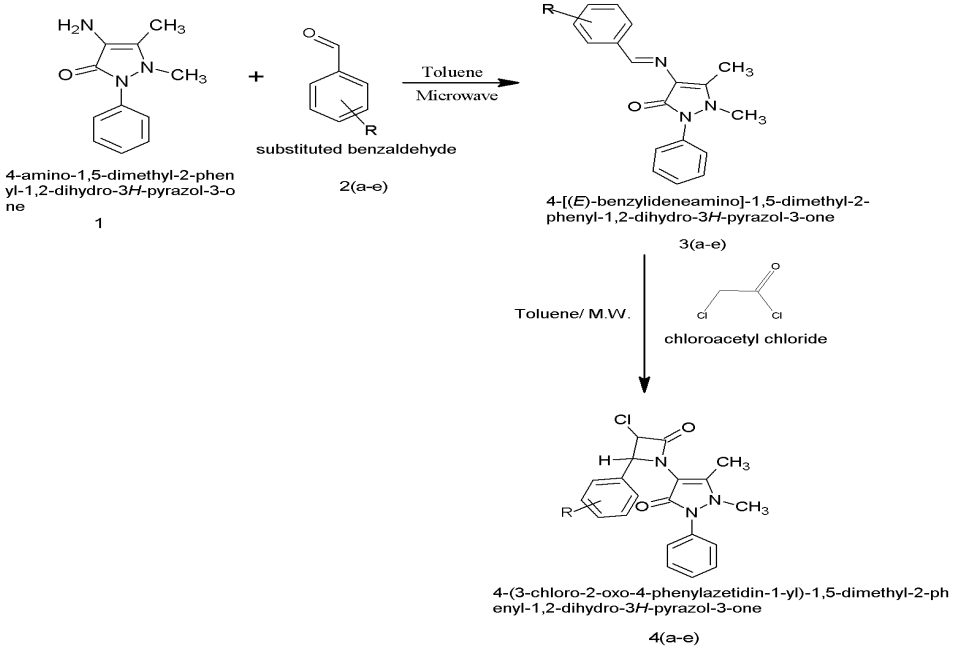
4e:- Yield 88.16%; White amorphous solid. MP; 181°C Found: C, 61.43; H, 5.11, N, 8.50
IR (KBr) cm^{-1} 837.11 (C-Cl), 1614.42 (5 member hetero-cyclic ring), 702.69 (mono substituted 6 membered ring), 837.11 (1, 2, 4, 5 substituted 6 membered ring), 2872.01 (C-H), 1045.42 (C-N), 1070.49 (C-O);
HPLC Experimental Parameters: Column specifications: Acclaim™ C-18, 5µ, 4.6 × 250mm; Wavelength: 200nm; Mobile phase: Acetonitrile: Methanol (90:10 v/v); Flow rate: 1ml/min; Column temperature: 28ºC; Injection volume: 20µL; Run time: 7mins; RF: 2.816



1.1.3. ANTIOXIDANT ASSAY:

Antioxidant activity of the test compounds was determined by Diphenylpicrylhydrazyl (DPPH) radical scavenging method [8]. All the synthesized test compounds were screened for their antioxidant activity by DPPH radical scavenging assay. Butyrated Hydroxy Toluene (BHT) was taken as standard. The concentrations of the sample were 0.5, 0.75 and 1.0 ppm. All the absorbance was recorded 517nm. The test compounds such as 4a, 4b, 4c, 4d and 4e showed IC50 at 0.9055, 1.424, 0.4035, 0.8964 and 1.105 ppm respectively.
Percentage inhibition= [(Absorbance of Control- Absorbance of Sample) / Absorbance of Control] * 100

2.1.4. Table 1: Schematic Representation of Titled Compounds



III. OBSERVATIONS

3.1 Table 2: Comparative table between Conventional Method & Microwave Irradiation Method.

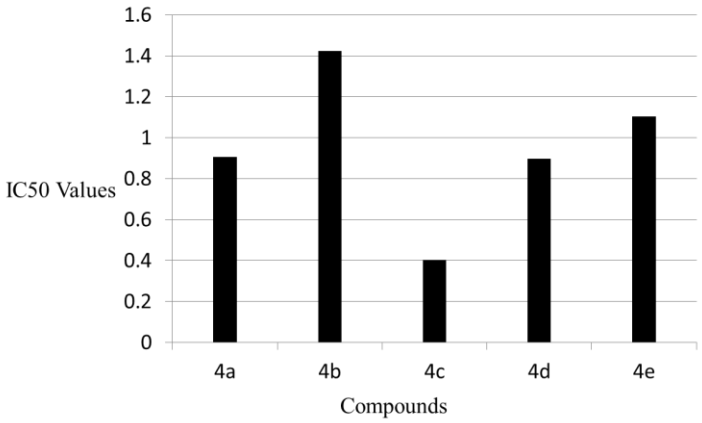
Comp.	R	M.P (ºC)	Time (Hrs.)		Yield (%)		% Composition		
			Conventional	MW	Conventional	MW	C	H	N
4a	4-F	170	23	0.58	51.65	82.37	C:62.20	4.40	10.89
							F:62.60	4.80	10.49
4b	4-Cl	176	24	0.58	49.12	84.23	C:59.66	4.23	10.44
							F:59.26	4.63	10.84
4c	3, 4- DiOH	155	26	0.66	54.23	88.97	C:60.02	4.50	10.51
							F:60.42	4.90	10.91
4d	4-OH -3-OCH_3	165	24	0.63	51.98	87.44	C:61.70	4.14	9.82
							F:56.70	4.43	9.42
4e	3, 4, 5-TriOCH_3	181	23	0.63	56.08	88.16	C:61.03	5.51	8.90
							F:61.43	5.11	8.50

Note:-C: Calculated, F: Found.

3.1 Table 3: Estimation of antioxidant activity of the compounds using DPPH

Compounds	4a	4b	4c	4d	4e
IC_{50} Values	0.9055	1.424	0.4035	0.8964	1.105

3.1 Table 3: Graph of IC_{50} values of synthesized compounds



IV. RESULTS

The yield of the product and the time required for the completion of the reaction in both the microwave assisted method and conventional method are showing strikingly that microwaves are going to be highly important in future synthesis of heterocycles. In the microwave assisted synthesis, the product increased by 55-75% and time of reaction was reduced drastically in all the reactions. After checking the purity of the compounds by analytical techniques such as HPLC, the structural elucidation was done with the help of Fourier Transformed Infrared Spectroscopy (FTIR). Each product showed the C-Cl stretching at range of 837-845cm^{-1} which confirms the presence of β- lactam ring. This confirms completion of the reaction. The compounds were screened for anti-oxidant property. The product had IC_{50} as low as 0.404ppm (µg/ml).

V. CONCLUSION

The research carried out focuses on two aspects those are comparison between microwave assisted and conventional way of synthesis of 4-Aminoantipyrine derivatives, the biological activity of the products formed. It is clearly observed that the microwave not only helps in increasing the yield in significant amount but it also reduces the reaction time to a greater extent. The microwave required fewer amounts of solvent compared to conventional method. The compounds were found to have substantial amount of anti-oxidant property.

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