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Research Article

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A convenient synthesis and characterization of some novel cynopyridines containing substituted benzyloxy phenyl ring system by microwave irradiation

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Abstract

A convenient microwave induced synthesis of cyanopyridine derivatives are obtained by the reaction of substituted chalcone with malononitrile in presence of ammonium acetate under microwave irradiation. [1]The synthesized compounds were characterized by their IR, [1]H NMR, mass spectral data and elemental analysis. The method has several advantages in comparison with conventional synthesis including clean reaction procedure, easy workup, and short reaction time giving excellent yields of product.

Keywords: Chalcones, Cynopyridine, Basic alumina, Benzyloxy phenyl ring, Microwave irradiation.

Introduction

The use of microwaves in organic synthesis (Microwave Induced Organic Reaction Enhancement (MORE))[2-3] has increased dramatically in the last years, receiving widespread acceptance and becoming an indispensable tool. In organic synthesis microwave technology has become a powerful tool, since by employing this technique it is generally possible to prepare organic compounds very fast, with better yields and high purity compared to other more conventional methods. Substituted pyridine derivative like cyanopyridines have found to possess a broad spectrum of biological activity such as potential antihypertensive, [4]arthropodicidal, antimicrobial,[5] antitubercular,[6] anti-inflammatory,[7] antitumor,[8] cardiovascular agents,[9] antiviral,[10] CNS depresant,[11] antipyretic properties,[12] IKK-β inhibitor properties[13] and antifungal[14]. Pyridine is also used as a denaturant for antifreeze mixtures as dying assistant in textiles and in fungicides. Therefore we focused on synthesis of some cynopyridine system.

In this paper we report the synthesis of some cynopyridine derivatives containing substituted benzyloxy phenyl ring system.

Materials and Methods

Experimental Section:- Melting points were determined in an open capillary tube and are uncorrected. IR spectra (ν_{max} in $cm^{-1,}$ KBr) were recorded on a Perkin-Elmer 16pc (FTIR) spectrophotometer. Mass spectra were taken on a Jeol D-300 (EI) and VG-70S mass spectrometer and ^{1}H NMR was recorded on $CDCl_3$ on a Varian CFT-20 or Brucker DRX-300 (300MHz) spectrometer using TMS as internal standard (chemical shifts in δ, ppm). All compounds gave satisfactory elemental analysis and spectral data. All the reactions were carried out in a domestic microwave oven. (Kenstar, output energy 1200W, frequency 2450 MHz, model no. MO9706).

General procedure for the synthesis of 2-amino-6-(p-chlorophenyl)-4-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-3-cyanopyridine(C-I):-

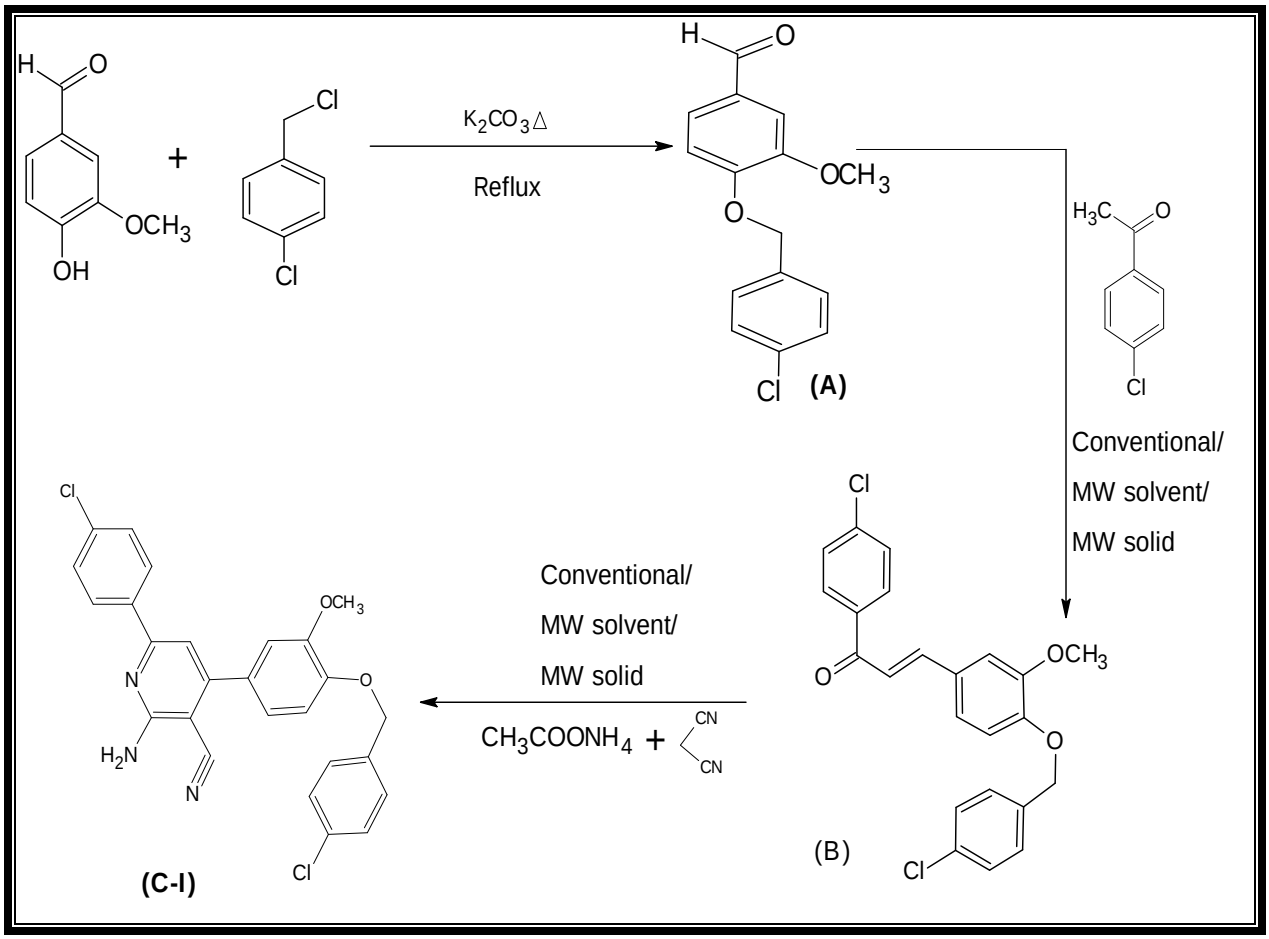
The synthesis of 1-(p-chlorophenyl)–3-[4'-(p-chlorobenzyloxy) -3'-methoxyphenyl]-propenone **(B)** was performed using 4-(p-Chlorobenzyloxy)-3-methoxybenzaldehyde **(A)** and 4'-chloroacetophenone using ethanol/alumina under microwave irradiation as reported. Further the cynopyridine derivatives were carried out by the three following methods:-

(a) Conventional (Classical) Method- A mixture of synthesized chalcone (0.01mol) and malononitrile (0.01mol), ammonium acetate (0.08mol) dissolved in ethanol (25mL) was refluxed for 8-10 hrs. Completion of reaction was monitored by TLC using benzene: ethyl acetate (9:1 v/v) as eluent. After completion of the reaction, the mixture is cooled, diluted with cold water and filtered. The separated solid was washed with water, dried and recrystallised with ethanol.

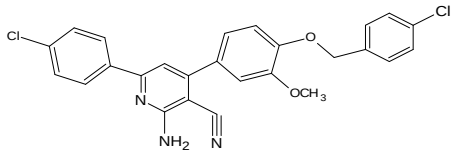
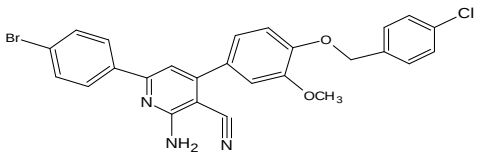
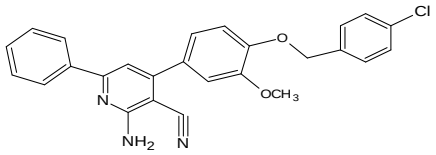
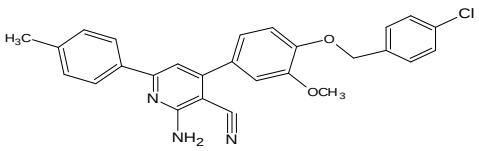
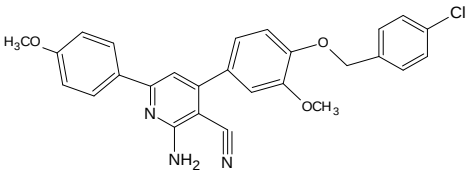
(b) Microwave Induced Solution Phase Method- Equimolar amounts (0.01mol) of synthesized chalcone and malononitrile and ammonium acetate (0.08mole) were dissolved in ethanol (15mL) in a borosil conical flask. The reaction mixture was subjected to microwave irradiation at 25% microwave power (300W) for 9-11 minutes with short interval of 20-30 sec. to avoid the excessive bumping and evaporation of solvent. After completion of the reaction (TLC), the mixture was cooled, diluted with water and filtered. The separated solid washed with water, dried and recrystallised with ethanol.

(c) Microwave Induced Solid Phase Method (Al_2O_3)- Equimolar amounts of (0.005mol) synthesized chalcone and malononitrile and ammonium acetate (0.04mole) was dissolved in ethanol (10-12mL) and the solution was adsorbed on basic alumina (5gm) in a small beaker. The mixture was mixed properly with help of glass rod, dried in air and irradiate inside the microwave oven at 50% (600W) power for 8-9 minutes. After the completion of the reaction (TLC), the product was extracted into hot ethanol (3x20mL). Removal of the solvent resulted the product which on recrystallisation with ethanol**.**

REACTION SCHEME



Molecular formula and structure of synthesized cynopyridine derivatives (C-I) to(C-V).

No.	Actophenone Derivatives	Substitute group	Molecular Formula of Synthesized Chalcones	Synthesized Cynopyridine Derivatives (C-I) to(C-V)
1	C_8H_7ClO	Cl	$C_{23}H_{18}Cl_2O_3$	$C_{26}H_{19}C_{l2}N_3O_2$ 
2	C_8H_7BrO	Br	$C_{23}H_{18}BrClO_3$	$C_{26}H_{19}BrClN_3O_2$ 
3	C_8H_8O	H	$C_{23}H_{19}ClO_3$	$C_{26}H_{20}ClN_3O_2$ 
4	$C_9H_{10}O$	CH_3	$C_{24}H_{21}ClO_3$	$C_{27}H_{22}ClN_3O_2$ 
5	$C_9H_{10}O_2$	OCH_3	$C_{24}H_{21}ClO_4$	$C_{27}H_{22}ClN_3O_3$ 

Physical characterization of synthesized cynopyridine derivatives (C-I) to(C-V).

Comp. No.	Molecular formula	M.W.	M.P. (°C)	Elemental analysis Calculated/ Found				
				% C	% H	% Cl	% O	N %
(C-I)	$C_{26}H_{19}Cl_2N_3O_2$	476.35 475.80	160	65.56 65.12	4.02 4.10	14.89 14.67	6.72 6.56	8.82 8.45
(C-II)	$C_{26}H_{19}BrClN_3O_2$	520.80 519.51	205	59.96 59.32	3.68 3.51	6.81 6.20	6.14 6.30	8.07 7.56
(C-III)	$C_{26}H_{20}ClN_3O_2$	441.90 440.01	178	70.67 69.98	4.56 4.12	8.02 7.79	7.24 7.10	9.51 9.31
(C-IV)	$C_{27}H_{22}ClN_3O_2$	455.93 454.73	149	71.13 70.83	4.86 4.38	7.78 7.34	7.02 7.18	9.22 8.98
(C-V)	$C_{27}H_{22}ClN_3O_3$	471.93 470.62	184	68.72 68.12	4.70 4.61	7.51 7.20	8.90 3.56	8.90 8.67

Experimental data of synthesized cynopyridine derivatives(C-I) to(C-V).

Comp. No.	Reaction Time			%Yield		
	Classical Method (*Hrs*)	MW Methods (*Min*)		Classical Method	MW Methods	
	(a)	(b)	(c)	(a)	(b)	(c)
(C-I)	8.5	9-10	8-10	59	81	87
(C-II)	10	9-11	9-10	62	80	86
(C-III)	9	8-10	8-9	68	78	88
(C-IV)	8.5	9-11	8-10	65	80	80
(C-V)	9.5	8-9	9-10	67	79	86

Spectral analysis of synthesized compounds

(C-I) 2-amino-6-(p-chlorophenyl)-4-[4'-(p-chloro benzyloxy)-3'-methoxyphenyl]-3-cyanopyridine:- IR ν max (KBr) cm^{-1} : 3360 (NH_2), 2203 (CN), 1586, 1511, 1473 (C=C/C=N), 846, 783 (SubstitutedPhenyl). ^1H NMR ($CDCl_3$, δppm):5.16 [s, 2H, OCH_2] , 5.26 [s, 2H, NH_2], 3.80 [s, 3H, OCH_3], 6.92-8.10 [m, 12H, Ar-H]. MS(m/z): 476$[M]^+$, 442$[C_{26}H_{20}ClN_3O_2]^+$,399$[C_{23}H_{20}ClO_2]^+$,354$[C_{22}H_{23}ClO_2]^+$,352$[C_{22}H_{21}ClO_2]^+$, 335$[C_{19}H_{14}ClN_3O]^+$,262$[C_{15}H_{15}ClO_2]^+$, 204$[C_{13}H_6N_3]^+$, 148$[C_{11}H_{17}]^+$, 140$[C_8H_9Cl]^+$, 126$[C_7H_7Cl]^+$, 124$[C_8H_{12}O]^+$, 119$[C_6H_5N_3]^+$.

(C-II)2-amino-6-(p-bromophenyl)-4-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-3-cyanopyridine:- IR ν max (KBr) cm^{-1} : 3352 (NH_2), 2201 (CN), 1594, 1505, 1465 (C=C/C=N), 823, 774 (Substituted Phenyl). ^1H NMR ($CDCl_3$, δppm): 5.18 [s, 2H, OCH_2], 5.30 [s, 2H, NH_2], 3.75 [s, 3H, OCH_3], 6.93-8.08 [m, 12H, Ar-H]. MS (m/z): 520$[M]^+$, 442$[C_{26}H_{20}ClN_3O_2]^+$, 486$[C_{26}H_{20}BrN_3O_2]^+$, 443$[C_{23}H_{20}BrClO_2]^+$,399$[C_{22}H_{23}BrO_2]^+$,397$[C_{22}H_{21}BrO_2]^+$, 380$[C_{19}H_{14}N_3O]^+$, 262$[C_{15}H_{15}ClO_2]^+$, 204$[C_{13}H_6N_3]^+$,185$[C_8H_9Br]^+$,148$[C_{11}H_{17}]^+$,126$[C_7H_7Cl]^+$,124$[C_8H_{12}O]^+$, 119$[C_6H_5N_3]^+$.

(C-III) 2-amino-6-phenyl-4-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-3-cyanopyridine:- IR ν max (KBr) cm^{-1} : 3328 (NH_2), 2215 (CN), 1593, 1502, 1457(C=C/C=N),833, 785(Substituted Phenyl). ^1H NMR ($CDCl_3$, δppm):5.21 [s, 2H, OCH_2] , 5.28 [s, 2H, NH_2], 3.78 [s, 3H, OCH_3], 6.95-8.11 [m, 13H, Ar-H].. MS (m/z) : 442$[M]^+$, 407$[C_{26}H_{21}N_3O_2]^+$, 364$[C_{23}H_{21}ClO_2]^+$, 318$[C_{22}H_{22}O_2]^+$, 301$[C_{19}H_{15}N_3O]^+$, 262$[C_{15}H_{15}ClO_2]^+$, 204$[C_{13}H_6N_3]^+$, 148$[C_{11}H_{17}]^+$, 126$[C_7H_7Cl]^+$, 124$[C_8H_{12}O]^+$, 119$[C_6H_5N_3]^+$, 106$[C_8H_{10}]^+$.

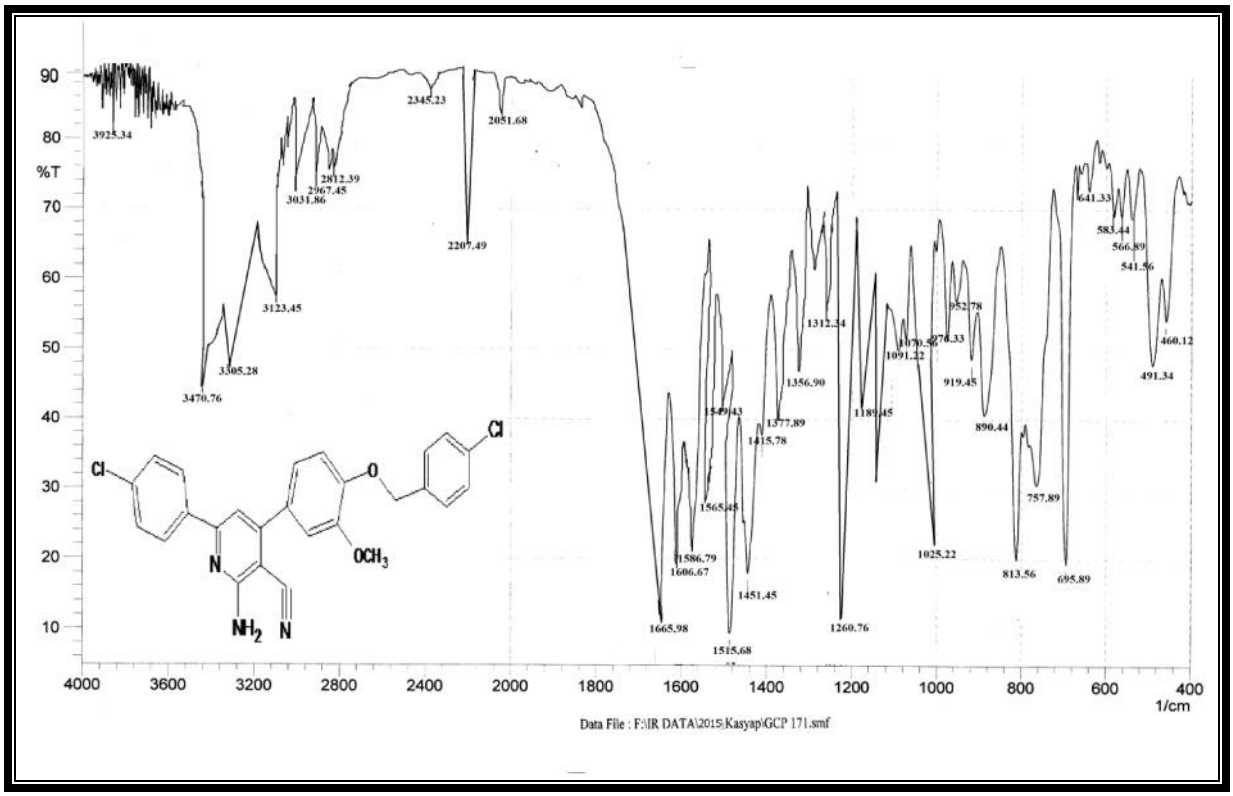
(C-IV)2-amino-6-(p-methylphenyl)-4-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-3-cyanopyridine:- IR ν max (KBr) cm^{-1} : 3351 (NH_2), 2207 (CN), 1598, 1513, 1451 (C=C/C=N), 835, 804 (Substituted Phenyl). ^1H NMR ($CDCl_3$, δppm): 5.19 [s, 2H, OCH_2], 5.25 [s, 2H, NH_2], 2.33 [s, 3H, CH_3], 3.78 [s, 3H, OCH_3], 6.86-8.05 [m, 12H, Ar-H].MS (m/z) : 456$[M]^+$, 442$[C_{26}H_{20}ClN_3O_2]^+$, 421$[C_{27}H_{23}N_3O_2]^+$, 378$[C_{24}H_{23}ClO_2]^+$, 334$[C_{23}H_{22}O_2]^+$, 332$[C_{23}H_{24}O_2]^+$, 315$[C_{20}H_{17}N_3O]^+$, 262$[C_{15}H_{15}ClO_2]^+$, 204$[C_{13}H_6N_3]^+$, 148$[C_{11}H_{17}]^+$, 126$[C_7H_7Cl]^+$, 124$[C_8H_{12}O]^+$, 120$[C_9H_{12}]^+$, 119$[C_6H_5N_3]^+$.

(C-V)2-amino-6-(p-methoxyphenyl)-4-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-3-cyanopyridine :- IR ν max (KBr) cm^{-1} : 3325 (NH_2), 2208 (CN), 1583, 1512, 1453 (C=C/C=N), 829, 739 (Substituted Phenyl). ^1H NMR ($CDCl_3$, δppm):5.20 [s, 2H, OCH_2], 5.31 [s, 2H, NH_2], 3.85 [s, 3H, OCH_3], 3.93 [s, 3H, OCH_3], 6.97-8.00 [m, 12H, Ar-H]. MS (m/z) : 471$[M]^+$, 442$[C_{26}H_{20}ClN_3O_2]^+$, 437$[C_{27}H_{23}N_3O_3]^+$, 395$[C_{24}H_{23}ClO_3]^+$, 348$[C_{23}H_{24}O_3]^+$, 346$[C_{23}H_{22}O_3]^+$, 331$[C_{20}H_{17}N_3O_2]^+$, 262$[C_{15}H_{15}ClO_2]^+$, 204$[C_{13}H_6N_3]^+$, 148$[C_{11}H_{17}]^+$, 136$[C_9H_{12}O]^+$, 126$[C_7H_7Cl]^+$, 124$[C_8H_{12}O]^+$, 119$[C_6H_5N_3]^+$.

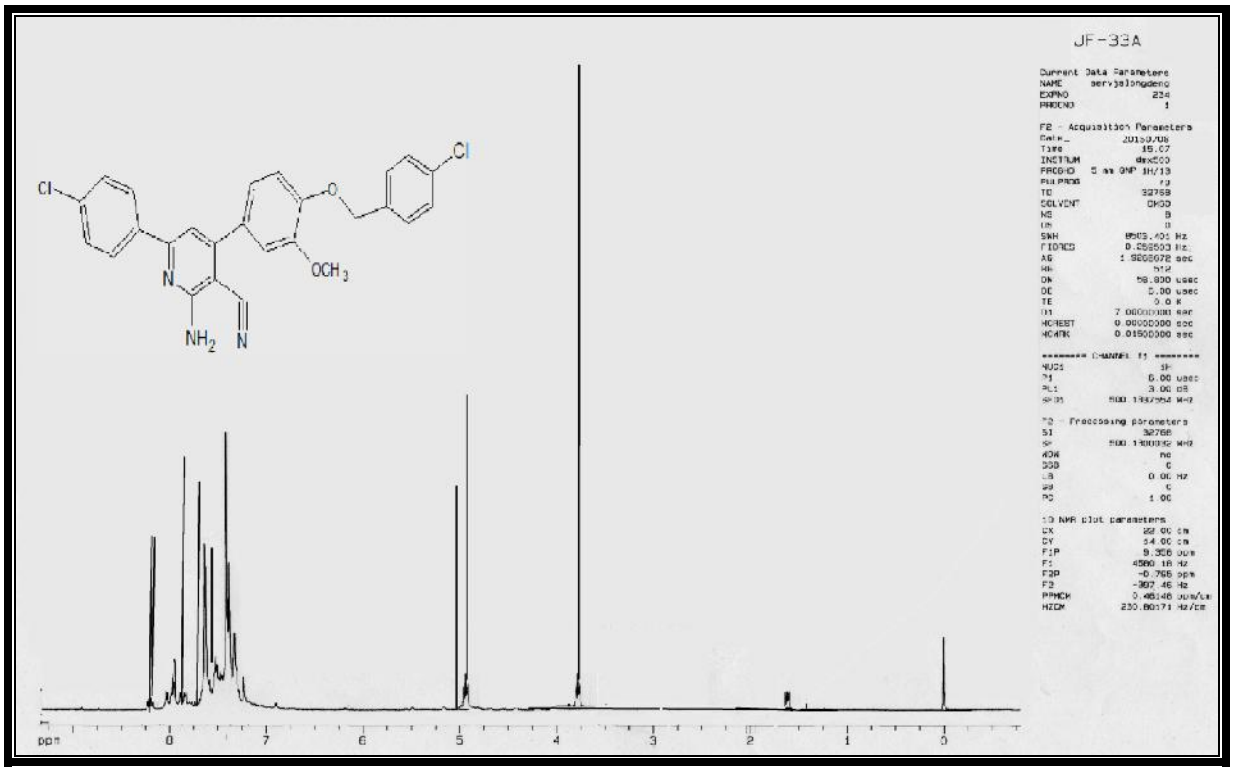
Results and Discussion

Reported synthesis of substituted 2-amino-3-cyanopyridines derivatives are obtained by refluxing synthesized chalcone with malononitrile in presence of ammonium acetate under microwave irradiation. In view of theses, we reported synthesis of novel cynopyridine derivatives containing benzyloxypheny ring system under microwave irradiation. Microwave irradiation has been used to accelerate organic reactions because of high heating efficiency, providing remarkable rate enhancement, dramatic reduction in reaction times with improvement in yield and quality of products. Reactions that require hours or even days by conventional heating can often be accomplished in second or minutes by microwave heating.[15]This technique has several advantages including clean reaction procedure, no need of catalyst, short reaction time and high yields of product. The obtained derivatives were characterized using spectroscopic technique, In IR spectra the disappearance of band 1660-1640 cm^{-1} due to carbonyl group of chalcones and appearance of characteristic strong absorption band in the region of 2215-2201 cm^{-1} due to –CN group conformed the formation of product. The NH_2 group was observed at 3360-3325 cm^{-1} and 1545-1510 cm^{-1} due to the stretching and bending vibration respectively. The PMR spectra showed a characterstic broad singlet around δ 5.20-5.30 due to two proton of – NH_2. Aromatic proton appeared as multiple at δ 6.80-8.10. The mass spectral fragments of agree with the assigned structures. The molecular ion peak values are in conformity with the molecular weight of the proposed structure. The mass spectral fragments of agree with the assigned structures. The molecular ion peak values are in conformity with the molecular weight of the proposed structure.

IR SPECTRUM OF 2-AMINO-6-(P-CHLOROPHENYL)-4-[4'-(P-CHLOROBENZYLOXY)-3'-METHOXYPHENYL]-3-CYANOPYRIDINE (C-I)



NMR SPECTRA OF 2-AMINO-6-(P-CHLOROPHENYL)-4-[4'-(P-CHLOROBENZYLOXY)-3'-METHOXYPHENYL]-3-CYANOPYRIDINE (C-I)



Conclusion

In summary we reported the synthesis of novel cynopyridine derivatives containing benzyloxy phenyl ring system. Microwave induced Solution Phase/solid phase methods found to be excellent and convenient reaction route in terms of simple reaction procedure, quick reaction time giving percent yield of product as compared to conventional method.

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