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A convenient one-pot synthesis of series of 3-(2,6-diphenyl-4-pyridyl)hydroquinolin-2-one under microwave irradiation and their antimicrobial activities

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A series of 3-(2,6-diphenyl-4-pyridyl)hydroquinolin-2-one **4a-x** compounds are synthesized in high yields by one pot cyclocondensation reactions under Krohnke's reaction conditions using 2-chloro-3-formyl quinoline **1a-d,** various acetophenone **2a-f,** *N*-phenacylpyridinium chloride **3** in the mixture of ammonium acetate and acetic acid by microwave irradiation. All the compounds have been characterized by elemental analysis, FT- IR, ^{1}H and ^{13}C NMR, and mass spectral analysis. These compounds have been screened for their antimicrobial activities.

Keywords: Microwave irradiation, 2-chloro-3-formyl quinoline, acetophenone, *N*-phenacylpyridinium chloride, Krohnke's reaction condition

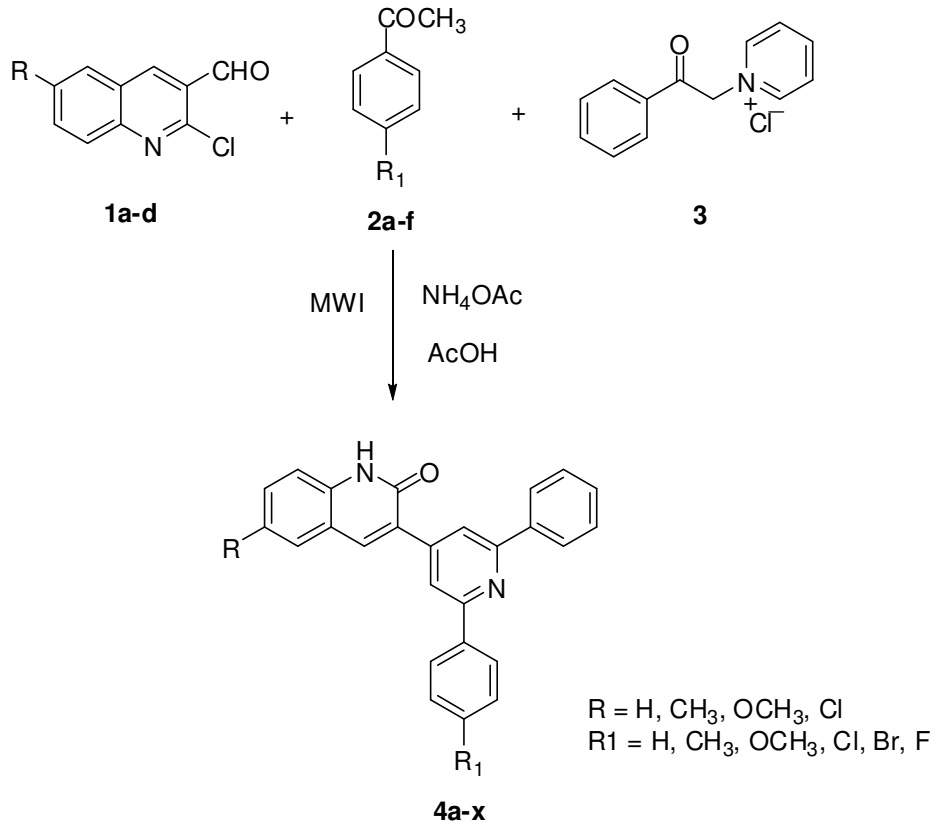
Polysubstituted pyridines have been synthesized using an enormous number of preparative approaches such as Hantzsch synthesis from a 1,5-diketone and a nitrogen derivatives[1,2], cyclization of chalcones and iminophosphoranes[3], reactions of unsaturated imines with enolates[4] and cyclization of α,β-unsaturated compounds with α-substituted ketones and a nitrogen source[5]. Among these approaches, the later approach is the most frequently employed. The two-step Krohnke synthesis[6-8] *via* condensation of α,β-unsaturated ketones with pyridinium salts in the presence of a mixture of ammonium acetate and acetic acid gives a variety of polysubstituted pyridines and has distinct advantages over the other routes. Multicomponent reactions (MCRs) offer significant advantages and are increasingly important in organic and medicinal chemistry. Chao-Guo Yan and his coworkers have described a simple but effective modification of the Krohnke's synthesis of pyridines in one-pot reactions of *N*-phenacylpridinium bromide with aromatic aldehydes and cyclic ketones under microwave irradiation to give annulated pyridine derivatives. Literature survey reveals that number of pyridine derivatives have been synthesized by krohnke reaction conditions using various aldehyde but not a single reference have been found where 2-chloro-3-formyl quinoline is used. We wish to report herein this heterocyclic aldehyde which is biologically active[9,10] with a view to obtain more active heterocyclic systems containing two biologically active moieties quinolines[11,12] and pyridine[13,14] by microwave irradiation.

Microwave irradiation is very attractive for chemical applications and has become a widely accepted non-conventional energy source for performing organic synthesis[15,16]. Compared with classical heating, microwave assisted organic synthesis is characterized by spectacular acceleration, higher yields, milder reaction conditions and shorter reaction times as well as allowing synthesis to become environmentally benign, improving many processes[17,18].

Results and Discussion

Under microwave irradiation, 2-chloro-3-formyl quinoline **1a-d**, acetophenone **2a-f,** *N*-phenacylpyridinium chloride **3** in the presence of ammonium acetate and acetic acid reacted smoothly to give **4a-x (Scheme I)** in high yield(82-92%, **Table I).** The required 2-chloro-3-formyl quinoline **1a-d** was prepared by Vilsmeier-Haack reaction[19] and *N*-phenacylpyridinium chloride **3** was prepared by literature procedure[20].

The formation of compounds **4a-x** involves the Krohnke mechanism **(Scheme II).** The reaction is homogeneous and proceeds *via* formation of 3-formyl-2(1*H*)-quinolones[21] from 2-chloro-3-formyl quinoline **1a-d** in the presence of the acetic acid and



Scheme I

then it reacts with acetophenone **2a-f** to form α,β-unsaturated ketone, which is reacted with *N*-phenacylpyridinium chloride **3** to give 1,5-diketone derivatives, then cyclized with ammonia and finally pyridine cation is eliminated with the formation of 3-(2,6-diphenyl-4-pyridyl)hydroquinolin-2-one **4a-x**[22-24]. The structure of compounds **4a-x** were confirmed by IR, ^{1}H NMR , ^{13}C NMR and mass spectra. IR spectra of compound **4c** exhibited absorptions at 3156 for (–NH), 3010 for (aromatic C=H stretching), 1655 for (carbonyl group) and 1400-1600 cm^{-1} for (C=C aromatic and C=N ~~of~~ stretching of pyridine). The ^{1}H NMR of compound **4c** showed singlet at δ 12.10 for (–NH) proton which is D_2O exchangeable, it also showed singlet at 3.85 for (-OCH_3) and aromatic protons resonate as multiplets at 7.25-8.60. The ^{13}C NMR spectrum of compound **4c** showed signals at δ 55.73 for aliphatic carbon and 114.62-160.72 for aromatic carbon, the carbonyl carbon was observed at δ 161.10. The structure was further confirmed by its mass spectral studies. It gave molecular ion peak at *m/z* 405 (M+1) corresponds to molecular formula $C_{27}H_{20}N_2O_2$ **(Scheme I)**. All the compounds were screened for their antibacterial and antifungal activities using ciprofloxacin, ampicillin and griseofulvin as standard drugs.

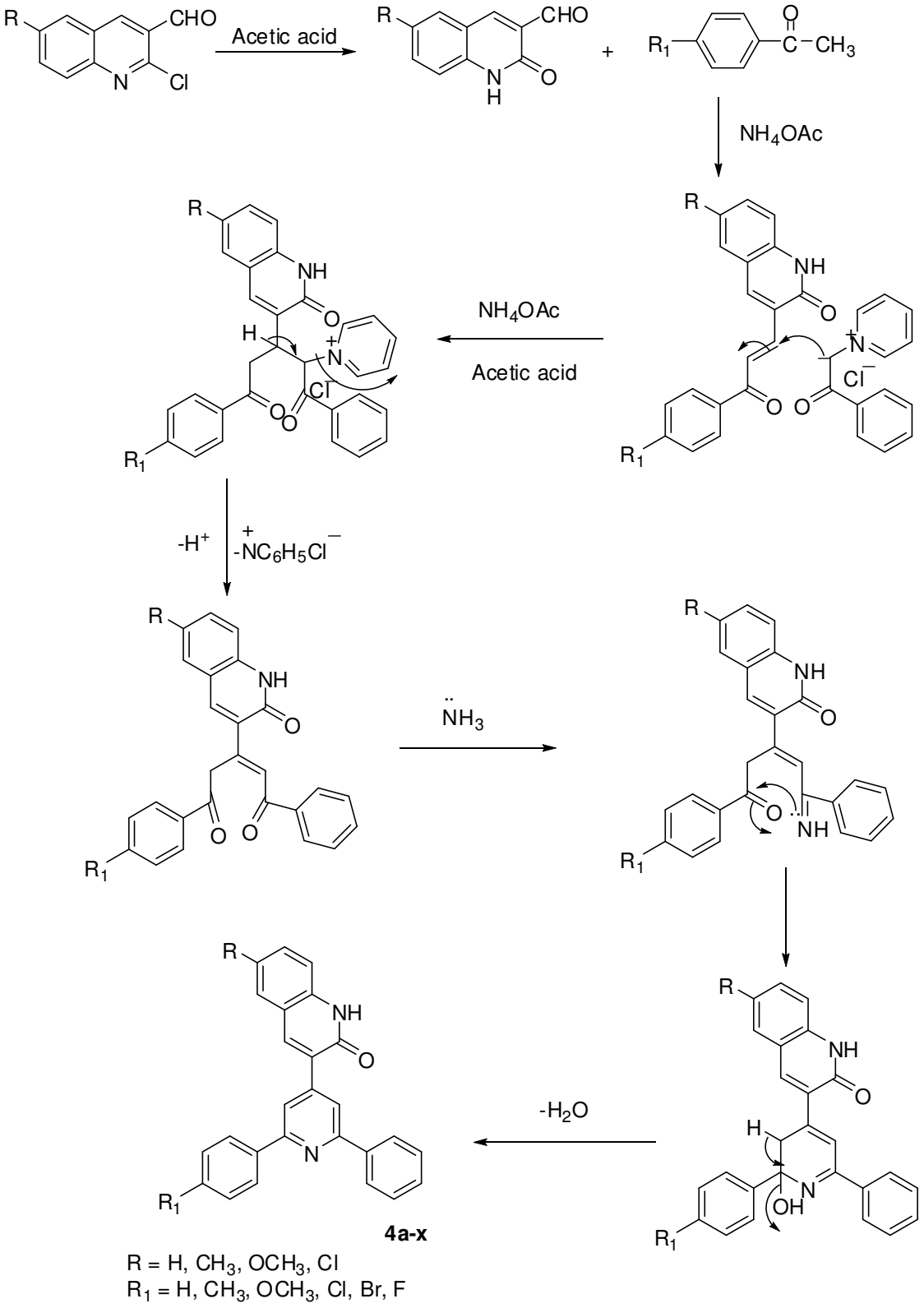
Evaluation of antimicrobial activity

The *in vitro* antimicrobial activity was carried out against 24 hr old cultures of three bacteria and two fungi by disc-diffusion method[25,26]. Compounds **4a-x** have been tested for their antibacterial activity against *Escherichia coli* as Gram-negative bacteria and *Becillus substilis* and *Staphylococcus aureus* as Gram-positive bacteria and antifungal activity against *Aspergillus Niger* and *Rhizopus.*

Nutrient agar and potato dextrose agar were used to culture the bacteria and fungus respectively. The compounds were tested at a concentration of 1000 μg/mL in DMF solution. Ciprofloxacin, ampicillin and griseofulvin were used as standards for comparison of antibacterial and antifungal activities respectively. Inhibition was recorded by measuring the diameter of the inhibition zone at the end of 24 hr for bacteria at 35°C and 48 h. for fungus at 28°C. The protocols are summarized in **Table II**.

Table I — Physical and analytical data of compounds **4a-x**

Compd	R	R_1	Yield (%)	m.p.(°C)	Mol. Formula (Mol. wt)	Colour	Found (Calcd) %		
							C	H	N
4a	H	H	92	279-80	$C_{26}H_{18}N_2O$ (374.44)	pale yellow	83.42 (83.40	4.80 4.84	7.44 7.48)
4b	H	CH_3	88	268	$C_{27}H_{20}N_2O$ (388.47)	white	83.42 (83.48	5.23 5.18	7.23 7.21)
4c	H	OCH_3	90	285	$C_{27}H_{20}N_2O_2$ (404.47)	pale yellow	80.3 (80.17	4.95 4.98	6.96 6.92)
4d	H	Cl	84	281-82	$C_{26}H_{17}ClN_2O$ (408.88)	white	76.33 (76.37	4.16 4.19	6.88 6.85)
4e	H	Br	86	283-84	$C_{26}H_{17}BrN_2O$ (453.34)	off-white	68.82 (68.88	3.83 3.78	6.13 6.17)
4f	H	F	85	295	$C_{26}H_{17}FN_2O$ (392.43)	pale yellow	79.64 (79.57	4.31 4.36	7.10 7.13)
4g	CH_3	H	91	280	$C_{27}H_{20}N_2O$ (388.47)	white	83.43 (83.48	5.22 5.18	7.17 7.21)
4h	CH_3	CH_3	82	289-90	$C_{28}H_{22}N_2O$ (402.49)	white	83.53 (83.55	5.46 5.50	7.02 6.96)
4i	CH_3	OCH_3	90	246-47	$C_{28}H_{22}N_2O_2$ (418.49)	white	80.40 (80.36	5.26 5.29	6.67 6.69)
4j	CH_3	Cl	80	>300	$C_{27}H_{19}ClN_2O$ (422.91)	yellow	76.65 (76.68	4.59 4.52	6.56 6.62)
4k	CH_3	Br	88	299-300	$C_{27}H_{19}BrN_2O$ (467.36)	white	69.33 (69.38	4.02 4.09	6.05 5.99)
4l	CH_3	F	85	>300	$C_{27}H_{19}FN_2O$ (406.46)	off-white	79.72 (79.78	4.75 4.71	6.84 6.89)
4m	OCH_3	H	90	>300	$C_{27}H_{20}N_2O_2$ (404.47)	yellow	80.21 (80.17	4.94 4.98	6.85 6.92)
4n	OCH_3	CH_3	86	220	$C_{28}H_{22}N_2O_2$ (418.49)	white	80.32 (80.36	5.26 5.29	6.74 6.69)
4o	OCH_3	OCH_3	88	195	$C_{28}H_{22}N_2O_3$ (434.49)	yellow	77.35 (77.40	5.07 5.10	6.46 6.44)
4p	OCH_3	Cl	82	>300	$C_{27}H_{19}ClN_2O_2$ (438.91)	grey	73.86 (73.88	4.40 4.36	6.33 6.38)
4q	OCH_3	Br	86	>300	$C_{27}H_{19}BrN_2O_2$ (483.36)	pale yellow	67.02 (67.09	4.00 3.96	5.75 5.79)
4r	OCH_3	F	80	>300	$C_{27}H_{19}FN_2O$ (422.46)	yellow	76.78 (76.76	4.48 4.53	6.59 6.63)
4s	Cl	H	85	>300	$C_{26}H_{17}ClN_2O$ (408.88)	off-white	76.32 (76.37	4.22 4.19	6.81 6.85)
4t	Cl	CH_3	83	299-300	$C_{27}H_{19}ClN_2O$ (422.91)	off-white	76.64 (76.68	4.56 4.52	6.57 6.62)
4u	Cl	OCH_3	86	265	$C_{27}H_{19}ClN_2O_2$ (438.91)	off-white	73.85 (73.88	4.32 4.36	6.44 6.38)
4v	Cl	Cl	85	292	$C_{26}H_{16}Cl_2N_2O$ (443.33)	pale yellow	70.42 (70.44	3.65 3.63	6.27 6.31)
4w	Cl	Br	90	>300	$C_{26}H_{16}BrClN_2O$ (487.78)	pale yellow	64.10 (64.02	3.26 3.30	5.79 5.74)
4x	Cl	F	88	>300	$C_{26}H_{16}ClFN_2O$ (426.87)	pale yellow	73.18 (73.15	3.73 3.77	6.53 6.56)


Acetic acid
NH4OAc
NH4OAc
Acetic acid
-H+
-NC6H5Cl+
NH3
-H2O
4a-x
R = H, CH3, OCH3, Cl
R1 = H, CH3, OCH3, Cl, Br, F

Scheme II

Table II — Antimicrobial activity of compounds **4a-x**

Compd	Inhibition Zone(in mm)				
	E. coli	*B. substilis*	*S. aureus*	*Rhizo-pus*	*A. niger*
4a	17	19	13	21	11
4b	15	20	14	18	13
4c	18	14	13	16	**19**
4d	16	16	15	15	17
4e	17	15	19	20	14
4f	19	21	15	16	15
4g	25	20	**21**	15	11
4h	18	**22**	16	14	--
4i	24	13	13	17	17
4j	23	11	14	18	16
4k	22	12	12	15	17
4l	25	13	12	18	16
4m	25	16	13	16	12
4n	**26**	17	15	15	13
4o	24	21	14	17	9
4p	21	21	14	15	**18**
4q	23	17	13	15	14
4r	**26**	17	14	14	17
4s	24	19	17	19	14
4t	**26**	21	15	18	15
4u	24	11	12	20	10
4v	23	12	10	**24**	15
4w	**26**	10	11	17	14
4x	24	12	11	14	12
Ciprofloxacin	**35**	**37**	**34**	**----**	**----**
Ampicillin	**31**	**33**	**33**	**----**	**-----**
Griseofulvin	**---**	**---**	**----**	**28**	**21**

Experimental Section

All melting points were taken in open capillaries and are uncorrected. The purity of the compounds were checked by TLC. Elemental analysis (% C, H, N) was carried out by Perkin-Elmer 2400 CHN elemental analyzer. IR spectra were recorded on a Shimadzu FTIR 8401 spectrophotometer in KBr. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer using solvent peak as internal standard. Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer. The microwave oven (700W) used was modified microwave oven (RAGA's electromagnetic systems).

Preparation of 3-(2,6-Diphenyl-4-pyridyl)hydro-quinolin-2-one 4a-x

General procedure: 2-Chloro-3-formyl quinoline (0.0026 mole, 0.5 g), acetophenone (0.0026 mole, 0.32g), *N*-phenacylpyridinium chloride (0.0026 mole, 0.59 g), ammonium acetate (0.026 mole, 2.0g) and acetic acid (5 mL) were charged in a 25 mL round bottom flask. The flask was heated for 3-5 min at 118°C under microwave irradiation (at 420W). The reaction was monitored by TLC, after the completion of reaction, the reaction mixture was cooled to RT and stirred for 30 min and the resulting solid was collected by filtration and washed with water. The crude product was purified by leaching in equimolar mixture of chloroform and methanol to obtain the pure solid sample **4a-x**.

Spectral Data

3-(2,6-Diphenyl-4-pyridyl)hydroquinolin-2-one 4a IR(KBr): 3150 (N-H stretching), 3005 (aromatic C-H stretching), 1660 (>C=O stretching), 1400-1620 cm^{-1} (C=C aromatic and C=N stretching of pyridine); ^{1}H NMR (DMSO-d_6): δ 7.25-8.60 (17H, m, Ar-H), 12.14 (1H, s, NH); ^{13}C NMR: δ 115.41, 118.54, 118.88, 119.78, 122.65, 127.27, 129.07, 129.27, 129.37, 129.64, 131.63, 139.39, 140.19, 146.38, 156.25, 161.17.

3-[2-(4-Methylphenyl)-6-phenyl-4-pyridyl]-hydroquinolin-2-one 4b IR(KBr): 3150 (N-H stretching), 3000 (aromatic C-H stretching), 3020 (methyl C-H stretching), 1650 (>C=O stretching), 1400-1600 cm^{-1} (C=C aromatic and C=N stretching of pyridine); ^{1}H NMR (DMSO-d_6): δ 7.2-8.5 (16H, m, Ar-H), 12.12 (1H, s, NH), 2.4 (3H, s, -CH_3); ^{13}C NMR: δ 20.80, 114.60, 115.35, 118.05, 118.14, 119.75, 122.60, 127.22, 128.50, 129.24, 129.46, 129.55, 131.54, 131.85, 139.38, 139.54, 140.03, 140.20, 146.20, 156.02, 156.08, 160.70, 161.15.

3-[2-(4-Methoxyphenyl)-6-phenyl-4-pyridyl]-hydroquinolin-2-one 4c IR (KBr): 3156 (N-H stretching), 3010 (aromatic C-H stretching), 1655 (>C=O stretching), 1400-1600 cm^{-1} (C=C aromatic and C=N stretching of pyridine); ^{1}H NMR (DMSO-d_6): δ 7.10-8.57 (16H, m, Ar-H), 12.10 (1H, s, NH), 3.85 (3H, s, -OCH_3); ^{13}C NMR: δ 55.73, 114.62, 115.39, 118.03, 118.11, 119.78, 122.63, 127.22, 128.60, 129.05, 129.23, 129.54, 131.56, 131.86, 139.35, 139.50, 140.04, 140.21, 146.24, 156.00, 156.03, 160.72, 161.17; Mass: *m/z* : 405 (M+1).

3-[2-(4-Methoxyphenyl)-6-phenyl(4-pyridyl)]-6-methylhydroquinolin-2-one 4i IR (KBr): 3155 (N-H stretching), 3005 (aromatic C-H stretching), 3025 (methyl C-H stretching), 1660 (>C=O stretching), 1410-1610 cm^{-1} (C=C aromatic and C=N stretching of

pyridine); ^{1}H NMR (DMSO-d_6): δ 7.10-8.4 (15H, m, Ar-H), 12.12 (1H, s, NH), 3.8 (3H, s, CH_3), 2.3 (3H,s, CH_3); ^{13}C NMR: δ 20.93, 55.72, 114.60, 115.32, 118.03, 118.10, 119.74, 122.52, 127.21, 128.42, 128.59, 129.22, 129.44, 129.52, 131.52, 131.87, 132.85, 137.41, 139.52, 139.78, 146.35, 156.00, 160.71, 161.07; Mass: *m/z* : 419 (M+1).

3-[2,6-Diphenyl(4-pyridyl)-6-chlorohydroquinolin-2-one 4s IR (KBr): 3160 (N-H stretching), 3000 (aromatic C-H stretching), 1665 (>C=O stretching), 1405-1600 cm^{-1} (C=C aromatic and C=N stretching of pyridine), 690 (C-Cl stretching); ^{1}H NMR (DMSO-d_6): δ 7.20-8.50 (16H, m, Ar-H), 12.14 (1H, s, NH); ^{13}C NMR: δ 114.55, 115.38, 118.85, 119.75, 122.67, 127.30, 129.00, 129.25, 129.35, 129.60, 131.61, 139.36, 140.21, 146.32, 156.22, 161.15.

3-[2-(4-Bromophenyl)-6-phenyl(4-pyridyl)]-6-methoxyhydroquinolin-2-one 4q IR (KBr): 3150 (N-H stretching), 3010 (aromatic C-H stretching), 1655 (>C=O stretching), 1400-1600 (C=C aromatic and C=N stretching of pyridine), 1040 (sym. stretching of –OCH_3), 560 cm^{-1} (C-Br stretching); ^{1}H NMR (DMSO-d_6): δ 7.25-8.40 (16H, m, Ar-H), 12.10 (1H, s, NH); ^{13}C NMR: δ 55.75, 114.60, 115.32, 118.08, 118.15, 119.72, 122.60, 127.25, 128.63, 129.08, 129.26, 129.50, 131.52, 131.82, 139.37, 139.52, 140.00, 140.24, 146.20, 156.03, 156.08, 160.75, 161.19.

Conclusion

A simple and efficient one-pot procedure has followed for generation of polysubstituted pyridines with microwave assistance. The advantages of this approach is that the reaction procedure is convenient, involves simple experimental procedures and product isolation is easy. Hence it is a useful modification and addition to the existing methods. It is one-pot reaction which allows the construction of relatively complicated nitrogen containing heterocyclic systems using simple starting materials. This method allows the introduction of various substituted alkyl and aryl groups into the 2-,4- and 6-positions of pyridine. It is worth mentioning that under microwave irradiation, all aromatic aldehydes and acetophenones those bearing electon-donating groups, form pyridine derivatives in high yields and those bearing electron-withdrawing groups, form pyridine derivatives in low yields. It can be concluded from **Table II** that among all the compounds **4t, 4w, 4n** and **4r** are highly active against bacteria *E. coli* while compound **4h** and **4g** exhibited highest activity against *B. substilis* and *S. aureus* respectively. The compound **4v** showed highest activity against fungus *Rhizopus* and compounds **4c** and **4p** showed highest activity against fungus *A. niger* while remaining compounds of the series were moderately active against microbes.

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