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Synthesis, Characterization and Antimicrobial Activity of Imidazole Derivatives Based on 2-chloro-7-methyl-3-formylquinoline

R. H. PARAB* and B. C. DIXIT

Chemistry Department, V.P. & R.P.T.P Science College, Vallabh Vidyanagar-388120, India
parabr@rocketmail.com

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Abstract: A series of oxazole and thereof imidazole derivatives were prepared from 2-chloro-7-methyl-3-formyl quinoline. The structures of all synthesized compounds were elucidated by elemental, IR, ^{1}HNMR, ^{13}CNMR spectra. Supplementary to these, they were assayed *in vitro* for their antimicrobial activity; it was revealed that some synthesized derivatives were exhibiting competent biological activity against both gram negative & gram positive bacterial species and fungal microorganisms.

Keywords: Quinoline, Imidazole, Antibacterial activity.

Introduction

Heterocyclic compounds of nitrogen containing five membered ring systems have been described for their biological activity against various micro organisms.[1,2] Besides this, the chemistry of quinoline and imidazoles have also been reviewed in literature. A number of derivatives of quinoline serve as valuable therapeutic agents.[1-5] Considerable interest has been created in the chemistry of quinoline derivatives due to their versatile therapeutic activities like bactericidal, antihistaminic, antimalarial, antidepressant, analgesic, anti-ulcer, antiviral, herbicidal, antitumor, anti-allergic, anticonvulsant, anti-inflammatory etc.[6-9] Almost every class of imidazole derivatives has been used for different reactions to produce enormous number of heterocycles. Later, in the last three decades many scientists have synthesized various imidazole heterocyclic precursors containing active hydrogen atom on nitrogen and evaluated in terms of their pharmacological activity.[10-15] The emergence of powerful and elegant imidazole has stimulated major advances in chemotherapeutic agents of remarkable significance in medicine, biology and pharmacy. Besides this, it is also reported[15-16] that imidazole compounds are one of the effective antifungal agents. Considering the importance of both moieties Quinoline and Imidazole, extending our previous work[17, 18] we planned to synthesize imidazole derivatives from 2-chloro-7-methyl-3-formylquinoline. The whole synthesis route is shown in scheme 1.

Material and Methods

Acetanilide and their derivatives were purified by crystallization in R-spirit. DMF and phosphorous oxychloride used were of analytical reagent grade. All of the organic solvents and Hippuric acid, acetic anhydride, sodium acetate used were of analytical reagent grade. Eight diamines were used after recrystallization. The 2-chloro-7-methyl-3-formyl quinoline was synthesized by Vilsmeier-Haack reaction by the procedure reported in the literature.[16,19] Melting points were measured in an open capillary tube and are uncorrected. Elemental analysis was obtained using Perkin Elmer (USA) 2400, series II CHN-analyser. In addition to this, the nitrogen content in all the imidazoles was estimated by Kjeldhal's method.[20] IR spectra were recorded on a NICOLET-400 D spectrophotometer, ^{1}H NMR spectra in $CDCl_3$/DMSO-d_6 at 400 MHz on a FT-NMR, R-1500 spectrometer (chemical shift in δ ppm) relative to TMS as an internal standard. Reactions were monitored by TLC, using silica gel as an adsorbent and ethyl acetate-hexane in different ratios as eluent.

Experimental

Synthesis of 2-chloro-7-methyl-3-formylquinoline

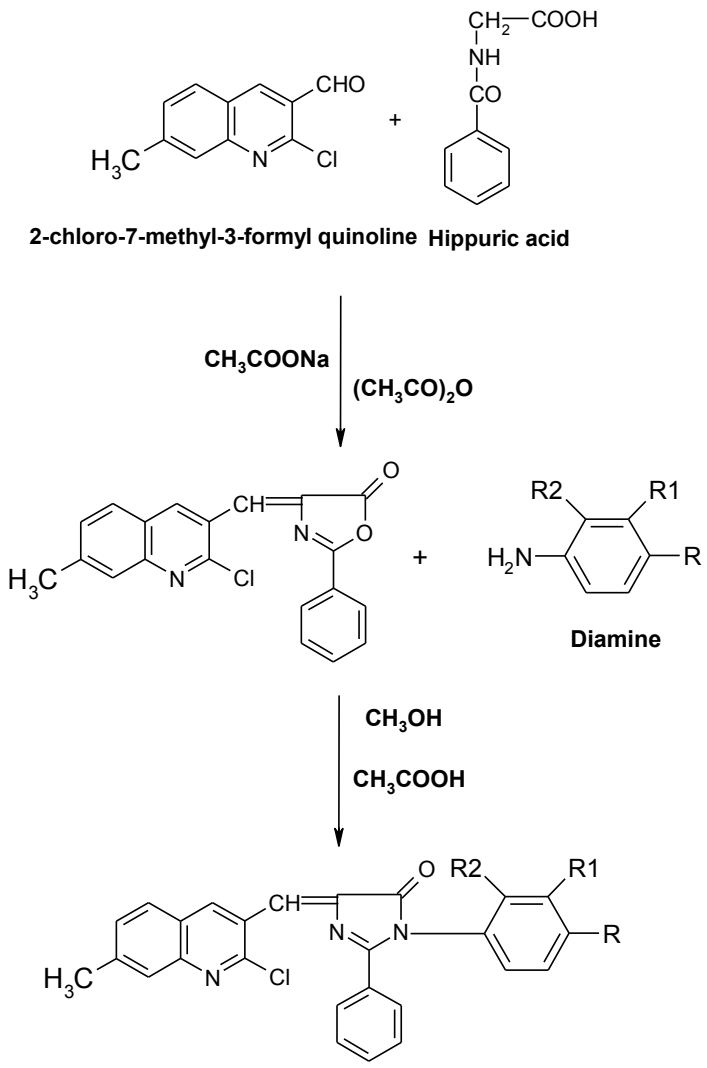
The 2-chloro-7-methyl-3-formylquinoline was synthesized by **Vilsmeier-Haack Reaction** by the procedure reported in the literature[16,19-24].

Dimethyl formamide (9.6 ml, 0.125 M) at 0 ^{0}C was taken in a three necked flask equipped with a drying tube and phosphoryl oxychloride (32.2 ml, 0.35 M) was added drop wise under continuous stirring. To this solution, 3-methyl acetanilide (0.05 M) was slowly added with continuous stirring. After five minutes, solution was heated under reflux for 1 hour at 80-90 ^{0}C. The reaction mixture was poured into ice water (300 ml) and stirred for further 30 mins at 0-10 ^{0}C. The 2-chloro-7-methyl-3-formylquinoline so obtained, was filtered and washed with water. It was crystallized using R-spirit. The yield was 82%.

(5Z)-3-(3-aminophenyl)-5-[(2-chloro-7-methyl-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4H-imidazol-4-one (IMMD)

(5*Z*)-3-(3-aminophenyl)-5-[(2-chloro-7-methyl-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro -4*H*-imidazol-4-one (IMMD) was prepared by refluxing benzoyl glycine (hippuric acid) and (0.25 mol) 2-chloro-7-methyl-3-formyl quinoline (0.25 mol) in acetic anhydride (0.75 mol) with freshly prepared sodium acetate (0.25 mol) for 2h (Erlenmeyer Oxazole Condensation). After cooling, ethanol (10 ml) was added and was kept overnight at 5^{0}C. The solid obtained was filtered, washed with alcohol, dried in vacuum and recrystallized by using benzene. As a result ((4*Z*)-4-[(2-chloro-7-methyl-3-quinolinyl)methylene]-2-phenyl-1,3-oxazol-5(4*H*)-one was separated out.

The synthesized ((4*Z*)-4-[(2-chloro-7-methyl-3-quinolinyl)methylene]-2-phenyl-1,3-oxazol-5(4*H*)-one (0.01 M) was added to a solution of m-phenylene diamine (0.01 M) in 20 ml ethyl alcohol containing few drops of glacial acetic acid and the mixture was heated and was later on cooled down. The solid mass, thus obtained was separated and was recrystallized by using methanol which can be designated as (5*Z*)-3-(3-aminophenyl)-5-[(2-chloro-7-methyl-3-quinolinyl) methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one (IMMD). The other 2-chloro 7-methyl-3-formylquinoline based imidazole derivatives were synthesized in a similar manner by using remaining seven different diamines.[25,26]



Where,

R, R_2 = H, R_1 = NH_2 : IMMD	R_1= R_2 =H R = $C_6H_4SO_2$-NH_2 : IMDS
R_1, R_2 = H, R = NH_2 : IMPD	R_1, R_2 =H R = C_7H_6-NH_2 : IMDM
R_1, R_2 = H, R = C_6H_4-NH_2 : IMBD	R_1= R_2 =H R = $C_6H_5SO_2$-NH_2 : IMDA
R_1= H, R_2 =CH_3 R = C_7H_6-NH_2 : IMOTD	R_1= NH_2, R_2 = H, R = CH_3 : IMDT

Scheme 1 Reaction protocol of 2-chloro-7-methyl-3-formyl quinoline based imidazole derivatives.

Antimicrobial assay: The antimicrobial activities were determined using agar–cup method by measuring the zone of inhibition in mm. All newly synthesized compounds were screened *in vitro* for their antibacterial activity against Gram positive species (*Bacillus subtilis*, *Bacillus megaterium*) and Gram negative species (*Escherichia coli*, *Pseudomonas aeruginosa*), while antifungal activity was tested against *Aspergillus niger* and *C. albicans* at concentration of 75 µg/ml. Streptomycin was used as a standard drug for antibacterial screening, while Imidil was used as a standard drug for antifungal screening and solvent DMSO was used as a control. Each experiment was made in triplicate and the average reading was taken. The results are summarized in Table-3.

Synthesis, characterization and antimicrobial activity of imidazole derivatives based on 2-chloro-7-methyl-3-formylquinoline

The test was performed by using the agar cup borer method, with some modifications using Streptomycin and Imidil as reference for bacterial and fungal culture respectively.[27] A test tube containing sterile melted top agar (1.5 %) previously cooled at room temperature with 0.2 ml suspension of the test culture, mixed methodically and poured in the petri dish containing sterile base agar medium (autoclaved at 121°C for 15 min.) then allowed it to solidify. The cup borer was sterilized by dipping into absolute ethanol and flaming it then allowed to cool it. With the help of sterile cup-borer, three cups in the agar-plate were marked and were injected with 0.1 ml of test solution, 0.1 ml of standard solution and 0.1 ml of DMSO solvent respectively. Then the plates were allowed to diffuse for 20 min. in refrigerator at 4-5°C. The plates were then incubated in upright position at 37°C for 24 hrs. After incubation, the relative susceptibility of the micro-organisms to the potential antimicrobial agent is demonstrated by a clear zone of growth inhibition around the cup. The inhibition zone caused by the various compounds on the micro-organisms was measured and the activity was rated on the basis of the size of the inhibition zone.

Results and Discussion

The elemental analysis of the prepared compounds is given in Table-1. Where,

Heterocyclic substrate	**Diamines**	**IUPAC name**	**Code**
2-chloro-7-methyl-3-formylquinoline	MPD	(5*Z*)-3-(3-aminophenyl)-5-[(2-chloro-7-methyl-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one	IMMD
	PPD	(5*Z*)-3-(4-aminophenyl)-5-[(2-chloro-7-methyl-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one	IMPD
	BD	(5*Z*)-3-(4'-amino[1,1'-biphenyl]-4-yl)-5-[(2-chloro-7-methyl-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one	IMBD
	OTD	(5*Z*)-3-(4'-amino-3,3'-dimethyl[1,1'-biphenyl]-4-yl)-5-[(2-chloro-7-methyl-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one	IMOTD
	DDS	(5*Z*)-3-{4-[(4-aminophenyl)sulfonyl]phenyl}-5-[(2-chloro-7-methyl-3-quinolinyl)methylene]-2-	IMDS

		phenyl-3,5-dihydro-4*H*-imidazol-4-one	
	DDM	(5*Z*)-3-[4-(4-aminobenzyl)phenyl]-5-[(2-chloro-7-methyl-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one	IMDM
	DASA	*N*-(4-aminophenyl)-4-{(4*Z*)-4-[(2-chloro-7-methyl-3-quinolinyl)methylene]-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl}benzenesulfonamide	IMDA
	DT	(5*Z*)-3-(5-amino-2-methylphenyl)-5-[(2-chloro-7-methyl-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one	IMDT

Table 1. Elemental analysis of imidazoles based on 2-chloro-7-methyl-3-formylquinoline.

Imidazole code	Molecular Formula	MW g/mol	Elemental Analysis						
			%C		%H		%N		
			Calc.	Found	Calc.	Found	Calc.	Found	Found*
IMMD	$C_{26}H_{19}ClN_4O$	438	71.15	71.12	4.36	4.30	12.76	12.70	12.71
IMPD	$C_{26}H_{19}ClN_4O$	438	71.15	71.14	4.36	4.31	12.76	12.70	12.72
IMBD	$C_{23}H_{23}ClN_4O$	514	74.63	74.60	4.50	4.45	10.88	10.81	10.88
IMOTD	$C_{34}H_{27}ClN_4O$	542	75.20	75.19	5.01	5.00	10.32	10.30	10.31
IMDS	$C_{32}H_{23}ClN_4O_3S$	578	66.37	66.30	4.00	4.02	9.68	9.60	9.65
IMDM	$C_{33}H_{25}ClN_4O$	528	74.92	74.90	4.76	4.70	10.59	10.55	10.59
IMDA	$C_{32}H_{24}ClN_5O_3S$	593	64.70	64.68	4.07	4.05	11.79	11.75	11.79
IMDT	$C_{27}H_{21}ClN_4O$	452	71.60	71.58	4.67	4.65	12.37	12.35	12.31

***** Found by the Kjeldhal's Method MW = Molecular Weight

In all the imidazole derivatives vinylic proton is seen around 6 ppm (δ). The aromatic protons are assigned to resonances in the range of (δ) 7.00 to 8.2 ppm. The resonance due to $–NH_2$ moiety is attributed to the peak in the range of 6.5 to 6.8 ppm. The resonance due to $–CH_3$ is observed at 2-2.2 ppm. The compounds containing 4,4'-diamino diphenyl methane has a $>CH_2$ moiety attached to benzene ring and this $>CH_2$ is highly deshielded. This is reflected in the proton NMR signal of $>CH_2$ group seen at 3.69 ppm. The ^{13}C NMR peaks are quite interesting in all these imidazoles derivatives where the peak around 165 ppm is attributed to C of >C=O (Table-2). In all the compounds the peak at 158 ppm is assigned to Cl-C=N moiety. The peak at 148 ppm is likely due to >C=N moiety. The peaks in the region 110-130 ppm are attributed to aromatic ring. The compounds containing 4,4'-diamino diphenyl methane shows a peak at 40 ppm which is due to $=CH_2$ group attached to both the rings.

Table 2. Assignment of NMR (^{1}H and ^{13}C) peaks in imidazole derivatives of 2-chloro-7-methyl-3-formyl quinoline.

Imidazole code	Peaks observed (δ) ppm	Assignment ^{1}H NMR	Peaks observed (δ) ppm	Assignment ^{13}C NMR
IMMD	2.47 6.03 6.80 7.10– 8.42	CH_3 = CH Vinylic - NH_2 Aromatic Protons	165 147 157 109 – 132 18	C = O C = N Cl-C = N C in aromatic ring CH_3
IMPD	2.47 6.0 6.78 7.2– 8.42	CH_3 = CH Vinylic - NH_2 Aromatic Protons	165 148 158 115 – 135 17	C = O C = N Cl- C = N C in aromatic ring CH_3
IMBD	2.47 5.7 6.64 7.2– 8.42	CH_3 = CH Vinylic - NH_2 Aromatic Protons	165 148 157 112 – 135 18	C = O C = N Cl- C = N C in aromatic ring CH_3
IMOTD	2.14 2.24 2.47 6.2 6.38 7.3– 8.42	CH_3 CH_3 CH_3 = CH Vinylic - NH_2 Aromatic Protons	165 147 158 110 – 135 17 18	C = O C = N Cl- C = N C in aromatic ring CH_3 CH_3
IMDS	2.47 6.0 6.43 7.2– 8.38	CH_3 = CH Vinylic - NH_2 Aromatic Protons	165 148 158 110 – 130 18	C = O C = N Cl- C = N C in aromatic ring CH_3
IMDM	2.47 3.69 6.2 6.42 7.2 – 8.42	CH_3 CH_2 = CH Vinylic - NH_2 Aromatic Protons	165 148 158 115 – 135 17 40	C = O C = N Cl- C = N C in aromatic ring CH_3 CH_2
IMDA	2.47 6.25 6.55 6.64 7.2– 8.42	CH_3 = CH Vinylic NH - NH_2 Aromatic Protons	165 148 158 112 – 132 18	C = O C = N Cl- C = N C in aromatic ring CH_3
IMDT	2.47 2.18 6.03 6.52 7.2 – 8.42	CH_3 CH_3 = CH Vinylic - NH_2 Aromatic Protons	165 147 156 112 – 130 17	C = O C = N Cl- C = N C in aromatic ring CH_3

Practically in all the compounds $–NH_2$ asymmetric stretching vibration is assigned to a peak around 3400 cm^{-1}, while a peak around 3250 cm^{-1} is attributed to $–NH_2$ symmetric

stretching vibration. The =CH stretching vibration in the vinyl moiety is attributed to the absorption at ~3040 cm^{-1}. The aromatic C-H stretching frequency, as expected is observed at around ~3010 cm^{-1}. The strong absorption at ~1700 cm^{-1} is found to be present in majority of the compounds. The absorption will have contributions from stretching of >C=O and >C=N. The strong absorption at 1650 cm^{-1} have contributions from υ C=N, υ C=C and bending of $-NH_2$. In most of the compounds the C-C stretching of the aromatic ring is around 1540 cm^{-1}.

A fairly strong absorption at ~1300 cm^{-1} is assigned to C-N stretching. The strong absorption in the region 810-840 cm^{-1} is due to C-H out of plane bending in aromatic ring. The C-Cl stretching is attributed to the strong absorption in the region 740-720 cm^{-1}. Compounds containing O=S=O moiety show strong absorption in the region of 1050-1200 cm^{-1} is due to O=S=O stretching. The C-H bending in the vinyl moiety is seen as a strong band around 800 cm^{-1} in all the compounds. The compounds containing $–CH_3$ group shows peaks due to asymmetric and symmetric bending of $–CH_3$ group at 1475 and 1375 cm^{-1} respectively and absorption at ~550 cm^{-1} in the bromo compounds is assigned to C-Br stretching.

The synthesized compounds were screened '*in vitro*' for antimicrobial activity. From the data presented in Table-3, it is clear that out of 8 imidazole compounds IMMD, IMBD, IMDM exhibited moderate inhibition against gram negative bacterial species and especially against *Escherichia coli* while IMBD, IMDM and IMOTD showed maximum activity against most gram negative organisms. Against gram positive organisms almost all compound of the series exhibited maximum inhibition, especially IMPD and IMBD showed highest inhibition against *B. megaterium*, while IMMD and IMDT showed good inhibition against fungal organism especially *C. albicans*. The other compounds exhibited moderate to less inhibition against fungal species, but IMMD showed good inhibition.

Table 3. Antimicrobial activity of imidazoles.

Compound code	**Inhibition zone against (in mm)**					
	E. coli	***P. aeruginosa***	***B. subtilis***	***B. megaterium***	***A. niger***	***C. albicans***
IMMD	16	13	25	27	15	19
IMPD	14	12	27	28	12	16
IMBD	20	17	28	30	16	17
IMOTD	19	16	20	23	14	15
IMDS	14	12	20	20	11	14
IMDM	20	14	21	25	14	13
IMDA	17	15	23	26	13	15
IMDT	15	12	19	20	17	20
Streptomycin	35	34	35	36	-	-
Imidil	-	-	-	-	33	35

Conclusion

The present study showed that the antimicrobial activity of newly synthesized compounds may change by introduction or elimination of a specific group. Thus, the imidazole derivatives could be powerful and elegant factor to stimulate major advances in chemotherapeutic agents of remarkable significance in medicine, biology and pharmacy.

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