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Synthesis, Characterization and Biological Evaluation of Quinoline Based Imidazole Derivatives

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A series of oxazole and imidazole derivatives were prepared from 2-chloro-3-formylquinoline. The structures of all the synthesized compounds were elucidated by elemental, IR, ^{1}H and ^{13}C NMR spectra. They were also assayed *in vitro* for their antimicrobial activity. It was revealed that some synthesized derivatives were exhibiting competent biological activity against both gram negative and gram positive bacterial species and fungal microorganisms.

Key Words: Quinoline, Imidazole, Antibacterial activity.

INTRODUCTION

A wide variety of heterocyclic compounds of nitrogen containing five membered ring systems have been described for their chemotherapeutic importance and biological activity against various bacterial and fungal micro organisms[1,2]. Besides this, the chemistry of quinoline and imidazoles have also been reviewed in a considerable number of publications and patents. A number of derivatives of quinoline serve as valuable therapeutic agents[1-5]. In past cinchona bark was introduced for the treatment of malaria and until recently quinine has remained the standard remedy for this disease. Several other synthetic antimalarial drugs are based on quinoline nucleus *e.g.*, chloroquine, paraquine *etc*. Considerable interest has been created in the chemistry of quinoline derivatives due to their versatile therapeutic activities like bactericidal, antihistaminic, antimalarial, antidepressant, analgesic, antiulcer, antiviral, herbicidal, antitumor, antiallergic, anticonvulsant, antiinflammatory *etc*[6-8]. Some of the therapeutically active compounds derived from 2-chloro-3-formylquinoline derivatives are reviewed here[7-9]. Almost every class of imidazole derivatives has been used for different reactions to produce enormous number of heterocycles. Later, in 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. They have a broad spectrum, high activity and mild side effects. Looking to the above importance of both moieties, quinoline

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and imidazole, it is planned to undertake synthesis of quinoline based imidazole derivatives. The entire synthesis route is shown in the scheme.

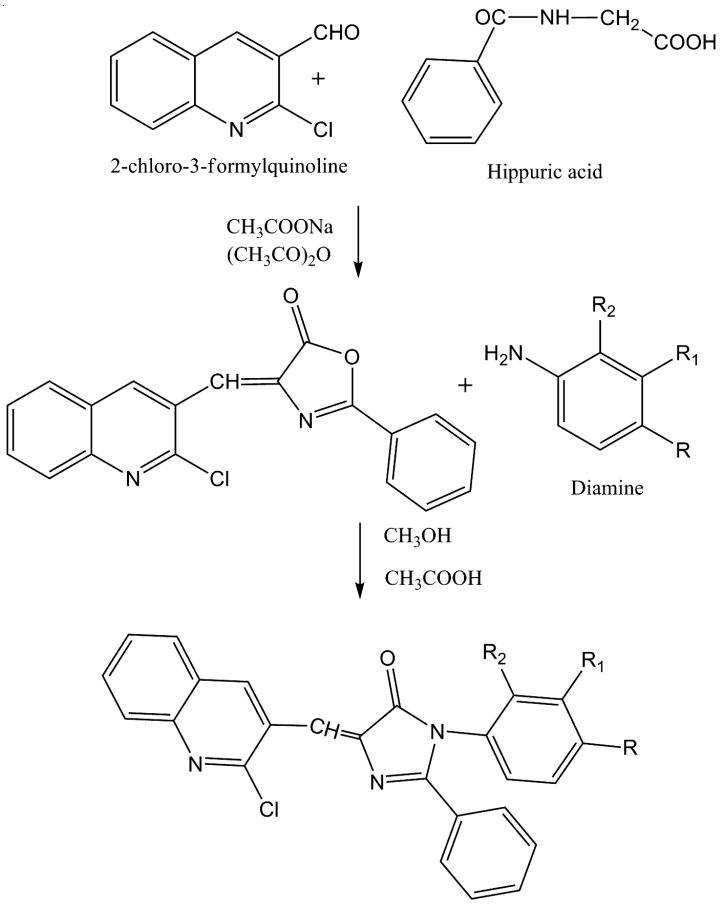
EXPERIMENTAL

Acetanilide and their derivatives were purified by crystallization in rectified-spirit. Dimethyl formamide 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. 2-Chloro-3-formyl quinoline was synthesized by Vilsmeier-Haack reaction by the procedure reported in the literature[16,17]. Melting points were measured in an open capillary tube and are uncorrected. Elemental analysis was obtained using Perkin-Elmer (USA) 2400, series II CHN-analyzer. In addition to this, the nitrogen content in all the imidazoles was estimated by Kjeldhal's method[18]. 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.

Synthesis of 2-chloro-3-formylquinoline: 2-Chloro-3-formyl quinoline was synthesized by Vilsmeier-Haack reaction by the procedure reported in the literature[19-21]. Accordingly, cold dimethyl formamide (9.6 mL, 0.125 M) at 0 °C was taken in a three necked flask equipped with a drying tube. The phosphoryl oxychloride (32.2 mL, 0.35 M) was added dropwise with continuous stirring. To this solution, acetanilide (0.05 M) was added slowly. After 5 min, the solution was heated under reflux for 1 h at 80-90 °C. The reaction mixture was poured into ice-cold water (300 mL) and stirred for 0.5 h at 0-10 °C. The obtained 2-chloro-3-formyl-quinoline product was filtered and washed with water. It was crystallized by using rectified-spirit (Yield *ca.* 90 %, m.p. 148 °C).

(4Z)-4-[(2-Chloro-3-quinolinyl)methylene]-2-phenyl-1,3-oxazol-5(4*H*)-one: It was prepared by refluxing benzoyl glycine (hippuric acid) (0.25 mol) and 2-chloro-3-formylquinoline (0.25 mol) in acetic anhydride (0.75 mol) with freshly prepared sodium acetate (0.25 mol) for 2 h (Erlenmeyer oxazole condensation). After cooling, ethanol (10 mL) was added and kept overnight at 5 °C, the solid obtained was filtered, washed with alcohol, dried in vacuum and recrystallized using benzene.

(5Z)-3-(3-Aminophenyl)-5-[(2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one (IMD): The above synthesized (4Z)-4-[(2-chloro-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 of ethyl alcohol containing few drops of glacial acetic acid and the mixture was heated for 45 min and was later on cooled down. The solid mass thus obtained was separated and was recrystallized using methanol. (Yield *ca.* 72 %, m.p. 154 °C).



where, R, R_2 = H, R_1 = NH_2	:	IMD	R_1 = R_2 = H, R = C_6H_4-SO_4-NH_2	:	IDS
R_1, R_2 = H, R = NH_2	:	IPD	R_1, R_2 = H, R = C_7H_6-NH_2	:	IDM
R_1, R_2 = H, R = C_6H_4-NH_2	:	IBD	R_1 = R_2 = H, R = C_6H_5-SO_2-NH_2	:	IDA
R_1 = H, R_2 = CH_3, R = C_7H_6-NH_2	:	IOTD	R_1 = NH_2, R_2 = H, R = CH_3	:	IDT

Scheme-I: Synthesis of (5Z)-3-(3-aminophenyl)-5-[(2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one

The other 2-chloro-3-formylquinoline based imidazole derivatives were synthesized in a similar manner by using remaining 7 different diamines[23,24].

Antimicrobial assay: Novel synthesized compounds were screened for their antimicrobial activity by using different bacterial and fungal microorganisms. The bacterial and fungal strains used for antibacterial activity study were *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Bacillus megaterium*, *Aspergillus niger* and *C. albicans*.

The test was performed by using the Agar cup borer method, with some modifications using streptomycin and imidile as reference for bacterial and fungal culture, respectively[25]. 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 h. 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 evaluated 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, **IMD**: (5Z)-3-(3-aminophenyl)-5-[(2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one, **IPD**: (5Z)-3-(4-aminophenyl)-5-[(2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one, **IBD**: (5Z)-3-(4'-amino[1,1'-biphenyl]-4-yl)-5-[(2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one, **IOTD**: (5Z)-3-(4'-amino-3,3'-dimethyl[1,1'-biphenyl]-4-yl)-5-[(2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one, **IDS**: (5Z)-3-{4-[(4-aminophenyl)sulfonyl]phenyl}-5-[(2-chloro-3-

TABLE-1
ELEMENTAL ANALYSIS OF IMIDAZOLES BASED ON 2-CHLORO-3-FORMYLQUINOLINE

Imidazole	m.f.	m.p. (ºC)	m.w. (g/mol)	Elemental analysis (%): Calcd. (found)			
				C	H	N	N (found)*
IMD	$C_{25}H_{17}N_4OCl$	154	424	70.67 (70.65)	4.03 (4.00)	13.19 (13.10)	13.15
IPD	$C_{25}H_{17}N_4OCl$	198	424	70.67 (70.60)	4.03 (4.02)	13.19 (13.12)	13.10
IBD	$C_{31}H_{21}N_4OCl$	187	500	74.32 (70.11)	4.23 (4.21)	11.18 (11.22)	11.20
IOTD	$C_{33}H_{25}N_4OCl$	207	528	74.92 (74.91)	4.76 (4.70)	10.59 (10.55)	10.56
IDS	$C_{31}H_{21}N_4O_3SCl$	185	564	65.90 (65.88)	3.75 (3.74)	9.92 (9.90)	9.92
IDM	$C_{32}H_{23}N_4OCl$	204	514	74.63 (74.50)	4.50 (4.45)	10.88 (10.85)	10.87
IDA	$C_{31}H_{22}N_5O_3SCl$	212	579	64.19 (64.25)	3.82 (3.80)	12.07 (12.05)	12.04
IDT	$C_{26}H_{19}N_4OCl$	212	438	71.15 (71.10)	4.36 (4.32)	12.76 (12.72)	12.73

*Found by the Kjeldhal's method.

quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one, **IDM**: (5Z)-3-[4-(4-aminobenzyl)phenyl]-5-[(2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one, **IDA**: N-(4-aminophenyl)-4-{(4Z)-4-[(2-chloro-3-quinolinyl)methylene]-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-}benzenesulfonamide, **IDT**: (5Z)-3-(5-amino-2-methylphenyl)-5-[(2-chloro-3-quinolinyl)-methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one.

In all the imidazole derivatives vinylic proton is seen around 6 ppm (δ). The aromatic protons are assigned to resonances in the range (δ) 7.00-8.20 ppm. The resonance due to $-NH_2$ moiety is attributed to the peak in the range of 6.5-6.8 ppm. The resonance due to $-CH_3$ is observed at 2.0-2.2 ppm. The compounds containing 4,4'-diamino diphenyl methane has a $>CH_2$ moiety attached to benzene ring and this $>CH_2$ is highly de-shielded. 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 imidazole 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.

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 *ca.* 3040 cm^{-1}. The aromatic C-H stretching frequency, as expected is observed at around *ca.* 3010 cm^{-1}. The strong absorption at *ca.* 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 ν(C=N), ν(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 *ca.* 1300 cm^{-1} is assigned to C-N stretching. The strong absorption in the region 840-810 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 1200-1050 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.

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 IMD, IBD, IDM exhibited moderate inhibition against gram negative bacterial species and especially against *S. typhi* while IDS, IDM and IOTD showed maximum activity against most gram negative organisms. Against gram positive organisms almost all all compound of the series exhibited maximum inhibition, especially IBD and IMD

TABLE-2
ASSIGNMENT OF NMR (^{1}H AND ^{13}C) PEAKS IN IMIDAZOLE DERIVATIVES OF 2-CHLORO-3-FORMYL QUINOLINE

Imidazole	Peaks observed (δ) ppm	Assignment of ^{1}H NMR	Peaks observed (δ) ppm	Assignment of ^{13}C NMR
IMD	6.04	=CH Vinylic	165	C = O
	6.90	$-NH_2$	148	C = N
	7.0-8.5	Aromatic protons	110-130	C in aromatic ring
			158	Cl-C=N
IPD	5.8	=CH Vinylic	165	C=O
	6.99	$-NH_2$	148	C=N
	7-8.20	Aromatic protons	110-130	C in aromatic ring
			158	Cl-C=N
IBD	5.70	=CH Vinylic	165	C=O
	6.80	$-NH_2$	148	C=N
	7.06-8.38	Aromatic protons	110-130	C in aromatic ring
			158	Cl-C=N
IOTD	2.10	CH_3	17	CH_3
	2.30	CH_3	18	CH_3
	6.20	=CH	165	C=O
	6.90	NH_2	148	C=N
	7.20-8.20	Aromatic protons	158	Cl-C=N
			110-130	C in aromatic ring
IDS	6.04	=CH Vinylic	164	C=O
	6.90	$-NH_2$	147	C=N
	7.00-8.50	Aromatic protons	158	Cl-C=N
			112-132	C in aromatic ring
IDM	3.34	$-CH_2$	40	CH_2
	6.20	=CH Vinylic	165	C=O
	6.80	$-NH_2$	148	C=N
	7.00-8.30	Aromatic protons	158	Cl-C=N
IDA	6.00	=CH Vinylic	164	C=O
	6.85	$-NH_2$	148	C=N
	7.64-8.38	Aromatic protons	158	Cl-C=N
	8.80	N-H	112-132	C in aromatic ring
IDT	2.30	CH_3	17	CH_3
	6.00	=CH	161	C=O
	6.80	NH_2	147	C=N
	7.00-8.70	Aromatic protons	149	Cl-C=N
			110-130	C in aromatic ring

showed highest inhibition against *B. megaterium*, while IMD and IDS showed good inhibition against fungal organism specially *C. albicans*. The other compounds exhibited moderate to less inhibition against fungal species.

Conclusion

Thus on the basis of present study, it is concluded that the antimicrobial activity of such compounds may change by introduction or elimination of a specific group. So the imidazole derivatives could be a powerful and an essential factor to stimulate major advances in chemotherapeutic agents of remarkable significance in medicine, biology and pharmacy.

TABLE-3
ANTIMICROBIAL ACTIVITY OF SYNTHESIZED COMPOUNDS

Compounds	Zone of inhibition (mm)					
	E. coli	*S. typhi*	*B. megaterium*	*B. subtillis*	*A. niger*	*C. albicans*
IMD	11	16	28	20	18	18
IPD	10	11	26	18	14	12
IBD	16	12	30	20	10	10
IOTD	08	18	21	15	12	12
IDS	07	20	20	14	10	18
IDM	12	18	24	18	–	10
IDA	10	–	26	18	06	10
IDT	06	16	18	12	–	15
Streptomycin	22	38	30	25	–	–
Imidil	–	–	–	–	35	32

Zone of inhibition in 'mm': antimicrobial activity of compounds at 10 mg % in DMSO.

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