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Synthesis, Characterization and Antimicrobial Activity of Imidazole Derivatives

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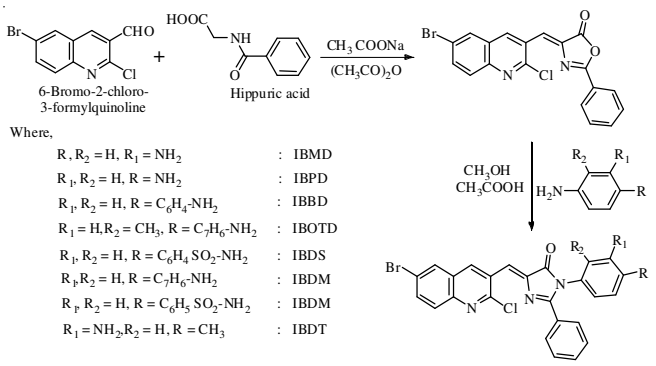
A series of oxazole and their imidazole derivatives were prepared from 6-bromo-2-chloro-3-formylquinoline. The structures of all the synthesized compounds were elucidated by elemental, IR, ^{1}H NMR, ^{13}C NMR spectra. They were assayed *in vitro* for their antimicrobial activity. It was revealed that some synthesized derivatives show remarkable 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 microorganisms[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]. Many years ago 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 developed 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[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 very broad spectrum, high activity and mild side effects. Looking to the above importance of both moieties, quinoline and imidazole, it is planned to synthesize quinoline based imidazole derivatives. The whole synthesis route is shown in **Scheme-I**.



where, IBMD = (5Z)-3-(3-aminophenyl)-5-[(6-bromo-2-chloro-3-quinolinyl)-methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one; IBPD = (5Z)-3-(4-aminophenyl)-5-[(6-bromo-2-chloro-3-uinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one; IBBD = (5Z)-3-(4'-amino[1,1'-biphenyl]-4-yl)-5-[(6-bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one, IBOTD = (5Z)-3-(4'-amino-3,3'-dimethyl[1,1'-biphenyl]-4-yl)-5-[(6-bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one; IBDS = (5Z)-3-{4-[(4-minophenyl)sulfonyl]phenyl}-5-[(6-bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one; IBDM = (5Z)-3-[4-(4-aminobenzyl)phenyl]-5-[(6-bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one; IBDA = N-(4-minophenyl)-4-{(4Z)-4-[(6-bromo-2-chloro-3-quinolinyl)-methylene]-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl}benzenesulfonamide; IBDT = (5Z)-3-(5-amino-2-methylphenyl)-5-[(6-bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4H-imidazol-4-one

Scheme-I: (5Z)-3-(3-Aminophenyl)-5-[(6-bromo-2-chloro-3-quinolinyl)-methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one

EXPERIMENTAL

Acetanilide and their derivatives were purified by crystallization in r-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. The 2-chloro-3-formyl quinoline was synthesized by Vilsmeier-Haack reaction as 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 6-bromo-2-chloro-3-formylquinoline: The 6-bromo-2-chloro-3-formylquinoline was synthesized by Vilsmeier-Haack reaction by the procedure reported in the literature[19-22]. For the preparation, cold dimethyl formamide (9.6 mL, 0.125 M) at 0 ºC was taken in a three necked flask equipped with a drying tube. The phosporyl oxychloride was added (32.2 mL, 0.35 M) drop wise with continuous stirring. To this solution, 4-bromo acetanilide (0.05 M) was slowly added with continuous stirring. After 5 min, the solution was heated under reflux for 1 h at 80-90 ºC. The reaction mixture was poured into ice water (300 mL) and stirred for 0.5 h at 0-10 ºC. The product so formed was filtered and washed with water. It was crystallized by using r-spirit. The yield was 85 % and melting point was 148 °C.

((4Z)-4-[(6-Bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-1,3-oxazol-5(4*H*)-one: It was prepared by refluxing with benzoyl glycine (hippuric acid) (0.25 mol) and 6-bromo-2-chloro-3-formyl quinoline (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 ºC, the solid obtained was filtered, washed with alcohol, dried in vacuum and recrystallized by using benzene. Thus, as a result ((4Z)-4-[(6-bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-1,3-oxazol-5(4*H*)-one was separated out.

(5Z)-3-(3-Aminophenyl)-5-[(6-bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one (IBMD): Now the synthesized ((4Z)-4-[(6-bromo-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 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 (5Z)-3-(3-aminophenyl)-5-[(6-bromo-2-chloro-3-quinolinyl)-methylene]-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one (IBMD) (Yield *ca.* 70 %, m.p. 151 ºC).

The other 6-bromo-2-chloro-3-formylquinoline based imidazoles derivatives were synthesized in a similar manner by using remaining seven different diamines[23,24]. The physico-chemical data of the synthesized compounds are given in Table-1.

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 the study of antibacterial activity were *Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Bacillus megaterium* and *Aspergillus niger*, *C. albicans*.

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[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 microorganisms 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 microorganisms was measured and the activity was rated on the basis of the size of the inhibition zone.

TABLE-1
ELEMENTAL ANALYSIS OF IMIDAZOLES BASED ON 6-BROMO-2-CHLORO-3-FORMYLQUINOLINE

Imidazole	m.f.	m.p. (ºC)	m.w. (g/mol)	Elemental analysis (%)						
				C		H		N		
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Found*
IBMD	$C_{25}H_{16}N_4OBrCl$	151	503	59.60	59.57	3.20	3.17	11.12	11.11	11.19
IBPD	$C_{25}H_{16}N_4OBrCl$	195	503	59.60	59.55	3.20	3.15	11.12	11.10	11.09
IBBD	$C_{31}H_{20}N_4OBrCl$	184	579	64.21	64.20	3.48	3.40	9.66	9.60	9.61
IBOTD	$C_{33}H_{24}N_4OBrCl$	204	607	65.20	65.18	3.98	3.96	9.22	9.20	9.18
IBDS	$C_{31}H_{20}N_4O_3SBrCl$	182	643	57.82	57.80	3.13	3.10	8.70	8.68	8.69
IBDM	$C_{32}H_{22}N_4OBrCl$	201	593	64.72	64.70	3.73	3.71	9.43	9.40	9.41
IBDA	$C_{31}H_{21}N_5O_3SBrCl$	209	658	56.50	56.52	3.21	3.20	10.63	10.62	10.60
IBDT	$C_{26}H_{18}N_4OBrCl$	209	517	60.31	60.30	3.50	3.49	10.82	10.81	10.80

*Estimated by the Kjeldhal's method.

RESULTS AND DISCUSSION

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 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 2.0-2.2 ppm. The compounds containing 4,4'-diamino diphenyl methane has a $>CH_2$ moiety attached to benzene ring and this $>CH_2$ is highly deshielded. This is reflected in the proton NMR signal of $>CH_2$ group seen at 3.69 ppm. ^{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 (^1H AND ^{13}C) PEAKS IN IMIDAZOLE DERIVATIVES OF 6-BROMO-2-CHLORO-3-FORMYL QUINOLINE

Imidazole	Peaks observed (δ) ppm	Assignment ^1H NMR	Peaks observed (δ) ppm	Assignment ^{13}C NMR
IBMD	6.03	=CH vinylic	165	C=O
	6.80	$-NH_2$	147	C=N
	7-8.36	Aromatic protons	158	Cl-C=N
			110-130	C in aromatic ring
IBPD	5.90	=CH vinylic	165	C=O
	6.80	$-NH_2$	147	C=N
	7.0-8.36	Aromatic protons	158	Cl-C=N
			115-135	C in aromatic ring
IBBD	5.9	=CH vinylic	165	C=O
	6.8	$-NH_2$	147	C=N
	7.3-8.36	Aromatic protons	157	Cl-C=N
			115-135	C in aromatic ring
IBOTD	2.14	CH_3	163	C=O
	2.24	CH_3	148	C=N
	6.3	=CH vinylic	158	Cl-C=N
	6.6	$-NH_2$	110-130	C in aromatic ring
	7.0 -8.36	Aromatic protons	18	CH_3
			19	CH_3
IBDS	6.04	=CH vinylic	165	C=O
	6.43	$-NH_2$	147	C=N
	7.00-8.36	Aromatic protons	158	Cl-C=N
			110-135	C in aromatic ring
IBDM	3.69	CH_2	165	C=O
	6.2	=CH vinylic	148	C=N
	6.43	$-NH_2$	158	Cl-C=N
	7.1-8.37	Aromatic protons	112-135	C in aromatic ring
			40	CH_2
IBDA	6.0	=CH vinylic	165	C=O
	6.64	$-NH_2$	147	C=N
	7.2-8.35	Aromatic protons	158	Cl-C=N
	8.6	N-H	110-130	C in aromatic ring
IBDT	2.18	CH_3	162	C=O
	6.0	=CH vinylic	147	C=N
	6.82	$-NH_2$	149	Cl-C=N
	7.2-8.00	Aromatic protons	110-130	C in aromatic ring
			18	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 *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 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 *ca.* 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 eight imidazole compounds IBMD, IBBD, IBDM exhibited moderate inhibition against gram negative bacterial species and especially against *Escherichia coli* while IBBD, IBDM and IBOTD showed maximum activity against most gram negative organisms. Against gram positive organisms almost all compound of the series exhibited maximum inhibition, especially IBPD and IBBD showed highest inhibition against *B. megaterium*, while IBMD and IBDT showed good inhibition against fungal organism especially *C. albicans*. The other compounds exhibited moderate to less inhibition against fungal species, but IBMD showed good inhibition.

TABLE-3
ANTIMICROBIAL ACTIVITY OF SYNTHESIZED COMPOUNDS

Compounds	Zone of inhibition (mm)					
	Escherichia coli	*Pseudomonas aeruginosa*	*Bacillus subtilis*	*Bacillus megaterium*	*Aspergillus niger*	*Candida albicans*
IBMD	15	19	21	19	20	19
IBPD	11	9	19	20	10	11
IBBD	20	22	22	22	13	13
IBOTD	11	15	19	13	15	12
IBDS	10	8	15	19	12	9
IBDM	6	18	25	20	14	16
IBDA	14	9	24	15	10	11
IBDT	8	13	21	13	16	17
Streptomycin	28	32	31	29	33	33
Imidil	–	–	–	–	34	34

Antimicrobial activity of compounds at 10 mg% in DMSO.

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