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Synthesis and Evaluation of 2-Chloro-3-[3-(6-nitro-1*H*-benzimidazol-2-yl)-4,5-dihydro-1*H*-pyrazol-5-yl]quinolines as Potent Antibacterial Agents

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New series of 2-chloro-3-[3-(6-nitro-1*H*-benzimidazol-2-yl)-4,5-dihydro-1*H*-pyrazol-5-yl]quinolines (**Va-k**) have been synthesized by the reaction of 3-(2-chloroquinolin-3-yl)-1-(6-nitro-1*H*-benzimidazol-2-yl)prop-2-en-1-one (**IVa-k**) with hydrazine hydrate which in turn were obtained by the condensation of 1-(6-nitro-1*H*-benzimidazol-2-yl)ethanone (**III**) with different 2-chloroquinoline-3-carbaldehydes. 1-(6-Nitro-1*H*-benzimidazol-2-yl)ethanone was obtained by the oxidation of 1-(6-nitro-1*H*-benzimidazol-2-yl)ethanol (**II**) prepared by the reaction of 4-nitro-1,2-phenylenediamine (**I**) with 2-hydroxypropanoic acid. The synthesized compounds were characterized by IR, ^{1}H NMR and mass spectral studies. These compounds were screened for their antibacterial activity by standard methods and found some of them active.

Keywords: Benzimidazoles, Chalcones, Quinolines, Pyrazolines, Antibacterial activity.

INTRODUCTION

Benzimidazoles are an important group of heterocyclic compounds, several derivatives of which have been marketed as biologically active products. The benzimidazole and its derivatives play an important role as a therapeutic agent *e.g.* antiulcer and anthelmintic drugs. Apart from this the benzimidazole derivatives exhibit pharmacological activities such as antimicrobial, antiviral, anticancer, antiinflammatory, analgesic, *etc*. [1].

The chalcones and their derivatives are important intermediates in organic synthesis. They serve as starting material for the synthesis of a variety of heterocyclic compounds which have physiological significance. Due to their different functionality these compounds confer biological activities, such as antimicrobial, antibacterial, antifungal, anticancer, antitubercular, antiviral, antinflammatory, antihyperglycemic, *etc*. [2,3].

It is known that 4,5-dihydro-1*H*-pyrazole and its derivatives exhibit extensive biological and pharmacological activities [4]. Chalcones have been reported to react with hydrazine and phenylhydrazine in acetic acid to yield pyrazolines through hydrazones as intermediates [5]. In the present work, 4,5-dihydro-1*H*-pyrazoles were synthesized by treating chalcones with hydrazine hydrate in alcoholic solution in the presence of acetic acid.

Therefore, the present study was designed to synthesize substituted 2-chloro-3-[3-(6-nitro-1*H*-benzimidazol-2-yl)-4,5-dihydro-1*H*-pyrazol-5-yl]quinolines for their possible biological activities by adopting the standard procedure. The synthetic strategy is developed in order to obtain 2-chloro-3-[3-(6-nitro-1*H*-benzimidazol-2-yl)-4,5-dihydro-1*H*-pyrazol-5-yl]quinolines (**Va-k**) have been synthesized by the reaction 3-(2-chloroquinolin-3-yl)-1-(6-nitro-1*H*-benzimidazol-2-yl)-prop-2-en-1-one (**IVa-k**) with hydrazine hydrate which in turn were obtained by the condensation of 1-(6-nitro-1*H*-benzimidazol-2-yl)ethanone (**III**) with different 2-chloroquinoline-3-carbaldehydes. 1-(6-Nitro-1*H*-benzimidazol-2-yl)ethanone was obtained by the oxidation of 1-(6-nitro-1*H*-benzimidazol-2-yl)ethanol (**II**) prepared by the reaction of 4-nitro-1,2-phenylenediamine (**I**) with 2-hydroxypropanoic acid.

EXPERIMENTAL

All the reagents and solvents were purchased and used without further purification. Melting points were determined by open capillary tube method which are uncorrected. Crude products were purified by recrystallization using a suitable solvent. IR spectra were recorded on SHIMADZU FTIR 8400S spectrometer using KBr pellet. NMR spectra were recorded on Bruker avance II 400 NMR spectrometer. The chemical shifts were reported as ppm down field using TMS as an internal standard.

Synthesis of 1-(6-nitro-1*H*-benzimidazol-2-yl)ethanol (II): Equimolar amount of 4-nitro-1,2-phenylenediamine (0.01

mol) (**I**) and lactic acid (0.01 mol), 4 N HCl are refluxed in synthetic microwave oven with condenser at the intensity of 65 % (450 W) for 160 min. The reaction was monitored by TLC, after the completion of the reaction; the mixture was cooled and neutralized with sodium bicarbonate and then the precipitate was filtered, washed with cold water, dried and recrystallized from absolute alcohol [6-8].

Synthesis of 1-(6-nitro-1*H*-benzimidazol-2-yl)ethanone (III): To a solution of compound **II** (10.358g, 50 mmol) in 40 mL dil. H_2SO_4 (5 %) was added dropwise with constant stirring a solution of $K_2Cr_2O_7$ (19.8g, 150 mmol) in 80 mL of dil. H_2SO_4 (25 %, v/v) at room temperature over a period of 20 min. Further the reaction mixture was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC), the separated solution (which is the chromium complex) was washed with water (3 × 10 mL), then suspended in 50 mL of water and treated with aqueous ammonia (1:1) to a pH of 6 to 6.5. The separated product was washed with water, dried and crystallized from boiling ethyl acetate to give pure product [9].

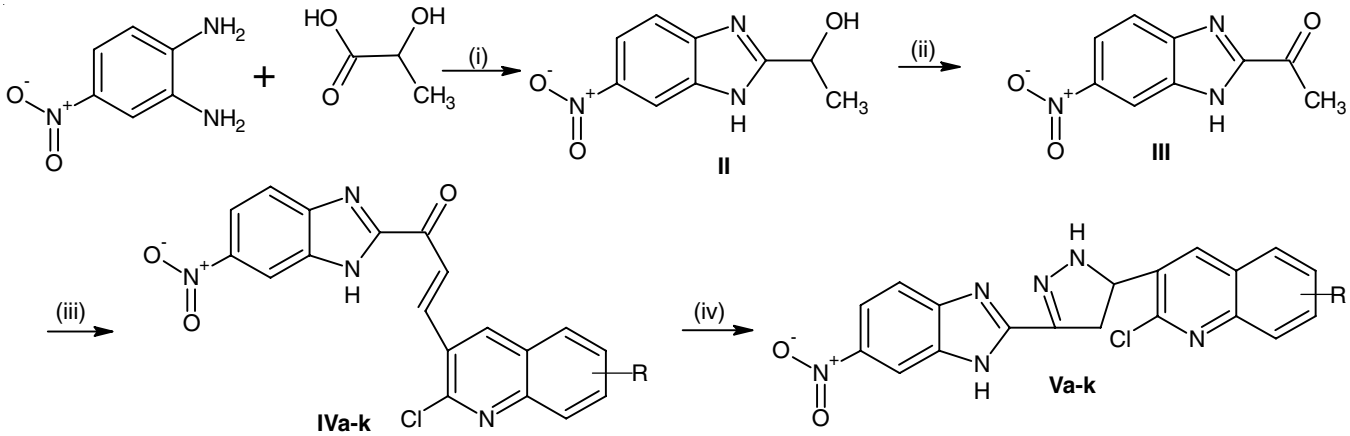
Synthesis of 3-(2-chloroquinolin-3-yl)-1-(6-nitro-1*H*-benzimidazol-2-yl)prop-2-en-1-one (IVa-k): To a solution of compound **III** (10 mmol, 3.78 g) in 30 mL aqueous NaOH (10 %) was added to the respective 2-chloroquinoline-3-carbaldehyde (10 mmol, 1.91g) at room temperature. The reaction mixture was stirred for 0.5 h. At the end of this period, the separated solid was filtered, washed with distilled water and dried. The crude product thus obtained was recrystallized from suitable solvent [10-16].

Synthesis of 2-chloro-3-[3-(6-nitro-1*H*-benzimidazol-2-yl)-4,5-dihydro-1*H*-pyrazol-5-yl]quinoline (Va-k): To a solution of 3-(2-chloroquinolin-3-yl)-1-(6-nitro-1*H*-benzimidazol-2-yl)prop-2-en-1-one (3.78 g, 0.01 mol) was dissolved in ethanol (40 mL) and glacial acetic acid (10 mL). Hydrazine hydrate (0.75 g, 0.015 mol) was then added and the reaction mixture refluxed for 4 h on a water bath. The solvent was reduced to half its volume [17]. The crystalline product which separated out on cooling was filtered, washed with water, dried and crystallized from ethanol (**Scheme-I**). The physico-chemical data of the all the synthesized compounds are given in Table-1.

Spectral data of selected compounds

Compound IVb: Yellow solid, yield 69 %, m.p. 226-228 ºC; IR (KBr, cm^{-1}): IR (KBr, cm^{-1}): 3600, 3150, 2850, 1655, 1600, 1550, 1425, 1350, 1225, 740; 1H NMR(400 MHz, $CDCl_3$): δ 2.7 (s, 3H, CH_3), 7.2-7.8 (m, 8H, ArH, -CO-CH=CH), 7.5 (m, $-NO_2$), 7.8(S, 1H, NH); MS: *m/z* 392 ($M^{+\bullet}$).

Compound IVe: Yellow solid, yield 83 %, m.p. 230-232 ºC; IR (KBr, cm^{-1}): 3550, 2850, 1650, 1500, 1450, 1350, 1225, 725; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.9 (s, 3H, OCH_3), 7.1-7.9 (m, 8H, ArH, -CO-CH=CH), 7.5 (m, $-NO_2$), 7.9 (s, 1H, NH); MS: *m/z* 408 ($M^{+\bullet}$).



R = (a) H; (b) 6-CH_3; (c) 7-CH_3; (d) 8-CH_3; (e) 6-MeO; (f) 7-MeO; (g) 8-MeO; (h) 6-Cl; (i) 7-Cl; (j) 6-Br; (k) 6-F

Scheme-I: (i) 4 N HCl, reflux with microwave irradiation, 160 min, (ii) $K_2Cr_2O_7$, H_2SO_4, 2 h, (iii) 2-chloroquinoline-3-carbaldehydes, EtOH, 10 % NaOH, 0.5 h, (iv) $NH.NH_2$, EtOH, CH_3COOH, reflux 4 h

TABLE-1
PHYSICAL CHARACTERIZATION OF 2-CHLORO-3-[3-(6-NITRO-1*H*-BENZIMIDAZOL-2-YL)-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL]QUINOLINES (**Va-k**)

Comp. code	R	m.f.	m.w.	m.p. (°C)	Elemental analysis (%)				
					C	H	Cl	N	O
Va	H	$C_{19}H_{13}N_6O_2Cl$	392.79	105	58.10	3.34	9.03	21.40	8.15
Vb	6-CH_3	$C_{20}H_{15}N_6O_2Cl$	406.82	107	59.05	3.72	8.71	20.66	7.87
Vc	7-CH_3	$C_{20}H_{15}N_6O_2Cl$	406.82	111	59.05	3.72	8.71	20.66	7.87
Vd	8-CH_3	$C_{20}H_{15}N_6O_2Cl$	406.82	109	59.05	3.72	8.71	20.66	7.87
Ve	6-MeO	$C_{20}H_{15}N_6O_3Cl$	422.82	103	56.81	3.58	8.38	19.88	11.35
Vf	7-MeO	$C_{20}H_{15}N_6O_3Cl$	422.82	110	56.81	3.58	8.38	19.88	11.35
Vg	8-MeO	$C_{20}H_{15}N_6O_3Cl$	422.82	107	56.81	3.58	8.38	19.88	11.35
Vh	6-Cl	$C_{19}H_{12}N_6O_2Cl_2$	427.24	108	53.41	2.83	16.60	19.67	7.49
Vi	7-Cl	$C_{19}H_{12}N_6O_2Cl_2$	427.24	107	53.41	2.83	16.60	19.67	7.49
Vj	6-Br	$C_{19}H_{12}N_6O_2BrCl$	471.69	112	48.38	2.56	7.52	17.82	6.78
Vk	6-F	$C_{19}H_{12}N_6O_2ClF$	410.79	106	55.55	2.94	8.63	20.46	7.79

TABLE-2
ANTIBACTERIAL ACTIVITY OF SYNTHESIZED COMPOUNDS

Comp. code	R	Zone of inhibition (mm)							
		Gram-positive bacteria				Gram-negative bacteria			
		S. aureus		*B. subtilis*		*P. mirabilis*		*E. coli*	
		50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL
Va	H	8	12	10	13	10	12	9	13
Vb	6-CH_3	22	24	19	21	23	25	21	24
Vc	7-CH_3	16	19	14	18	13	15	12	17
Vd	8-CH_3	18	20	19	22	17	20	19	22
Ve	6-MeO	11	14	10	13	12	14	11	13
Vf	7-MeO	16	19	16	21	16	20	17	22
Vg	8-MeO	7	11	9	12	8	13	10	14
Vh	6-Cl	20	23	19	23	20	25	20	24
Vi	7-Cl	23	25	22	24	23	27	22	26
Vj	6-Br	21	24	22	25	20	24	19	23
Vk	6-F	19	21	20	22	18	21	19	23
Standard (ciprofloxacin 50 µg/mL)		25		26		27		27	

DMSO (control): No activity.

Compound IVh: Yellow solid, yield 82 %, mp 237-239 ºC; IR (KBr, cm^{-1}): 3600, 3150, 2850, 1700, 1625, 1500, 1475, 1350, 1225, 850,750; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.2-7.9 (m, 8H, ArH, -CO-CH=CH),), 7.5 (m, -NO_2), 7.9 (s, 1H, NH); MS: *m/z* 413 ($M^{+\bullet}$).

Compound Vb: Yellow solid, yield 62 %, m.p. 105-107 ºC; IR (KBr, cm^{-1}): 3342, 3184, 1693, 1599, 1475, 1392, 1205, 763, 705; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.7 (s, 3H, CH_3), 5.3 (dd, 1H, pyrazoline-5H), 7.1-7.9 (m, 9H, ArH), 7.5 (m, -NO_2); 7.8 (S, 1H, NH); MS: *m/z* 406 ($M^{+\bullet}$).

Compound Vc: Yellow solid, yield 69 %, m.p. 109-111 ºC; IR (KBr, cm^{-1}): 3180, 3057, 1622, 1514, 1487, 1386, 1215, 806; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.5 (t, 3H, CH_3) 6.8 (dd, 1H, pyrazoline-5H), 7.1-7.9 (m, 9H, ArH), 7.5 (m, -NO_2), 7.8 (S, 1H, NH); MS: *m/z* 406 ($M^{+\bullet}$).

Compound Vh: Yellow solid, yield 72 %, m.p. 106-108 ºC; IR (KBr, cm^{-1}): 3190, 3068, 1662, 1585, 1487, 1336, 1261, 825, 734; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.8 (dd, 1H, pyrazoline-5H), 7.2-7.8 (m, 9H, ArH), 7.5 (m, -NO_2), 7.8 (S, 1H, NH); MS: *m/z* 427 ($M^{+\bullet}$).

Compound Vk: Yellow solid, yield 70 %, m.p. 104-106 ºC; IR (KBr, cm^{-1}): 3196, 3061, 1674, 1504, 1490, 1338, 1267, 1149, 831; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.8 (dd, 1H, pyrazoline-5H), 7.2-7.9 (m, 9H, ArH), 7.5 (m, -NO_2), 7.8 (S, 1H, NH); MS: *m/z* 410 ($M^{+\bullet}$).

Antibacterial activity: Various organisms like *Staphylococcus aureus*, *Bacillus subtilis*, *Proteus mirabilis* and *Escherichia coli* were procured from Microbes Speciality Lab, Shree B.M. Patil Medical College Hospital and Research Centre, Vijayapur, India. The inhibition zones of synthesized compounds were determined using cup-plate method. The Petri dishes were washed thoroughly and sterilized in hot air oven at 160 ºC for 1 h. Sterile nutrient agar media (30 mL) for bacteria was poured into sterile Petri dishes and allowed to solidify. The medium was seeded with the organism by spread plate method using sterile cotton swabs. Bores were made on the medium using sterile borer. Solutions of the synthesized compounds at a concentration of 50 and 100 µg/mL were prepared in DMSO. Each solution (50 µL) was placed in cups by means of sterile pipette. In each plate one cup was used for standard, one for control and other two for test solutions. The plates thus prepared were incubated at 37 ºC for 24 h and examined for inhibition zones. The experiment was performed in duplicate and the average diameter of zones of inhibition was recorded. Ciprofloxacin (50 µg/mL) was used as standard [18,19].

RESULTS AND DISCUSSION

The antibacterial results (Table-2) revealed that the synthesized compounds showed a varying degree of inhibition against the tested microorganisms. Among the compounds synthesized, compounds **Vb**, **Vh**, **Vi** and **Vj** exhibited good antibacterial activity, while compounds **Vc**, **Vd**, **Vf** and **Vk** have shown moderate activity against both organisms.

Conclusion

Eleven new compounds of 2-chloro-3-[3-(6-nitro-1*H*-benzimidazol-2-yl)-4,5-dihydro-1*H*-pyrazol-5-yl]quinolines (**Va-k**) were synthesized. All the synthesized compounds were characterized by IR, ^{1}N MR and mass spectral techniques. The synthesized compounds were also screened for antimicrobial activity. The synthesized compounds exhibited moderate to good antibacterial activity.

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