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Synthesis and Evaluation of 2-Chloro-3-[3-(6-Methyl-1*H*-Benzimidazol-2-Yl)-4, 5-Dihydro-1*H*-Pyrazol-5-Yl] Quinolines as Potent Antimicrobial Agents

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ABSTRACT

A new series of 2-chloro-3-[3-(6-methyl-1*H*-benzimidazol-2-yl)-4,5-dihydro-1*H*-pyrazol-5-yl]quinoline (Va-k) have been synthesized by the reaction of 3-(2-chloroquinolin-3-yl)-1-(6-methyl-1*H*-benzimidazol-2-yl)prop-2-en-1-one (IVa-k) with hydrazine hydrate in ethanol and glacial acetic acid. The synthesized compounds were characterized by their IR, ^{1}H NMR and Mass spectral studies. Further, compounds were screened for their antimicrobial activity by cup plate method, using Ciprofloxacin and Fluconazole as a standard drugs. Results of the activities reveal that, compounds exhibited moderate to good antibacterial and antifungal activities.

Keywords: 6-Methylbenzimidazoles, Chalcones, Pyrazolines, Antimicrobial activity.

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INTRODUCTION

Benzimidazole is a heterocyclic aromatic organic compound. Owing to the vast importance and varied bioactivities exhibited by benzimidazoles, efforts are made from time to time to get libraries of those compounds and screen them for potential biological activities. These observations have encouraged us to synthesize some new products containing the benzimidazole moiety hoping to obtain new compounds with potential biological activity [1]. The benzimidazole has been a crucial pharmacophore and privileged structure in medicinal chemistry. Encompassing a plethora of useful biological activities such as antimicrobial [2], antioxidant[3], antiviral [4], antihypertensive [5], antiprotozoal [6], anti inflammatory [7] and antifilarial agents [8].

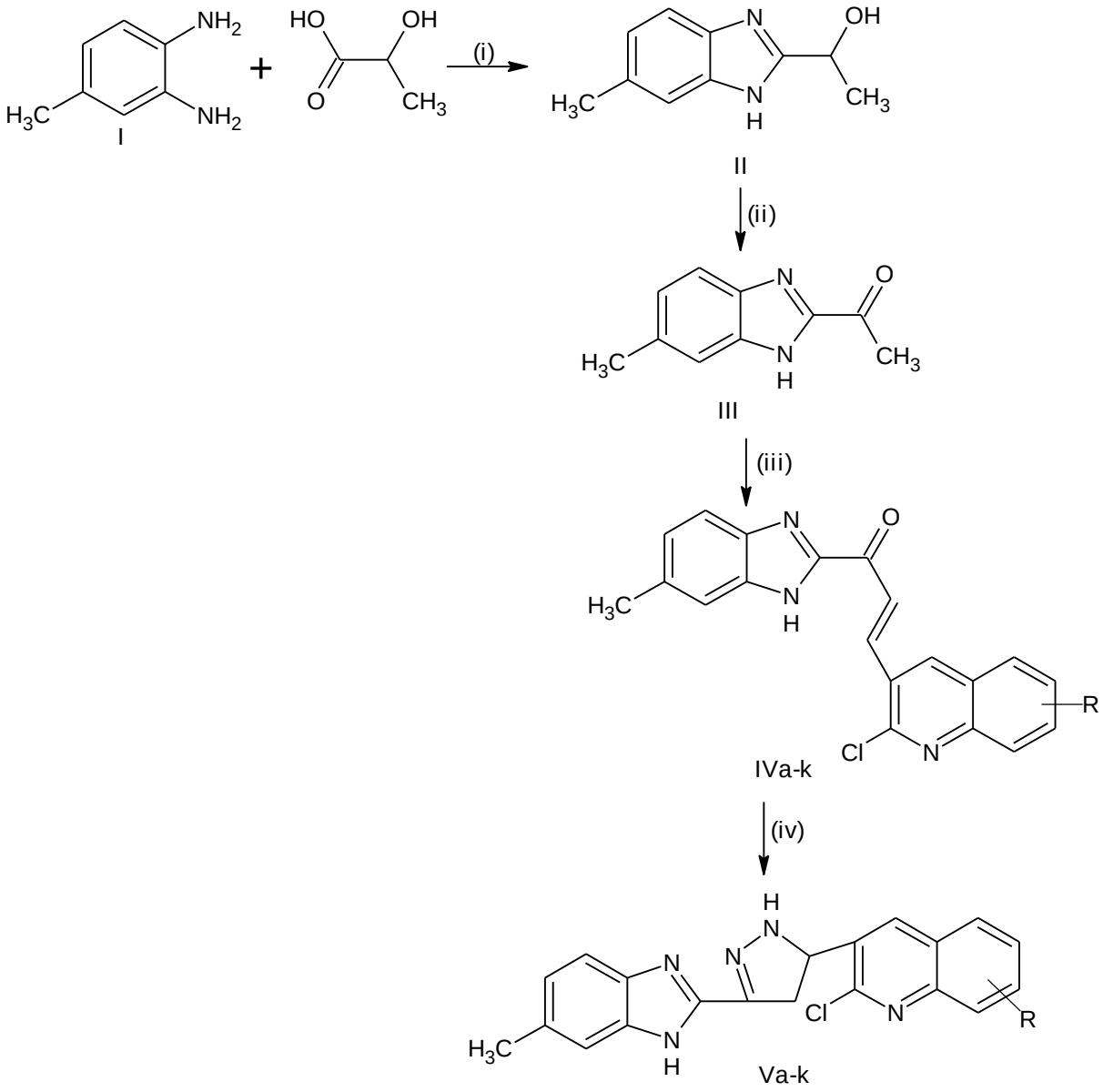
Pyrazolines are well known important nitrogen containing five membered heterocyclic compounds. They possess a wide spectrum of biological activities such as anticancer [9], antioxidant [10], antibacterial [11], antifungal [12], antidepressant [13-15], anti-inflammatory [16], anticonvulsant [17], antitumor [18], analgesic properties [19].

Pyrazolines are used extensively as useful synthon in organic synthesis. Among varied pyrazoline derivatives, 2-Pyrazolines appear to be the foremost often studied pyrazoline type compounds. A classical synthesis of those compounds involves the base catalyzed Claisen-Schmidt condensation of aryl methyl ketones and aldehydes to give chalcones that endure a subsequent cyclization reaction with hydrazines affording 2-Pyrazolines [20].

It is known that 4,5-dihydro-1H-pyrazole and its derivatives exhibit extensive biological and pharmacological activities. Thus considerable efforts are made to design and synthesize functional pyrazoline derivatives over the past few years. Although there are reports of synthesis of these substituted heterocycles, the development of synthetically vital functionalized new pyrazolines remains a challenge and has become a far tried analysis endeavor [21].

Antimicrobial agents are one in every of the foremost necessary weapons in the resistance of infection caused by microorganism strains. In the last few years, increase the resistance of micro-organisms toward antimicrobial agents is a serious health problem, so there is a need for safe, effective and novel antimicrobial agents [22].

Therefore, the present study was designed to synthesize and evaluation of 2-chloro-3-[3-(6-methyl-1*H*-benzimidazol-2-yl)-4, 5-dihydro-1*H*-pyrazol-5-yl] quinolines as potent antimicrobial agents by adopting the standard procedure.



Scheme

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.

Reagents and conditions:- (i) Lactic acid, 4N HCl, MW irradiation 320 minutes (ii) $K_2Cr_2O_7$, H_2SO_4 (25% v/v) 2 hrs, (iii) 10% NaOH, 2-chloroquinoline-3-carbaldehydes, Ethanol, 0.5 hrs, (iv) Hydrazine hydrate, Ethanol, Glacial acetic acid, 4 hrs.

EXPERIMENTAL

By open capillary tube method, melting points were checked and are uncorrected. By using TLC plates, TLC analysis was performed. By using KBr method, on a Shimadzu FTIR 8400S

spectrometer IR spectra were recorded. On Bruker Avance II of 400 MHz NMR spectrometer, NMR spectra and Mass spectra on a Waters, Q-TOF Micro ma SS spectrometer.

Synthesis of 1-(6-methyl-1*H*-benzimidazol-2-yl)ethanol (II)

4-methyl-o-phenylenediamine (0.01,mole) (I) was mixed with Lactic acid (0.01 mole) and 4N hydrochloric acid under Phillips conditions and heated to reflux in a synthetic microwave system, at an intensity of 65% (450 W) for 320 minutes. TLC was monitored, after completion of reaction period; cooled mixture was neutralized by sodium bi carbonate. The solid was separated, filtered and recrystallization was carried out from absolute alcohol. m.p-186-88ċ [23-25].

Synthesis of 1-(6-methyl-1*H*-benzimidazol-2-yl)ethanone (III)

To a solution of 1-(6-methyl-1*H*-benzimidazol-2-yl)ethanol (II) (8.8g, 50 mmole) in dilute H_2SO_4 (5%, 40 ml) was added a solution of $K_2Cr_2O_7$ (44g, 150 mmole) in dilute H_2SO_4 (25%, 80 ml) with constant stirring, drop wise for 20 minutes at an ambient temperature. The stirring further continued for 2 hours. On completion of reaction period (TLC monitored), separated solid (a chromium complex) dispersed in water and adjusted a pH up to 6 to 6.5 with aqueous ammonia (1:1). Solid product then washed, dried and recrystallized by ethyl acetate to obtain a purified compound. m.p-195-97ċ [26-27].

Synthesis of 3-(2-chloroquinolin-3-yl)-1-(6-methyl-1*H*-benzimidazol-2-yl) prop-2-en-1-one (IVa-k)

1-(6-methyl-1*H*-benzimidazol-2-yl)ethanone (III) (10 mm ole, 1.74g) and substituted 2-chloroquinoline-3-carbaldehydes (10 mm ole, 1.91g) were mixed in 30 ml of aqueous Na OH (10%). Continuing stirring up to 30 minutes, TLC was checked for completion of reaction. Solid filtered was dried. In addition, purified by recrystallization from a suitable solvent [28-34].

Similarly, **3-(2-chloroquinolin-3-yl)-1-(6-methyl-1*H*-benzimidazol-2-yl) prop-2-en-1-one (IVa-k)** were synthesized.

IVb: yield 77%, m.p-250-52ċ; IR (KBr): 3275, 3064, 2918, 1658, 1579, 1427, 1217, 763 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.52 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 5.14 (s, 1H, NH-benzimidazole), 6.63 (d, 1H, 1-ethylene), 7.73 (d, 1H, 1-ethylene), 7.10-7.68 (m, 3H, benzimidazole), 7.29-8.52 (m, 4H, quinoline). MS: *m/z* 361.80 (M+•).

IVe: yield 86%, m.p-262-64ċ; IR (KBr): 3271, 3192, 2848, 1664, 1554, 1234, 804 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.49 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 5.14 (s, 1H, NH-benzimidazole), 6.63 (d, 1H, 1-ethylene), 7.73 (d, 1H, 1-ethylene), 7.07-7.37 (m, 3H, benzimidazole), 7.52-8.53 (m, 4H, quinoline). MS: *m/z* 377.80 (M+•).

IVh: yield 88%, m.p-278-80ċ; IR (KBr): 3282, 2850, 1660, 1566, 1413, 1334, 802,719 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.30 (s, 3H, CH_3), 5.21 (s, 1H, NH-benzimidazole), 6.58 (d, 1H, 1-ethylene), 7.18 (d, 1H, 1-ethylene), 7.04-7.49 (m, 3H, benzimidazole), 7.67-8.23 (m, 4H, quinoline). MS: *m/z* 382.20 (M^+ +1).

Synthesis of 2-chloro-3-[3-(6-methyl-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-methyl-1*H*-benzimidazol-2-yl)prop-2-en-1-one (3.68g, 0.01 mole) was dissolved in ethanol (40 ml) and glacial acetic acid (10 ml). Hydrazine hydrate (0.75g, 0.015 mol) was then added and the reaction mixture refluxed for 4 hrs on a water bath. The solvent was reduced to half its volume. The crystalline product which separated out on cooling was filtered, washed with water, dried and crystallized from ethanol [35].

Similarly, **2-chloro-3-[3-(6-methyl-1*H*-benzimidazol-2-yl)-4, 5-dihydro-1*H*-pyrazol-5-yl]quinoline (Va-k)** were synthesized.

Vb : Yellow solid, yield 55%, m.p-168-70ċ; IR (KBr): 3190, 3053, 1664, 1579, 1479, 1228, 767 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 1.89 (d, 2H, methylene), 2.63 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 3.59 (d, 1H, methine), 5.44 (d, 1H, NH-benzimidazole), 7.04 (s, 1H, hydrazid) 7.37-7.55 (m, 3H, benzimidazole), 7.69-8.80 (m, 4H, quinoline). MS: *m/z* 375.80 (M+•).

Vd: Brown solid, yield 60%, mp 174-76ċ; IR (KBr): 3217, 3047, 1658, 1543, 1479, 1228, 767, cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 2.03 (d, 2H, methylene), 2.18 (d, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.75 (d, 1H, methine), 5.29 (d, 1H, NH-benzimidazole), 7.03 (s, 1H, hydrazid) 7.35-7.46 (m, 3H, benzimidazole), 7.70-8.35 (m, 4H, quinoline). MS: *m/z* 375.82 (M+•).

Vf : Brown solid, yield 64%, mp 183-85ċ; IR (KBr): 3216, 3086, 1624, 1570, 1448, 1228, 763 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 2.17 (d, 2H, methylene), 2.40 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.92 (s, 1H, methine), 5.31 (d, 1H, NH-benzimidazole), 7.01 (s, 1H, hydrazid) 7.53-7.80 (m, 3H, benzimidazole), 8.12-8.54 (m, 4H, quinoline). MS: *m/z* 391.83 (M+•).

Vh : Brown solid, yield 52%, mp 190-92ċ; IR (KBr): 3227, 3066, 1627, 1570, 1427, 1217, 806, 736 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 2.17 (d, 2H, methylene), 2.48 (s, 3H, CH_3), 3.73 (d, 1H, methine), 5.34 (d, 1H, NH-benzimidazole), 7.04 (s, 1H, hydrazid) 7.37-7.53 (m, 3H, benzimidazole), 7.58-8.24 (m, 4H, quinoline) MS: *m/z* 397.25 (M^+ +1).

Table 1: **Physical Characterization of 2-chloro-3-[3-(6-methyl-1*H*-benzimidazol-2-yl)-4, 5-dihydro-1*H*-pyrazol-5-yl] quinoline (Va-k)**

Sl. No	Compoud Code	R	Molecular Formula	Molecular Weight	M.P Ċ	% Yield
1	Va	H	$C_{20}H_{16}ClN_5$	361.82	162-164	50
2	Vb	6-CH_3	$C_{21}H_{18}ClN_5$	375.85	168-170	55
3	Vc	7-CH_3	$C_{21}H_{18}ClN_5$	375.85	171-173	57
4	Vd	8-CH_3	$C_{21}H_{18}ClN_5$	375.85	174-176	60
5	Ve	6-Ome	$C_{21}H_{18}ClN_5O$	391.85	180-182	67
6	Vf	7-Ome	$C_{21}H_{18}ClN_5O$	391.85	183-185	64
7	Vg	8-Ome	$C_{21}H_{18}ClN_5O$	391.85	187-189	59
8	Vh	6-Cl	$C_{20}H_{15}Cl_2N_5$	396.27	190-192	52
9	Vi	7-Cl	$C_{20}H_{15}Cl_2N_5$	396.27	194-196	54
10	Vj	6-Br	$C_{20}H_{15}BrClN_5$	440.72	204-206	70
11	Vk	6-F	$C_{20}H_{15}ClFN_5$	379.81	198-200	62

Biological Evaluation [36-41]

Antibacterial activity:

The synthesized compounds are tested for antibacterial activity against two Gram-positive bacteria viz., *Bacillus subtilis, Staphylococcus aureus,* and two Gram-negative bacteria viz., *Proteus Mirabilis* and *Escheria coli*. The standard drug used was antibiotic Ciprofloxacin and DMSO as a solvent. Test compounds and the standard drug were used at a concentration 100µg/ml and 50µg/ml. The zones of inhibition of compounds were recorded once incubation of twenty four hours at 37ºC.

The results of the antibacterial activity reveals that, the compounds **Vb, Vd** and **Vf** displayed relatively high antibacterial activity, while compounds **Vc, Ve, Vh** and **Vi** showed reasonable antibacterial activity. **Va, Vj** and **Vk** showed moderate activity and the remaining compound **Vg** showed low activity.

Antifungal activity:

The antifungal activity of the products has been screened against two fungi viz., *Aspergilus Niger* and *Candida albicans* by cup-plate method. Fluconazole was used as a standard drug and DMSO as a solvent. Test compounds and standard drug were used at a concentration of 100µg/ml and 50µg/ml. The zones of inhibition of compounds were recorded once incubation of forty eight hours at 25ºC.

Further from antifungal activity results, compounds **Vb, Vd** and **Vf** showed excellent results for antifungal activity, while the compounds **Vc, Ve, Vh** and **Vi** also showed high antifungal activity. **Va, Vj** and **Vk** showed moderate activity and remaining compound **Vg** exhibited low activity.

Table 2: Antibacterial and antifungal activity of synthesized compounds (Va-k)

Compound	Antibacterial activity [a, b]				Antifungal activity [a, b]	
	B. subtilis	S. aureus	P.mirabilis	E. coli	A. niger	C. albicans
Va	12/10	11/09	10/08	11/10	08/06	09/07
Vb	24/22	25/24	23/21	24/23	18/16	19/17
Vc	17/15	16/14	15/14	16/15	14/12	15/13
Vd	25/23	24/21	22/21	25/23	17/15	18/16
Ve	18/16	17/14	14/13	15/14	13/11	14/12
Vf	23/22	22/20	24/22	22/20	18/16	17/15
Vg	07/05	08/05	10/07	09/06	06/03	07/04
Vh	18/16	17/15	16/14	19/17	13/10	12/11
Vi	17/16	17/15	19/17	18/16	14/13	13/11
Vj	11/09	10/08	10/09	10/07	09/07	08/06
Vk	13/11	11/10	12/09	12/10	10/08	09/07
Ciprofloxacin[b]	26	26	26	26	-	-
Fluconazole[b]	-	-	-	-	23	23

[a]Zone of inhibition at 100µg/ml.

[b]Zone of inhibition at 50µg/ml.

Minimum inhibitory concentration was found at 40µg/ml concentration.

RESULTS AND DISCUSSION

All compounds were screened for their antibacterial activity against two Gram-positive bacteria viz., *Bacillus subtilis*, *Staphylococcus aureus*, and two Gram-negative bacteria viz., *Proteus Mirabilis* and *Escheria coli* by the Cup-plate method using standard drug Ciprofloxacin. Similarly all the synthesized compounds were also screened for their antifungal activity against two fungi viz., *Aspergilus Niger* and *Candida albicans* by standard procedure using standard drug Fluconazole. Compounds **Vb, Vd** and **Vf** displayed relatively high antibacterial and antifungal activity.

Minimum inhibitory concentration (MIC) was determined by broth dilution method and it was found at 40µg/ml concentration.

CONCLUSION

A new series of compounds of 2-chloro-3-[3-(6-methyl-1*H*-benzimidazol-2-yl)-4, 5-dihydro-1*H*-pyrazol-5-yl]quinoline (Va-k) were synthesized and characterized. The synthesized compounds were also screened for antimicrobial activity. The results of antimicrobial testing revealed the compounds **Vb, Vd and Vf** have shown promising antimicrobial activity. Therefore, this work would be fruitful matrix for the development of novel class of antimicrobial agents.

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