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Synthesis And Anti-Inflammatory Activity of Some New 2-Chloro-3-[3-(6-Nitro-1*H*-Benzimidazol-2-Yl)-1*H*-Pyrazol-5-Yl]Quinolines

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Abstract*: A new series of pyrazole substituted 6-nitrobenzimidazoles have been synthesized by the oxidation of pyrazoline substituted 6-nitrobenzimidazole derivatives with iodobenzene diacetate in dichloromethane. All synthesized compounds are characterized on the basis of IR, [1]H NMR and Mass spectral studies. These compounds were evaluated for anti-inflammatory activity. Results reveal that, some of the compounds exhibited good anti-inflammatory activity.*

Keywords: *Anti-inflammatory activity, 6-nitrobenzimidazoles, Chalcones, Pyrazolines, Pyrazoles.*

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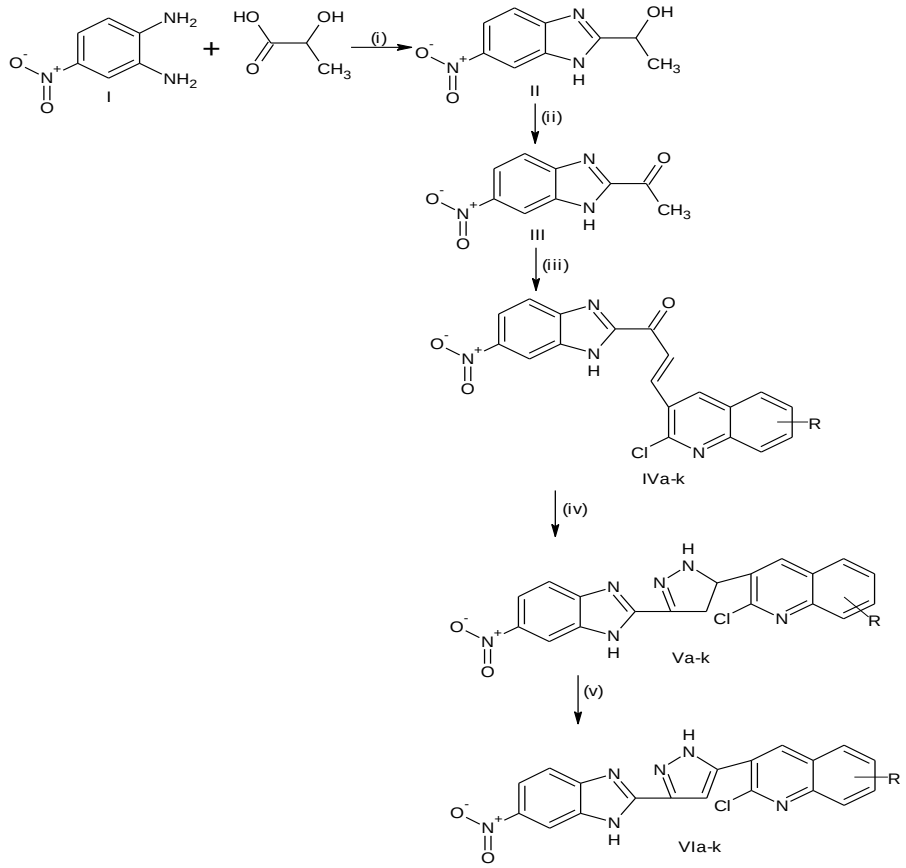
I. Introduction

Benzimidazoles are considered an important class of bioactive heterocyclic compounds with a number of biological activities. In particular, this nucleus is part of vitamin B12 [1]. This cyclic system is present in numerous antioxidant [2], anti-filarial [3], anthelmintic [4], antiviral [5], analgesic [6], anti-inflammatory [7] and antitumor activities [8]. Due to the considerable importance and different bioactivity of benzimidazoles, efforts have been made from time to time to generate libraries of these compounds and to analyze them for possible biological activities.

Several pyrazole derivatives have emerged as a group of compounds with a wide range of useful medicinal properties, including analgesics [9], antipyretics [10], anti-inflammatory [11], germicides [12] and anti fungal [13]. Inflammation is a local reaction of vascular elements and supporting elements of a tissue to a lesion resulting in the formation of a protein-rich exudates; it is a protective response of the non-specific immune system, which is used to locate, neutralize or destroy a harmful agent in order to prepare for the healing process. The cause of inflammation consists of physical agents, chemical agents, immunological reactions and infections by pathogenic organisms. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in elective treatment for various inflammatory conditions such as arthritis, rheumatism and to alleviate pain and pain in daily life. Classical NSAIDs are effective in limiting the biosynthesis of prostaglandins, some of which are pro-inflammatory. This is essentially due to the inhibition of the enzyme cyclooxygenase (COX) which limits speed and involves the inflammatory cascade. Among the various types of NSAIDs, imidazole and imidazole condensed with six-membered rings occupy a central position among those compounds used as analgesic and anti-inflammatory agents [14]. We have already reported the synthesis of several new biologically active benzimidazoles. Continuing our work on biologically active benzimidazoles, we have synthesized 1-(1H-benzimidazol-2-yl)-3- (2-chloroquinolin-3-yl) prop-2-en-1-one for their anti-inflammatory properties.



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) 4N HCl, reflux with microwave irradiation, 160 min, (ii) $K_2Cr_2O_7$, H_2SO_4, 2 hrs, (iii) 2-chloroquinoline-3-carbaldehydes, 10% NaOH, 0.5 hrs, (iv) $NH.NH_2$, EtOH, CH_3COOH, reflux 4 hrs, (v) iodobenzene diacetate , dichloromethane, 4hrs.

II. Materials And Methods

All solvents and reagents were purchased. The melting points are examined with the open capillary tube method. Using KBr pellet technique, IR spectra of compounds were observed on the Shimadzu FTIR Spectrophotometer 8400S. ^{1}H NMR spectra were recorded on Bruker Avance II from 400 NMR spectrophotometer and MASS spectra on a Waters, Q-TOF Microma SS spectrophotometer.

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

Equimolar amount of 4-nitro-O-phenylenediamine (0.01 moles) (I) and lactic acid (0.01 moles), 4N HCl are refluxed in a synthetic microwave oven at 65% intensity (450 W) for 160 minutes. The reaction was monitored by TLC, after 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 m.p-190ċ [15-16]

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

To a reaction mixture of 1-(6-nitro-1*H*-benzimidazol-2-yl)ethanol **(II)** (10.358 g, 50 mmoles) in dilute H_2SO_4 (5%, 40 ml) was added under stirring a solution of $K_2Cr_2O_7$ (44 g, 150 mmoles) in aqueous H_2SO_4 (25% v/v; 80 ml) drop wise over a period of 20 Minutes recorded. Stirring continued for 2 hours at ambient temperature, the solid (which is the chromium complex) was separated, suspended in 50 ml of water. The pH was adjusted to 6-6.5 with aqueous ammonia (1:1). Then the solid product was filtered, washed with water and dried. The product is further recrystallized from ethyl acetate m.p-202-204ċ [17, 18].

Synthesis of 3-(2-chloroquinolin-3-yl)-1-(6-nitro-1H-benzimidazol-2-yl)prop-2-en-1-one (IV)

To a reaction mixture of 1-(6-nitro-1*H*-benzimidazol-2-yl)ethanone (**III)** (2.07 g 10 mmoles) in aqueous NaOH (10%, 30 ml) was added respective 2-chloroquinoline-3-carbaldehyde (1.91 g, 10 mmoles) and left at ambient temperature for 30 minutes. After completion of the reaction, the separated solid product was filtered off, washed and dried with water. Further, it was recrystallized from ethanol. [19-25]

Chalcone derivatives (**IVa-k)** were prepared by similar method.

IVb: yield 69 %, m.p-226-228ċ; IR (KBr): 3600, 3150, 2850, 1655, 1600, 1550, 1425, 1350, 1225, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.75 (s, 3H, CH_3), 7.50 (m, $-NO_2$), 7.52-7.54 (d, 2H, CO-CH=CH), 7.26-7.80 (m, 7H, ArH), 8.69 (s, 1H, NH); MS: *m/z* 393.16 (M^+ +1).
IVe: yield 83%, m.p-230-232ċ; IR (KBr): 3550, 2850, 1650, 1500, 1450, 1350, 1225, 725 cm^{-1}; ^1H NMR (400 MHz, CDCl3): δ 3.95 (s, 3H, OCH_3), 7.51 (m, $-NO_2$), 7.17-7.18 (d, 2H, CO-CH=CH), 7.17-7.95 (m, 7H, ArH), 8.61(s, 1H, NH); MS: *m/z* 409.79 (M^+ +1).
IVh: yield 82%, m.p-237-239ċ; IR (KBr): 3600, 3150, 2850, 1700, 1625, 1500, 1475, 1350, 1225, 850, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.25-7.27 (d, 2H, CO-CH=CH), 7.52 (m, $-NO_2$), 7.25-8.02 (m, 7H, ArH), 8.65 (s, 1H, NH); *m/z* 415.21 (M^+ +2).

Synthesis of 2-chloro-3-[3-(6-nitro-1H-benzimidazol-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]quinoline (V)

To a reaction mixture of 3-(2-chloroquinolin-3-yl)-1-(6-nitro-1*H*-benzimidazol-2-yl)prop-2-en-1-one **(IV)** (3.78 g, 0.01 moles) was dissolved in ethanol (40 ml) and glacial acetic acid (10 ml). Hydrazine hydrate (0.75 g, 0.015 moles) was then added and the reaction mixture was heated to reflux on a water bath for 4 hours. The solvent was reduced to half its volume. The crystalline product precipitated on cooling was filtered off, washed with water, dried and crystallized from ethanol [26].

Pyrazoline derivatives (Va-k) were prepared by similar method.

Vb : yield 62%, m.p-105-107ċ; IR (KBr): 3342, 3184, 1693, 1599, 1475, 1392, 1205, 763, 705 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 2.26 (s, 3H, CH_3), 2.75 (d, 2H, CH_2-Pyrazoline), 5.34 (d, 1H, pyrazoline), 7.54 (m, $-NO_2$), 6.88-7.78 (m, 8H, ArH), 8.39 (S, 1H, NH); MS: *m/z* 407.11 (M^+ +1).
Vc : yield 69%, m.p-109-111ċ; IR (KBr): 3180, 3057, 1622, 1514, 1487, 1386, 1215, 806 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 2.58 (s, 3H, CH_3), 2.54 (d, 2H, CH_2-Pyrazoline), 6.85 (d,1H, Pyrazoline), 7.52 (m-NO_2), 7.00-7.76 (m, 8H, ArH), 8.16 (s, 1H, NH); MS: *m/z* 407.82 (M^+ +1).
Vh : yield 72%, m.p-106-108ċ; IR (KBr): 3190, 3068, 1662, 1585, 1487, 1336, 1261, 825, 734 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 2.95 (d, 2H, CH_2-Pyrazoline), 6.85 (d, 1H, Pyrazoline), 7.40 (m-NO_2), 7.26-7.87 (m, 8H, ArH), 8.31 (s, 1H, NH); MS: *m/z* 429.24 (M^+ +2).
Vk : yield 70%, m.p-104-106ċ; IR (KBr): 3196, 3061, 1674, 1504, 1490, 1338, 1267, 1149, 831 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 4.91 (d, 2H, CH_2-Pyrazoline), 6.86 (d, 1H, Pyrazoline), 7.52 (m-NO_2), 7.23-7.88 (m, 8H, ArH), 8.35 (s, 1H, NH); MS: *m/z* 412.78 (M^+ +2).

Synthesis of 2-chloro-3-[3-(6-nitro-1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]quinoline (VI)

To a stirred solution of 2-chloro-3-[3-(6-nitro-1H-benzimidazol-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]quinoline (V) (0.392 g, 0.001 moles) in dichloromethane (20 ml) was added iodobenzene diacetate (0.386 g, 0.0012 moles) at room temperature. The resulting mixture was stirred for 4 hours. Dichloromethane was evaporated to give a gum which was treated with pet-ether to remove iodobenzene and then purified by recrystallization from ethanol to give the product [27].

Pyrazole derivatives (VIa-k) were prepared by similar method.

VIc: yield 74%, m.p-81ċ; IR (KBr): 3171, 3051, 2918, 2850 1624, 1581, 1518, 1491, 1228, 734 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 2.69 (s, 3H, CH_3), 7.27 (s, 1H, -CH=C-), 7.56 (m-NO_2), 7.83 (s, 1H, -N=CH-), 7.14-7.83 (m, 7H, Ar-H), 8.72 (s, 1H, NH); MS: *m/z* 405.80 (M^+ +1).
VIf: yield 68%, m.p-83ċ; IR (KBr): 3070, 2918, 2848, 1620, 1548, 1491, 1209, 746 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 3.82 (s, 3H, OCH_3), 7.27 (s, 1H, -CH=C-), 7.38 (m-NO_2), 7.78 (s, 1H, -N=CH-), 7.27-7.80 (m, 7H, Ar-H), 7.69 (s, 1H, NH); MS: *m/z* 421.82 (M^+ +1).
VIh: yield 72%, m.p-84ċ; IR (KBr): 3157, 3063, 2958, 1622, 1496, 1230, 746 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 7.27 (s, 1H, -CH=C-), 7.87 (s, 1H, -N=CH-), 7.55 (m-NO_2), 6.85-7.99 (m, 7H, ArH), 8.74 (s, 1H, NH); MS: *m/z* 427.22 (M^+ +2).

VIk: yield 77%, m.p-80ċ; IR (KBr): 3182, 3061, 2918, 1656, 1539, 1273, 827 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 7.29 (s, 1H, -CH=C-), 7.69 (s, 1H, -N=CH-), 7.50 (m-NO_2), 6.86-7.89 (m, 7H, ArH), 8.74 (s, 1H, NH); MS: *m/z* 410.04 (M^+ +2).

TABLE NO.1 – Physical Characterization of synthesized compounds **(VIa-k)**

Sl. No	Comp. Code	R	Molecular Formula	Molecular Weight	M.P Ċ	C%	H%	Cl%	N%	O%	
1	VIa	H	$C_{19}H_{11}ClN_6O_2$	390.78	78	58.40	2.84	9.07	21.51	8.19	-
2	VIb	6-CH_3	$C_{20}H_{13}ClN_6O_2$	404.80	82	59.34	3.24	8.76	20.76	7.90	-
3	VIc	7-CH_3	$C_{20}H_{13}ClN_6O_2$	404.80	81	59.34	3.24	8.76	20.76	7.90	-
4	VId	8-CH_3	$C_{20}H_{13}ClN_6O_2$	404.80	80	59.34	3.24	8.76	20.76	7.90	-
5	VIe	6-Meo	$C_{20}H_{13}ClN_6O_3$	420.82	79	57.08	3.11	8.42	19.97	11.41	-
6	VIf	7-Meo	$C_{20}H_{13}ClN_6O_3$	420.82	83	57.08	3.11	8.42	19.97	11.41	-
7	VIg	8-Meo	$C_{20}H_{13}ClN_6O_3$	420.82	77	57.08	3.11	8.42	19.97	11.41	-
8	VIh	6-Cl	$C_{19}H_{10}Cl_2N_6O_2$	425.22	84	53.67	2.37	16.67	19.76	7.53	-
9	VIi	7-Cl	$C_{19}H_{10}Cl_2N_6O_2$	425.22	85	53.67	2.37	16.67	19.76	7.53	-
10	VIj	6-Br	$C_{19}H_{10}BrClN_6O_2$	469.67	87	48.59	2.15	7.55	17.89	6.81	17.01(Br)
11	VIk	6-F	$C_{19}H_{10}ClFN_6O_2$	408.77	80	55.83	2.47	8.67	20.56	7.83	4.65 (F)

BIOLOGICAL EVALUATION

Anti-inflammatory activity:-

The synthesized compounds are analyzed for anti-inflammatory activity by in-vitro method using the inhibition of the albumin denaturation technique. [28-30].

All the compounds that are both test drugs and standard drug were dissolved in DMF and diluted with saline phosphate buffer (pH 7.4) in such a way that DMF concentration in all solutions was less than 2.5%. The test solution (1ml, 100ug/ml) was mixed with 1 ml of 1% albumin solution in saline phosphate buffer and incubated at 27±1ċ in an incubator for 15 minutes. Denaturation was induced by keeping the reaction mixture in a 60±1ċ water bath for 10 minutes. After cooling, the turbidity was measured at 660 nm with a UV spectrophotometer. The denaturing inhibition rate was calculated from the control in which no drug was added. Each experiment was performed in triplicate and the average was taken. Diclofenac sodium was used as a standard drug. The inhibition percentage was calculated.

% Inhibition of denaturation= [(Vt/Vc)-1] × 100

Where, Vt = mean absorption of test compound,

Vc= mean absorption of control

III. Results And Discussion

Scheme summarizes the synthetic pathway to obtain **1-(6-nitro-1*H*-benzimidazol-2-yl)ethanol (II)** by reacting 4-nitro-O-phenylenediamine **(I)** with lactic acid. This on oxidation gives **1-(6-nitro-1*H*-benzimidazol-2-yl)ethanone (III)**. Further condensation with different aromatic/heteroaromatic aldehydes gives **3-(2-chloroquinolin-3-yl)-1-(6-nitro-1*H*-benzimidazol-2-yl)prop-2-en-1-one (IVa-k)**. This on reaction with hydrazine hydrate in ethanol and glacial acetic acid gives **2-chloro-3-[3-(6-nitro-1*H*-benzimidazol-2-yl)-4,5-dihydro-1*H*-pyrazol-5-yl]quinoline (Va-k)**. Further on treating with iodobenzene diacetate in dichloromethane gives the title compounds **2-chloro-3-[3-(6-nitro-1*H*-benzimidazol-2-yl)-1*H*-pyrazol-5-yl]quinoline (VIa-k)**.

The IR spectrum of **IVb** showed characteristic absorption peaks at 3150 (NH), 1600 (C=O) and 1550 (C=N). The ^1H NMR spectrum of **IVb** showed a singlet observed at δ 2.75 and assigned to the CH_3 protons. A multiplet at δ 7.26-7.80 (8H) was due to aromatic protons. A doublet was at δ 7.52-7.54 responsible for (CO-CH=CH) of chalcone moiety. (M^+ +1) Molecular ion peak appeared at 393.16.

The IR spectrum of **Vb** showed characteristic absorption peaks at 3342 (NH), 1693 (C=O) and 1599 (C=N). The ^1H NMR spectrum of **Vb** showed a singlet for CH_3 proton was observed at δ 2.26. A singlet of -CH_2 protons of the pyrazoline core was at δ 2.75 and also a singlet at δ 5.34 of pyrazoline nucleus were observed. A singlet of (m-NO_2) of aromatic ring was observed at δ 7.54 also a multiplet of aromatic protons was observed at δ 6.88-7.78 (8H) and one NH at δ 8.39. (M^+ +1) Molecular ion peak was observed at 407.11

The IR spectrum of **VIc** showed characteristic absorption peaks at 3171 (NH), 1624 (C=O) and 1581 (C=N). The ^1H NMR spectrum of **IVc** showed a singlet that was at δ 2.69, which was assigned to the CH_3 protons. A singlet was observed at δ 7.27 and δ 7.83 of –CH=C- and –N=CH- of pyrazole nucleus respectively. A singlet of (m-NO_2) of aromatic ring was observed at δ 7.56, a multiplet at δ 7.14-7.83 (7H) accounted for aromatic protons and one NH at δ 8.72. (M^+ +1) Molecular ion peak was observed at 405.80.

Similarly, the structures of the remaining compounds were confirmed by the spectral data. In addition, they were tested for anti-inflammatory activity.

TABLE NO. 2 - Anti-inflammatory activity of synthesized compounds.

Compound	Mean absorbance± S.D	% inhibition of denaturation
Control	0.1938 ±0.00349	
Via	0.2228 ± 0.00105	14.98
VIb	0.3543 ± 0.00156	82.81
Vic	0.3189 ± 0.00030	64.55
VId	0.3534 ± 0.00058	82.35
Vie	0.3122 ± 0.00345	61.09
VIf	0.3543 ± 0.00041	82.81
VIg	0.2330 ± 0.00115	20.22
VIh	0.2986 ± 0.00100	54.07
Vii	0.2872 ± 0.00160	48.19
VIj	0.2781 ± 0.00141	43.49
VIk	0.3429 ± 0.00190	76.93
Standard	0.3639 ± 0.00090	87.77

S.D =Standard deviation (Average of three determination)
Standard=Diclofenac sodium

Among the synthesized compounds, VIb, VId and VIf showed excellent activity, compounds VIc VIe and VIk showed good activity, and compounds VIh, VIi and VIj showed low activity. The compounds VIa and VIg showed a very poor activity

IV. Conclusion

A protocol was developed for the synthesis of new 2-chloro-3-[3-(6-nitro-1H-benzimidazol-2-yl)-1H-pyrazol-5-yl] quinolin series. It has been found that the preferred synthetic route shows a good yield for the synthesis of benzimidazoles. The product structures have been confirmed by their spectral studies. Furthermore, these compounds were tested for anti-inflammatory activity. Many of the tested products showed good activity.

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