Synthesis of Benzimidazole Derived Chalcones and their Heterocyclic Derivatives

Mohamad F.Ali, Abdulrahim M Khlafulla, Reem mohamed

***Abstract*— A number of benzimidazole derivatives were prepared via the condensation reaction of o-phenylene diamine with various aromatic carboxylic acids in the presence of hydrochloric acid. The acetylated benzimidazoles then allowed to react with benzaldehyde derivatives to give chalcones. In order to achieve the final heterocyclic compounds those chalcones were treated with hydroxylamine hydrochloride, hydrazine hydrate and thiourea through Claisen-Schmidt condensation. The structure of all synthesized compounds were established by physical and spectral methods.**

***Index Terms*— Synthesis, benzimidazole, chalcone, heterocyclic compounds, Introduction.**

I. INTRODUCTION

Literature survey shows that benzimidazole derivatives play a vital role in biological fields such as antidiabetic [1], antimicrobial [2], antiviral [3], antispasmodic [4], and anticancer [5] activities. α,β-Unsaturated ketones are biogenetic precursors of flavonoids in higher plants. Also known chemically as chalcones, they consist of open-chain flavonoids in which the two aromatic rings are joined by a three carbon chain [6]. They display a wide range of pharmacological properties, including cytotoxity towards cancer cell lines [7,8], antimitotic [9], antimutagenic [10] and antitumor-promotingactivities; antibacterial [11], antiviral [12], anti-inflammatory [13], antiulcerative [14] and hepatoprotective activities [15].

In this work we aimed to couple two biological active moieties, benzimidazol moiety which are known for their many therapeutic applications (such as antimicrobial, anti-inflammatory, and anticancer..etc.); and a chalcones since the presence of α,β-unsaturated carbonyl system of chalcones makes it biologically active. They have shown antibacterial activity against S. aureus, E. coli, C. albicans, T. utilis, S. sake, W.anomala and some other organisms [16].

Led by these considerations, it appeared of interest to synthesize novel pyrazole, isoxazole, and pyrimidine derivatives and make them available may be for investigation of their pharmacological activities in future

II. EXPERIMENTAL

The melting points of all synthesized compounds are uncorrected, and were determined on SMP-3 digital melting point apparatus made by Bibby Steriline Ltd, Stone, UK.

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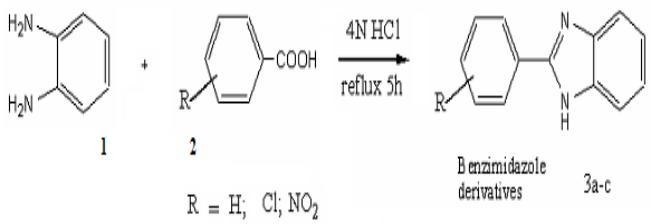
IR spectra were recorded on Perkin-Elmer-1800 FTIR spectrophotometer in the frequency range 4000-450 cm^{-1} in Nujol mull and as KBr pellets

^{1}H NMR spectra ($CDCl_3$) were recorded on Bruker Advance II 400 NMR spectrophotometer using TMS as internal standard; $^{13}CNMR$(100MHz, $CDCl_3$).

Benzimidazole derivatives(3a-c) were prepared according to the general procedure [17] and as follows:
o-Phenylene diamine (15 mmol) and substituted benzoic acid (30 mmol) were stirred in 4N HCl (40ml) under reflux for 5 hours. After cooling at room temperature, the pH was adjusted to 7.0 with NaOH (Solid). The resulting solid was filtered, washed with cold water, dried in vacuum pump and recrystallized from the alcohol. Scheme 1



Scheme1: Synthesis of benzimidazole derivative

General procedure for synthesis of 1-(1H)-benzo[d]imidazol-1-yl)ethanone (4a-c)

A solution of benzimidazole derivative (3a-c) (0.01mol) and acetic anhydride (20ml) in absolute ethanol (25ml) were taken into 100 ml round bottom flask. The reaction mixture was refluxed for 3 hrs. After completion of the reaction, it was poured into ice water, and the resulted precipitate was filtered. Crystallization from aqueous ethanol to give the products (4a-c) purity was confirmed by thin layer chromatography (hexane: methanol 9:1)
1-(2-phenyl-1H-benzo[d]imidazol-1-yl)ethanone (4a)

White solid, yield: 65 %, mp. 234-236°C ; IR (KBr): 1680.22 (C=O), 1595 (C=N);
^{1} HNMR ($CDCl_3$): δ, 1.74 (s, 3H, acyl- CH_3), 7.49 (dd,2H, Ar), 7.3 (dd,2H, Ar)
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): : 127-140 (C, benzimidazole),27.5-129.3 (Ar- C), 204(C, C=O); 24(C, CH_3)
1-(2-(4-Chlorophenyl)-1H-benzo[d]imidazol-1-yl)ethanone (4b).

Bright pink needles, yield: 85%, mp. 239-241°C ; IR= 829cm^{-1}(Ar-Cl) ^{1}HNMR ($CDCl_3$): δ, 1.74 (s, 3H, acyl-CH_3), 7.65 (dd,2H, Ar, benzimidazole), 7.40 (dd,2H, Ar, benzene)

^{13}CNMR ($CDCl_3$-δ ppm):125.39(C,Ar Cl),115-138 (C, benzimidazole), 204(C, C=O); 24(C, CH_3).

1-(2-(4-Nitrophenyl)-1H-benzo[d]imidazol-1-yl)ethanone (4c)

Brown solid, yield: 63%, mp. 270 °C; IR, 1588 (NO_2asym) and 1347(NO_2sym) ^{1}HNMR ($CDCl_3$): δ, 7.72-8.20 (m, 4H, Ar), 1.76 (s,3H,$COCH_3$).

.General procedure for synthesis of chalcones (5a-c) from N-acetyl-benzimidazole derivatives (4a-c) [2] shown scheme2.

N-Acetyl- benzimidazole derivative (0.01 mole, 1.73g) was dissolved in ethanol and sodium hydroxide solution (30 ml, 40%) was added and the mixture was cooled. To this was added (0.01 mole, 1.51g) nitro-benzaldehyde dissolved in a minimum quantity of ethanol and then the reaction mixture was stirred for a period of 4-5 hours and was left overnight. Conc.HCl was added drop by drop till the solution was slightly acidic. The solid separated was filtered, washed with water and dried. The crude product was crystallized from aqueous ethanol (50%). Purity was confirmed by thin layer chromatography using the solvent system, hexane: chloroform: methanol (60: 20: 20) .

IR(KBr), 1625-1650cm^{-1} (-CO-CH=CH-);
^{1}HNMR ($CDCl_3$): δ(ppm): 6.55 (d, 1H, HC-C=O),), 7.70 (d, 1H, C=CH-), 7.20–8.14 (m, 13H, Ar-H).

Next step, cyclization of chalcones (5a-c)with some amines. Scheme 3.

General procedure for the synthesis of 4-nitrophenyl-4,5-dihydro pyrazole derivatives 6_{a-c}) (4-Nitrochalcone (0.02mol) was dissolved in 50. ml absolute ethanol. To this mixture, hydrazine hydrate (0.04 mol) was added drop wise at room temperature, and the reaction mixture was refluxed for 7 hrs at 70°C. The reaction mixture was cooled in ice bath. The resulting solid was then filtered and washed with cold water.

1-(4,5-Dihydro-5-(4-nitrophenyl)-1H-pyrazol-3-yl)-2-phenyl -1H-benzo[d]imidazole (6a)

Brown solid, 65%, mp 165–167 °C. IR(KBr), 3098 cm^{-1} (NH), 1590cm^{-1} (C=N), 1334cm^{-1}(C-N) .
^{1}HNMR ($CDCl_3$) : δ 6.78 (d,1H,NH); 1.8-2.2 (dd,2H,methylene); 3.7(m,1H,methine); 7.23-8.12 (m,13H,Ar-H)
^{13}CNMR ($CDCl_3$) δ (ppm): 38.9 (CH_2), 47.8 (CH), 153, 146, 144, 138, 115-130.6
(C-Ar).
2-(4-Chlorophenyl)-1-(4,5-dihydro-5-(4-nitrophenyl)-1H-pyrazol-3-yl)-1H-benzo[d]imidazole (6b)

Yellow solid, 70%, mp 153–156 °C. IR(KBr), 3098 cm^{-1} (NH), 1590cm^{-1} (C=N), 1334 cm^{-1} (C-N)
^{1}HNMR ($CDCl_3$) : δ 6.78 (d,1H,NH); 1.8-2.2 (dd,2H,methylene); 37(m,1H,methine);7.23-8.12 (m,13H,Ar-H)
^{13}CNMR ($CDCl_3$) δ (ppm): 38.9 (CH_2), 47.8(CH),153,146,144,136(Ar-Cl),115-130.6(C-Ar).

1-(4,5-Dihydro-5-(4-nitrophenyl)-1H-pyrazol-3-yl)-2-(4-nitrophenyl)-1H-benzo[d]imidazole (6c)

Yellow solid, 57%, m.p. 176-178°C. IR(KBr), 3098 cm^{-1} (NH), 1590cm^{-1} (C=N), 1334 cm^{-1} (C-N);
^{1}HNMR ($CDCl_3$) : δ 6.78 (d,1H,NH); 1.8-2.2 (dd,2H,methylene); 37(m,1H,methine);7.23-8.12 (m,13H,Ar-H)
^{13}CNMR ($CDCl_3$) δ (ppm): 38.9 (CH_2),47.8(CH),153,146,144,136(Ar-Cl),115-130.6(C-Ar).

General procedure for the synthesis of 4-nitrophenyl-4,5-dihydroisoxazol derivatives (7_{a-c})

To a mixture of 4-nitrochalcone (1 g), and hydroxylamine hydrochloride (0.5 g) in water (5 ml) and ethanol (20ml) a solution of NaOH (10%, 10ml) was added. The reaction mixture was refluxed for 7 hrs, the completion of reaction was monitored by TLC, and it was then kept overnight at room temperature. After cooling in ice, the reaction mixture was acidified with dil.HCl. The resulting white solid was filtered, washed with water and the product was crystallized from aqueous ethanol (10%).
1-(4,5-Dihydro-5-(4-nitrophenyl)isoxazol-3-yl)-2-phenyl-1H -benzo[d]imidazolole (7a)
White needles with yield 63%,m.p. 169-172°C; IR (KBr), 1255.7cm^{-1} (C-O-N, St), 1612cm^{-1}(C=N,St),1471(Ar-C=C).
^{1}HNMR($CDCl_3$):δ1.4-1.6 ppm (dd,2H,methylene);4.1ppm(t,1H,methine);7.23-8.12 (m,13H,Ar-H).
^{13}CNMR ($CDCl_3$) δ (ppm): 30.9 (CH_2), 75.8 (CH), 160 (C=N),153,150.4 148.4, 144, 138, 115-130.6
2-(4-Chlorophenyl)-1-(4,5-dihydro-5-(4-nitrophenyll)isoxazol-3-yl)-1H-benzo[d]imidazole (7b)

White crystals in 72% yield, m.p. 175-177°C; IR(KBr), 1255.7cm^{-1} (C-O-N, St), 1612cm^{-1}(C=N, St), 1471(Ar-C=C).
^{1}HNMR ($CDCl_3$) : δ 1.4-1.6 ppm (dd,2H,methylene); 4.1ppm(t,1H,methine);7.23-8.12 (m,13H,Ar-H)
^{13}CNMR ($CDCl_3$) δ (ppm): 30.9 (CH_2), 75.8 (CH), 160 (C=N),153,150.4 148.4, 144, 138, 115-130.6

1-(4,5-Dihydro-5-(4-nitrophenyl)isoxazol-3-yl)-2-(4-nitrophenyl)-1H-benzo[d]imidazole (7c)

White crystals in 62% yield, m.p. 171-173°C; IR(KBr), 1255.7cm^{-1} (C-O-N, St), 1612cm^{-1}(C=N, St), 1471(Ar-C=C)
^{1}HNMR ($CDCl_3$) : δ 1.4-1.6 ppm (dd,2H,methylene); 4.1ppm(t,1H,methine);7.23-8.12 (m,13H,Ar-H)
^{13}CNMR ($CDCl_3$) δ (ppm): 30.9 (CH_2), 75.8 (CH), 160 (C=N),153,150.4 148.4, 144, 138, 115-130.6
General procedure for the synthesis of 4-nitrophenyl-4,5-dihydro pyrimidine thione derivative (8a-c)

chalcone (5) (0.01mole), thiourea (0.02 mole; 1.52 g) and KOH (0.02 mole; 1.12 g) were taken in a 100 ml round bottom flask. To the above reaction mixture ethanol (30ml) was added then the reaction mixture was refluxed for 5 hrs. It was then cooled and poured into cold water. The product which appeared after acidification with dill HCl, was filtered, washed with water and dried, then was recrystalized from ethanol.

4,5-Dihydro-4-(4-nitrophenyl)-6-(2-phenyl-1H-benzo[d]imidazole-1-yl)pyrimidine-
2(1H)thione (8a)

Yellow crystals in 65% yield, m.p. 149-151°C. IR(KBr), 3407.1(NH , St), 1584(C=N, St), 1334(C-N, St), 1490 (-S=C-N),
1470 (Ar-C=C)
^{1}HNMR ($CDCl_3$) : δ 1.85(d,2H,methylene), 2.20,(d,1H,NH,pyrimidine), 3.76 (dt, 1H,methine)
^{13}CNMR ($CDCl_3$) δ (ppm): 180.7 (C=S), 165 (C=N), 55.6 (CH), 40.9 (CH_2).

6-(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-4,5-dihydro-4-(4-nitrophenyl)pyrimidine-2(1H)-thione (8b)
^{13}CNMR ($CDCl_3$) δ (ppm): 180.7 (C=S), 165 (C=N), 48.6 (CH), 34.9 (CH_2).

Pale yellow crystals, yield 60.73%, mp 155-158°C; IR(KBr), 3407.1(NH , St), 1584(C=N, St), 1334(C-N, St), 1490 (S=C-N) 1470(Ar-C=C)
^{1}HNMR ($CDCl_3$): δ 1.85(d, 2H, methylene), 2.20,(d,1H,NH,pyrimidine), 3.76 (d, 1H,methine)

4,5-dihydro-4-(4-nitrophenyl)-6-(2-(4-nitrophenyl)-1H-benzo[d]imidazol-1-yl)pyrimidine-2(1H)-thione (8c)

Dark yellow crystals, yield 55%. mp 142-145°C;
IR(KBr), 3407.1(NH , St), 1584(C=N, St), 1334(C-N, St), 1490 (-S=C-N).

^{1}HNMR ($CDCl_3$) : δ 1.85(d,2H,methylene), 2.20,(d,1H,NH,pyrimidine), 3.76 (d, 1H,methine)
^{13}CNMR ($CDCl_3$) δ (ppm): 180.7 (C=S), 165 (C=N), 48.6 (CH), 34.9 (CH_2).

III. Result and Discussion

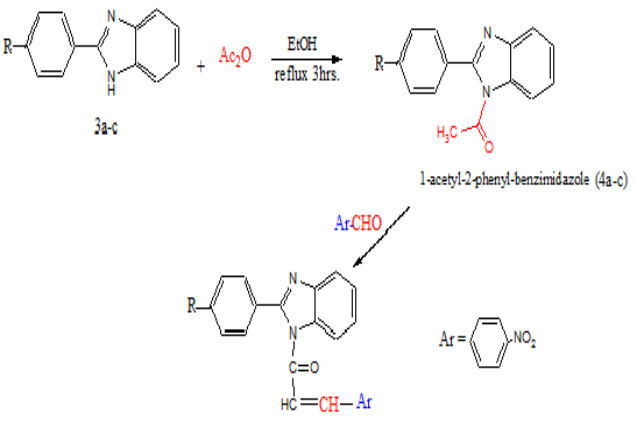
The synthetic procedures adopted to obtain the target compounds are depicted in scheme (3).
The starting compounds [(2-substitutedphenyl) benzimidazole,(3a-c)] were prepared following the method described in the literature [17], and they were confirmed chemically and by comparison their melting points with those of the compounds reported earlier by us [18]. The N-acetylderivatives,4a-c, were obtained by refluxing the compounds 3a-c with acetic anhydride in absolute ethanol, and then these acetyl derivative were converted into their chalcones by treatment them with 4-nitrobenzaldehyde in 40% alkaline medium as given in scheme 2.

Finally, the chalcone derivatives (5a-c) were cyclized with different amines to produce the target compounds, pyrazole, oxazoline, and pyrimidine derivatives (6-8a-c) as shown in scheme 3, The structures of the new resulted compounds were determined from their physical and spectral data.

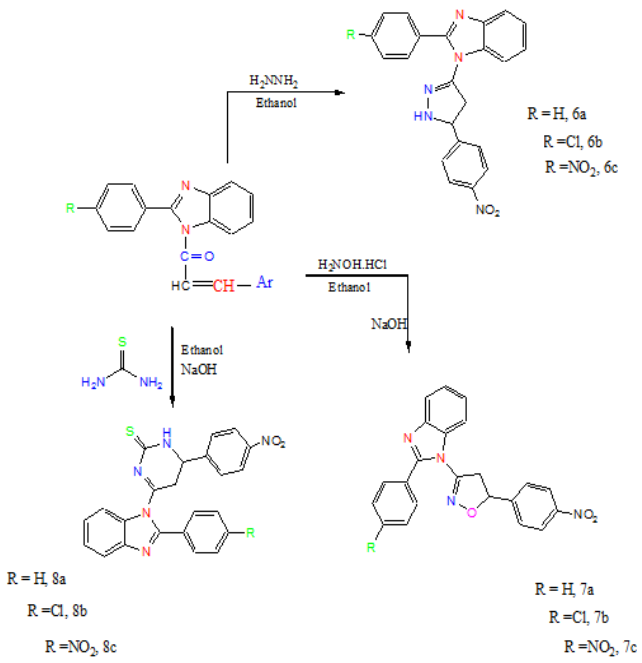
The IR spectra of compounds 4a-c showed the characteristic band at 1689 cm^{-1} which indicates the presence of a –C=O group, and absence of a band at 3320 cm^{-1} ,(NH), that exhibited by compounds (3a-c), while the ^{1}HNMR spectra showed a singlet peak at 1.74 ppm for the CH_3 protons (acetyl group), which is confirmed the acetylation.
The formation of chalcons (5a-c) is established by appearance the characteristic absorption peak of the chalcone unit (-CH=CH-C=O) at 1625-1650 cm^{-1}. Also, its ^{1}HNMR spectra exhibit doublet signal at 7.70 ppm for β-proton in addition to doublet observed at 6,55 ppm for α-proton, while the aromatic protons resonate as multiplet at expected regions.

The structure of cyclized product (6) was appropriately established by spectroscopic data, the IR spectra revealed the absorption bands at 3095 cm^{-1} and at 1590 cm^{-1} due to NH and C=N groups, and showed no absorption at the C=O region which indicated the cyclization, (see the cyclization mechanism drawn in scheme 4), the ^{1}HNMR data of compound (6a) showed doublet at 6.78 ppm for NH proton and exhibits doublet of doublet at 1.8-2.2 ppm for methylene protons (CH_2 pyrazole ring), in addition to doublet signal at 3.7 ppm for methine proton which is consistent with the structure.

The IR spectrum of isoxazoline (7) showed no carbonyl absorption, and it revealed absorption bands at1612cm^{-1} and 1255cm^{-1} due to C=N and C-O-N stretching frequencies respectively. Finally, the formation of pyrimidine moiety is confirmed by its IR spectrum which showed the appearance of a band at 1490 cm^{-1} (S=C-N), and showed disappearance of a carbonyl absorption band. Furthermore, the ^{13}C-NMR spectrum also supports the proposed structure by giving a signal for C=S bond at 180.7 ppm with absence of carbonyl signal confirming the cyclisation of the chalcone to produce a pyrimidine ring,(the spectral data for all the compounds are illustrated in the experimental part). A further study to acquire more information concerning pharmacological activity is in progress.

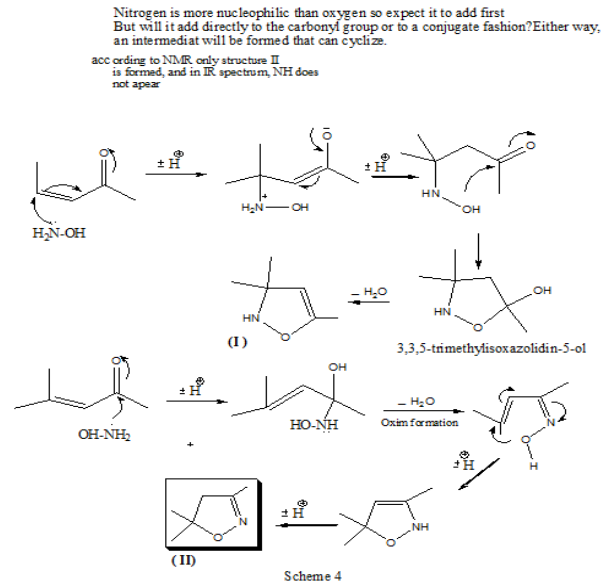


Schem 2 : synthesis of chalcone derivatives (5a-c)



Scheme 3. The synthesis rout of the cyclized products (6-8a-c)

The mechanism of cyclization



Scheme 4

IV. Conclusion:

We have synthesized a systematically substituted series of new chalcones and their heterocyclic moieties for structure activity relationship studies.

It is noteworthy to mention that the pyrazolo, isoxazolines, and pyrimidines derivatives having with variety of substituents such as chloro, nitro were prepared in good yield.

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