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Baghdad Science Journal **Vol.13(1)2016**

DOI: http://dx.doi.org/10.21123/bsj.2016.13.1.0082

Synthesis and Characterization of Some New Benzimidazole Derivatives

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Received 26, November, 2014
Accepted 14, January, 2015

Abstract:

In this paper the new starting material 2-(5-chloro-1*H*-benzo[*d*]imidazole-2-yl) aniline (1) was synthesized by the condensation reaction of 4-chloro-*o*-phenylenediamine and anthranilic acid .The new Mannich base derivatives were synthesized using formaldehyde and different secondary amines to synthesize a new set of benzimidazole derivatives(2-5). Also, the new Schiff-base derivatives (6-10) were synthesized from the reaction of compound (1) with various aromatic aldehydes and the closure-ring was done successfully using mercapto acetic acid to get the new thiazolidine derivatives(11-12).These new compounds were characterized using some physical techniques like:FT-IR Spectra and ^{1}HNMR Spectra.

Key words: Benzimidazole, Mannich bases, Schiff's bases, Thiazolidine.

Introduction:

Benzimidazole is a heterocyclic aromatic organic compound. It is a Bicyclic compound composed of the fusion of benzene and imidazole. The most noticeable benzimidazole compound in nature is N-ribosyl-dimethyl benzimidazole, which used as an axial ligand for cobalt in vitamin B_{12} [1]. Benzimidazole derivatives have important functions in medical field with many pharmacological activities such as antimicrobial, antiviral, antidiabetic and anticancer activity.It is an important pharmacophore in drug field due to being a good bio activity of naturally forming nucleotides [2-5]. Mannich reactions have become important tools for the synthesis of new compounds. Mannich bases can either be directly used as intermediate chemical synthesis [6].They are organic compounds with the general formula R-CH_2-N<[7][8]. Also,Schiff's bases are condensation products of primary amines with carbonyl compounds and they were first known by Schiff in 1864 [9].A broad variety of benzimidazole derivatives have been well-known for their chemotherapeutic importance. for example: the presence of mannich side chains in a drug may fight the water bacteria through the formation of hydrochlorides[10] ,schiff's bases have anti cancer activity in animal inspection[11].

Materials and Methods:

Melting points were recorded with Sturat Melting point apparatus and were un corrected.Infra red spectra (FT-IR) were recorded on Shimadzu FT-IR-8300 spectrophotometer in Ibn Sina State Company(ISSC). ^{1}H-NMR spectra were carried out in Al-al Bayt University (Jordan) operating at 300 MHz in (DMSO - d_6) on Fourier transform Varian spectrometer.

Synthesis of Compounds:

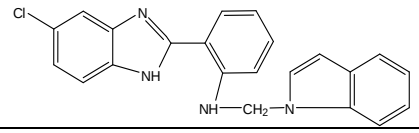
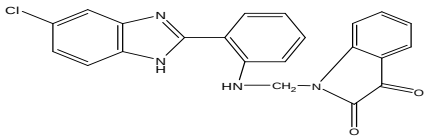
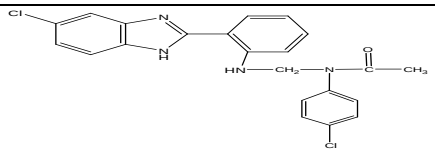
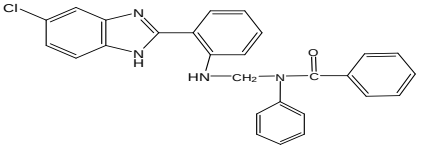
1) Synthesis of 2-(5-chloro-1*H*-benzo[*d*] imidazol-2-yl) aniline (1)

A mixture of a compound 4-chloro-1,2-diamino benzene (0.15mol) and anthranilic acid(0.1 mol)was refluxed with hydrochloric acid (4 M, 80 ml) for 24 hr. The reaction mixture was cooled at the room temperature and neutralized with sodium hydroxide (10 %) up to pH 8–9. The obtained solid was filtered off. The Products were purified by recrystallizing from methanol to get beige powder of compound(1), (yield 76% , M.P (272-274) ^{o}C.

2) Synthesis of Mannich Bases (2-5)

Compound (1) , (2.435 g,0.01 mol) was dissolved in hot methanol (25ml) and the compounds having secondary amine such as indole , isatine , 4-chloro acetanilide, benzanilide were added slowly to this hot solution, then formaldehyde (0.01 mol) was added all at once and refluxed for (4 hours) .The contents were kept overnight in the freezer. The corresponding crystals of mannich bases obtained were recrystallized from ethanol.

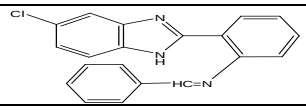
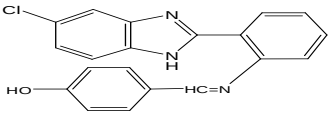
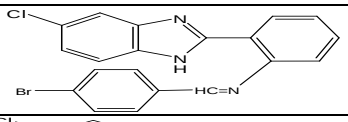
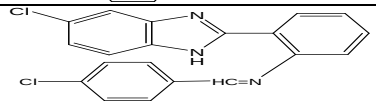
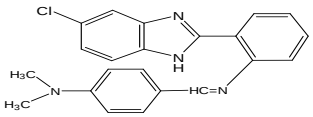
Table (1): The physical properties of Mannich bases (2-5)

Compd. No.	Nomenclature and Chemical formula	Structure formule	Yield %	Color	M. P. ^{o}C
2	[N-((1*H*-indol-1-yl)methyl)-2-(5-chloro-1*H*-benzo[*d*] imidazole-2-yl) aniline] [$C_{23}H_{19}ClN_4$]		81	Beige	122-124
3	[1-((2-5-chloro-1*H*-benzo[*d*] imidazole-2-yl)phenyl amino) methyl)indoline-2,3-dione] [$C_{22}H_{15}ClN_4O_2$]		86	Red	118-120
4	[N-((2-5-chloro-1*H*-benzo[*d*] imidazole-2-yl)phenyl amino) methyl)-N-(4-chloro phenyl) acetamide] [$C_{22}H_{18}Cl_2N_4O$]		70	brown	130-132
5	[N-((2-5-chloro-1*H*-benzo[*d*] imidazole-2-yl)phenyl amino) methyl)-N-phenyl benzamide] [$C_{27}H_{21}ClN_4O$]		55	Light brown	138-140

3) Synthesis of Schiff Bases (6-10)

A mixture of compound (1) (0.2435g ,0.001mol)and aldehydes (0.001 mol) in absolute ethanol (15 ml) and (3)drops of glacial acetic acid were refluxed for (6 hours). The mixture was cooled , collected by filtration and recrystallized from methanol.

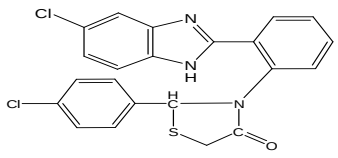
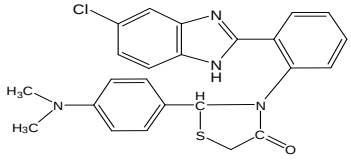
Table (2): The physical properties of Schiff bases (6-10)

Compd. No.	Nomenclature and Chemical formula	Compound Structure	Yield %	Color	M. P. °C
6	[N-benzilidine-(2-(5-chloro-1*H*-benzo[*d*] imidazol-2-yl)aniline] [$C_{20}H_{14}ClN_3$]		62	Light yellow	160-162
7	[4-((2-(5-chloro-1*H*-benzo[*d*]imidazol -2-yl)phenyl imino) methyl phenol] [$C_{20}H_{14}ClN_3O$]		73	Beige	228-230
8	[N-(4-bromo benzilidine)- 2-(5-chloro-1*H*-benzo[*d*] imidazol-2-yl)aniline] [$C_{20}H_{13}BrClN_3$]		79	Dark yellow	212-214
9	[2-(5-chloro-1*H*-benzo[*d*]imidazol -2-yl) –N-(4-chloro benzilidine)aniline] [$C_{20}H_{13}Cl_2N_3$]		83	Light yellow	206-208
10	[4-(2-(5-chloro-1*H*-benzo[*d*]imidazol -2-yl) phenyl imino)methyl)–N,N- dimethylaniline] [$C_{22}H_{19}ClN_4$]		81	Yellow	218-220

4) Synthesis of Compounds [(2-Aryl-4-Oxo-1,3-Thiazolidin)– Hydrazino Acetyl] benzimidazole (11-12)

A mixture of the compounds (9or10) (0.01 mmole), 10 ml absolute ethanol were refluxed for 15 minutes. Then mercapto acetic acid (0.01 mmole) was added drop wise during 15 minutes while the mixture is hot. After that the mixture was refluxed for 10 hr, evaporated and treated with saturated solution of sodium bicarbonate filtered off and set aside at R.T up to dryness and recrystallized from ethanol to give the thiazolidine compounds.

Table (3): The physical properties of compound (11-12)

Compd. No.	Nomenclature	Structure formula	Yield %	Color	M. P. °C
11	[3-(2-(5-chloro-1*H*-benzo[*d*]imidazol -2-yl)phenyl)-2-(4-chloro phenyl) thiazolidin-4-one] [$C_{22}H_{15}Cl_2N_3OS$]		94	Yellow	232-234
12	[3-(2-(5-chloro-1*H*-benzo[*d*]imidazol -2-yl)phenyl)-2-(4-di methyl amino) phenyl) thiazolidin -4-one] [$C_{24}H_{21}ClN_4OS$]		92	Orange	249-251

Spectroscopic data of the synthesized compounds:

The structure of the synthesized compounds has been characterized and confirmed by FT-IR spectra, and ^{1}H.NMR spectra for some of them.

2-(5-chloro-1*H*-benzo[*d*]imidazol-2-yl) aniline (1) FTIR (KBr) cm^{-1}: 3406-3433(NH_2),3329 (NH) , 3070(ArC-H) , 1608 (-C=N), 752(C-Cl). ^{1}HNMR (DMSO-d_6): δ11.027 (bs,1H,NH),

δ(6.1- 6.9) (m,7H, C-H aromatic), δ 4.043 (s,1H,NH_2) .

N-((1*H*-indol-1-yl)methyl)-2-(5-chloro-1*H*-benzo[*d*]imidazole-2-yl)aniline(2)

FTIR(KBr)cm^{-1}: 3417 (NH)Amine, (3402,3290) (NH) Imidazole(taut.), 3082 (Ar-C-H), 2962 (Aliphatic-C-H), 1612 (-C=N), 744 (C-Cl).

1-((2-5-chloro-1*H*-benzo[*d*] imidazole-2-yl) phenyl amino) methyl) indoline-2,3-dione (3)

FTIR (KBr)cm^{-1}: 3394 (NH)Amine ,3244 (NH)Imidazole, 3066(Ar-C-H) , 2947 (Aliphatic-C-H), 1612 (-C=N), 1735 (C=0), 752 (C-Cl). ^{1}HNMR (DMSO-d_6): δ4.8 (s,2H,CH_2-N), δ (6.2-8.2)(m,11H, aromatic C-H), δ 3.7 (s,1H,NH-CH_2), δ 10.75 (s,1H,NH of imidazole).

N-((2-5-chloro-1*H*-benzo[*d*]imidazole-2-yl)phenylamino)methyl)-N-(4-chlorophenyl)acet amide (4) FTIR (KBr)cm^{-1}: 3302 (NH)Amine ,3263, 3194 (NH)Imidazole (taut.), 3078(Ar-C-H) , 2981 (Aliphatic-C-H), 1604 (-C=N),1666 (C=O),752(C-Cl). ^{1}HNMR (DMSO-d_6): δ (3.8 -4.2) (s,2H, CH_2-N), δ (6.9-8.9) (m,11H, aromatic C-H), δ 4.9 (s,1H,NH-CH_2), δ 10.75 (s,1H, NH of imidazole).

N-((2-5-chloro-1*H*-benzo[*d*] imidazole-2-yl) phenyl amino) methyl) -N-phenyl benzamide (5)

FTIR (KBr) cm^{-1}: 3475(NH)Amine, 3344, 3124 (NH) Imidazole(taut.), 3051 (Ar-C-H), 2789 (Aliphatic-C-H), 1654 (C=O), 1600 (-C=N), 752(C-Cl). ^{1}HNMR (DMSO-d_6): δ (3.9 -4.16) (s, 2H, CH_2- N), δ (6.9-8.9) (m,11H, aromatic C-H), δ 4.9 (s,1H,NH-CH_2), δ 10.75 (s,1H,NH of imidazole).

N-benzilidine-(2-(5-chloro-1*H*-benzo[*d*] imidazol-2-yl) aniline (6) FTIR (KBr)cm^{-1}: 3367,3194 (NH) Imidazole (taut.), 3082 (Ar-C-H), 2935 (Aliphatic-C-H), 1658, 1612 (-C=N), 752 (C-Cl) .

4-((2-(5-chloro-1*H*-benzo[*d*]imidazol-2-yl) phenylimino) methylphenyl (7) FTIR(KBr)cm^{-1}: 3421 (C-O-H) , 3383, 3325 (NH)Imidazole (taut.), 3074 (Ar-C-H), 2835 (Aliphatic-C-H), 1678, 1608 (-C=N), 750 (C-Cl).

N-(4-bromo benzilidine)- 2-(5-chloro-1*H* -benzo[*d*]imidazol-2-yl)aniline (8) FTIR (KBr)cm^{-1}: 3360, 3329 (NH) Imidazole (taut.), 3078(Ar-C-H), 2850 (Aliphatic-C-H), 1608, 1573 (-C=N), 756(C-Cl), 524 (C-Br).

[2-(5-chloro-1*H*-benzo[*d*]imidazol-2-yl) –N-(4-chloro benzilidine)aniline (9) FTIR(KBr)cm^{-1}: 3452, 3402 (NH) Imidazole (taut.),3097(Ar-C-H), 2931 (Aliphatic-C-H), 1610(-C=N),748 (C-Cl) .

[4-(2-(5-chloro-1*H*-benzo[*d*]imidazol-2-yl)phenylimino)methyl)–N,N-dimethylaniline(10) FTIR (KBr)cm^{-1}:3078 (Ar-C-H), 2962 (Aliphatic-C-H),1612 (-C=N),748(C-Cl). ^{1}HNMR (DMSO-d_6): δ 3.4 (s,6H,N(CH_3)$_2$), δ 8.4(s,1H,CH=N), δ (6.15-8) (m,11H, aromatic C-H), δ 11.027 (s,1H, NH of imidazole).

3-(2-(5-chloro-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(4-chlorophenyl) thiazolidin-4-one(11)

FTIR(KBr) cm^{-1}:3429,3365 (NH) Imidazole(taut.), 3078 (Ar-C-H), 2981 (Aliphatic-C-H), 1732 (C=O), 1577 (-C=N), 783 ,767 (C-Cl) , 524 (C-S) . ^{1}HNMR (DMSO-d6) : δ 3.4 (s,2H,S-CH_2), δ 6.1 (s,1H,N-CH), δ (7-7.9) (m,11H, aromaticCH), δ 9.2 (s,1H,OH) , δ 11.027 (s,1H,NH of imidazole).

3-(2-(5-chloro-1*H*-benzo[*d*]imidazol-2-yl) phenyl)-2-(4-di methyl amino) phenyl) thiazolidin -4-one (12)

FTIR (KBr) cm^{-1}:3429,3365 (NH) Imidazole (taut.), 3078(Ar-C-H) , 2981 (Aliphatic-C-H), 1732 (C=O),1577 (-C=N), 783,767(C-Cl), 524 (C-S) . ^{1}HNMR (DMSO-d6): δ3 (s,6H,N(CH_3)$_2$), δ 3.4 (s,2H,S-CH_2) , δ 4.7 (s, 1H,N-CH),δ(6.7-7.9)(m,11H, aromatic CH), δ9.2(s,1H,OH),δ11.156 (s,1H,NH of imidazole).

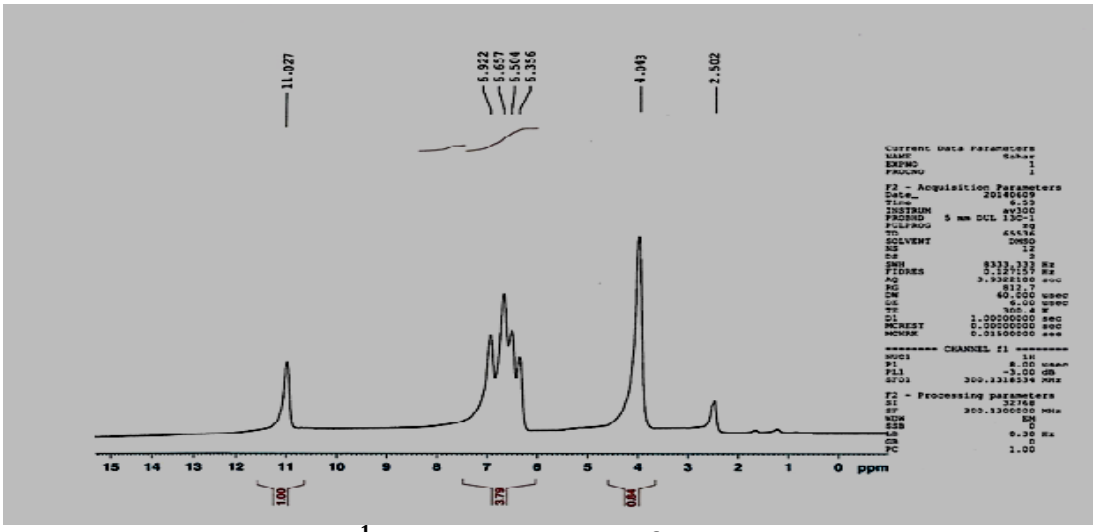


Fig.(1):^{1}H-NMR Spectrum of compound (1)

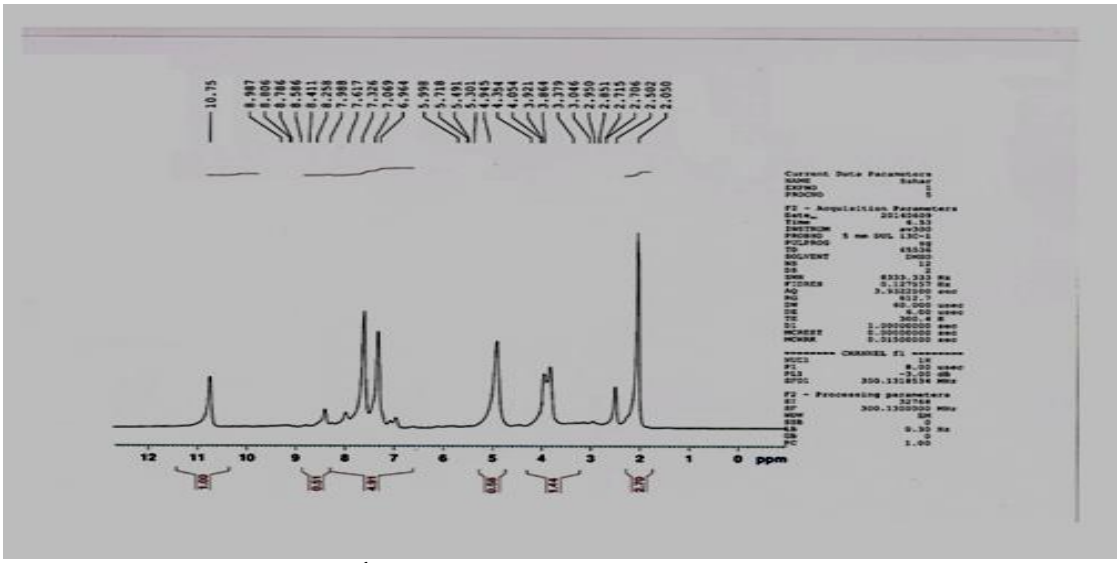
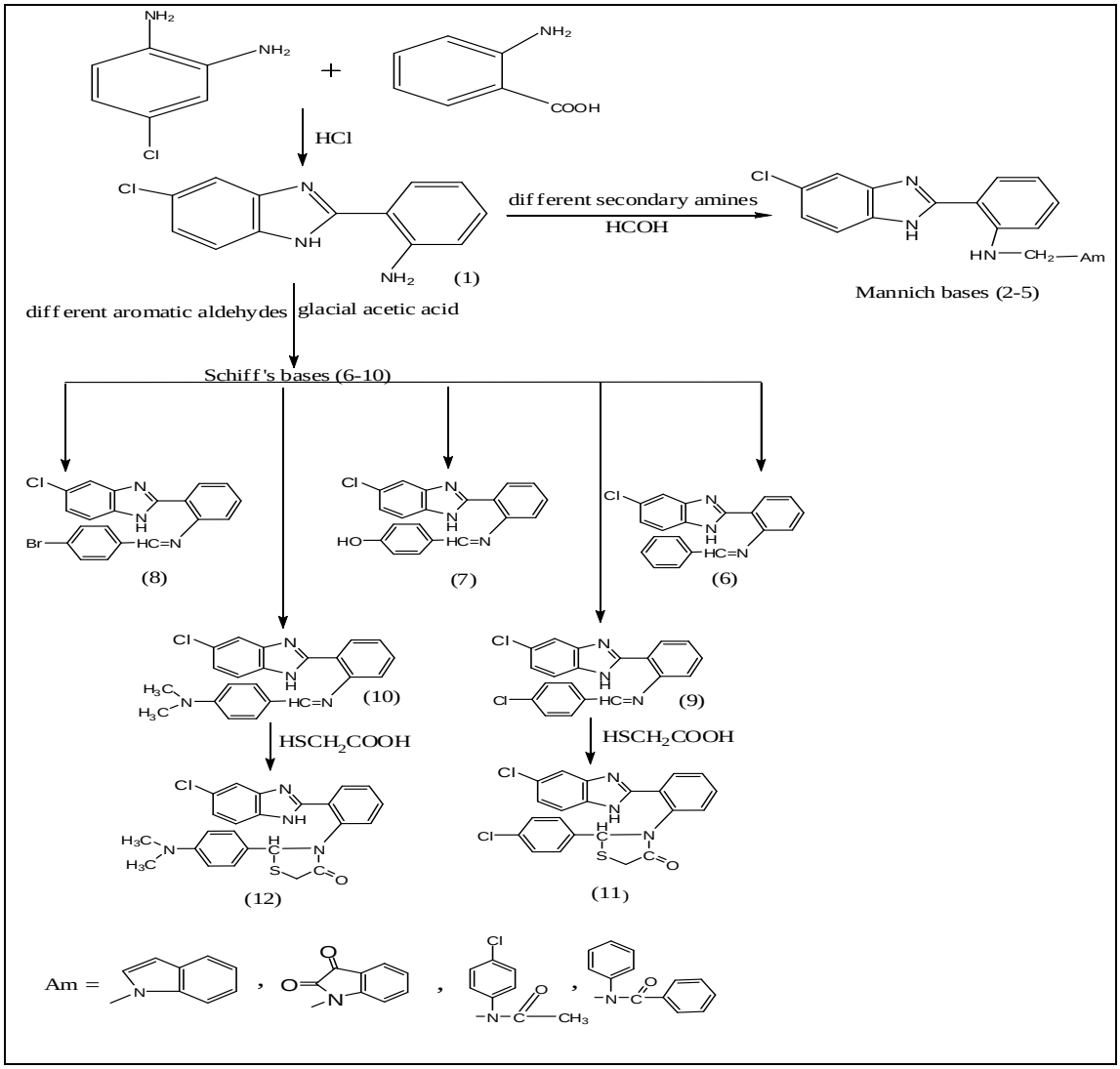


Fig.(2):^{1}H-NMR Spectrum of compound (4)

Results and Discussion:

This paper reports a simple and an effective method for the synthesis of some new benzimidazole derivatives which were obtained in good to excellent yield . In the present work 2-(5-chloro-1*H*-benzo[*d*] imidazole-2-yl)aniline (1)which was synthesized from the condensation reaction of 4-chloro-*o*-phenylenediamine with anthranilic acid was used as the key intermediate for further synthesis Thus, the compound (1)was allowed to undergo the Mannich reaction with different secondary amines namely indole, isatine, 4-chloro acetanilide, and benzanilide using formaldehyde in absolute methanol to give compounds (2-5) respectively. Also, the condensation reaction of the compound (1) with different aromatic aldehydes ,namely, benzaldehye,4-hydroxy-benzaldehyde, 4-bromo benzaldehyde, 4-chloro Benzaldehyde, and N,Ndimethyl benzaldehyde in absolute ethanol afforded the corresponding Schiff's bases(6-10).On the other hand, the cyclo condensation of some substituted Schiff's bases (9,10) with thioglygolic acid afforded the corresponding thiazolidine (11,12) respectively [12] .The reactions sequence was illustrated in the scheme (1) :



Scheme (1) : The reactions sequence for the synthesis of some new benzimidazole derivatives

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تحضير وتشخيص بعض المشتقات الجديدة من البنزايميدازول

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الخلاصة :

في هذا البحث تم تحضير المادة الاولية الجديدة 2 - (5-كلورو-*H*1-بنزو[د] ايميدازول-2-يل) انيلين (1) من تفاعل التكثيف بين (4-كلورو-1،2- داي امينو بنزين) مع حامض الانثرانيليك.

كما تم انجاز تحضير مشتقات قواعد مانخ الجديدة (2-5) بأستعمال الفورمالديهايد مع مختلف الامينات الثانوية لتحضير مجموعة جديدة من مشتقات البنزوايميدازول.

كذلك تم تحضير مشتقات قاعدة شف الجديدة(6-10) من تفاعل مختلف الالديهايدات مع المادة الاولية الجديدة (1) .

و تم غلق المشتقات الجديدة لقواعد شف (9-10) بنجاح بأستعمال (2- مركبتو حامض الخليك) للحصول على مشتقات الثايوزوليدين الجديدة (11-12).

و تم تشخيص المركبات الجديدة باستعمال بعض التقنيات الفيزيائية مثل : طيف الاشعة تحت الحمراء وطيف الرنين النووي المغناطيسي للبروتون .

الكلمات المفتاحية : بنزايميدازول ، قواعد مانخ ، قواعد شف ، ثايوزوليدين .