Synthesis and Characterization of Some new Heterocyclic Derivatives from 3-Amino-4-Hydroxy Benzoic acid and Study their Biological Activity

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Abstract
The aim of this study is the synthesis of heterocyclic compounds in several steps, including the first step is the reaction of 4,5-dichloro-2- phenylenediamine with 3- amino- 4- hydroxybenzoic acid to obtain an imidazole derivative (1), which reacts with salicyldehyde to give a Schiff base derivative (2). The second step involves the reaction (2) with each of (chloroacetyl chloride, alanine, sodium azide, thioglycol acid, anthranilic acid, maleic anhydride) to get (beta-lactam derivatives (3), imidazolidine (4), tetrazole(5), thiazolidine(6), hydroquinazoline(7) and oxazepine(8)) resefectively.All prepared compounds have been diagnosed by (FT-IR and 1H-NMR) Spectroscopy and after diagnosis of spectra compound their biological effect was studied of anticancer.
Keyword: Schiff base, heterocyclic, anticancer.

1. Introduction

Heterocyclic compounds are organic compounds that contain in their composition one heterogeneous atom such (N, O, S)(1). Heterocyclic compounds form a part of large number, of pharmaceutical relevant molecule and have major biological significance and compounds currently account for about 70 % of all clinically used drugs(2, 3).These compound include beta-lactam, imidazolidine, tetrazol, thiazine, hydroquinazoline and oxazepane (4, 5). In recent years it has been used as a source for the synthesis of new compounds with diverse biological characteristics, especially compounds that contain nitrogen and sulfur in their composition (6). Thiazine is a hetero cyclic compound have various biological activities such as antibacterial, anti-inflammatory, insecticide, analgesic for pain and blood pressure (7).In this work, Schiff base were prepared from the condensation reaction between an aldehyde or a ketone with an amine. many Schiff base compounds have been synthesized since 1864 with wide areas of biological applications(8). Like anticancer, antitumor, anti-malarial(9, 10).

2. Materials

All chemicals' compounds in this work were of a high purity, include: 4, 5- dichloro phenylene diamine, 3-amino-4- hydroxy benzoic acid, (Sigma Aldrich, Germany), salicyldehyde (Riedel de Haen, Germany) hydrochloride (Sigma Aldrich, Germany)
INSTRUMENTS (FTIR) Spectra (400-4000cm-1) in KBr disk were recorded on SHIMADZU FTIR – 8400S Fourier transform 1H-NMR were recorded on Varian Agilent USA at(500MHZ) with (DMSO-d6) measurements were made at Department of Chemistry.Tehran University, Iran.

Preparation of compound (1) (11)

A mixture of (0. 003mol) 4, 5- dichloro phenylene diamine with of (0. 003mol) 3-amino-4- hydroxy benzoic acid in flask round-bottom containing a magnetic stirrer. Then it was dissolved in 30 ml of (4N) HCl at a concentration and then escalated for (six hours) to produce a light brown precipitate. The mixture was left for (24hr). Recrystallized it with absolute ethanol.

Preparation of compound (2) (12)

A mixture of equimolar quantities (0.005mol) of compound [1] and (0.61ml) (0.005mol) of syldehyded and (3 drops) of glacialacetic acid was refluxed for (8) h in 30 ml ethanol. The reaction mixture was cooled and kept for (24 hs). The crystals found was filtered, dried and recrystallized from ethanol.

Preparation of compound (3) (13)

To Triethyl amine (0.006 mol) in 1, 4-dioxane, chloroacetyl chloride (0.003 mol) was added drop wise to a solution of the compounds (2) (0.001 mol) and at 10 temperatures. The reaction mixture was stirred for (14h). The solid obtained was recrystallized from ethanol.

Preparation of compound (4) (14)

A mixture of schiff bases (2) (0.0011mol) and alanine (0.0011mol) was dissolved in THF (10ml) and refluxed for (36 hs). The reaction was cooled and recrystallized from absolute ethanol.

Preparation of compound (5) (15)

Compounds of (2) (0.001mole) was dissolved in (10mL) dioxane and mixed with (0.002mole) sodium azide. These mixtures were refluxed for (44) hs at (60) 0C. The crystals found was filtered, dried and recrystallized from ethanol.

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Preparation of compound (6) (16)

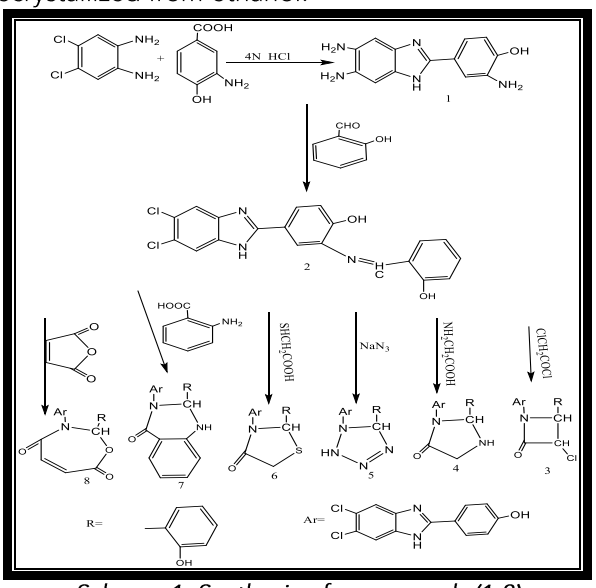
4-Mercaptobenzoic acid (0.002 mol) in 1,4- dioxane (10ml) was added to (0.001 mol) of Schiff bases (2). Then added to mixture (0.5gm) anhydrous zinc chloride with stirring then the mixture was refluxed for (14 hours). The reaction mixture was cooled and kept for (24 hs). The crystals found was filtered, dried and recrystallized from ethanol.

Preparation of compound (7) (17)

A mixture of Schiff base (2) (0.0011mole) and) (2-amino benzoic acid (0.002mole) was dissolved in (22mL) 1,4-dioxane. With the addition of (3) drops from DMF. The mixture was refluxed for(24hrs) in water bath at (55 0C), the precipitate was filtered and recrystallized from ethanol.

Preparation of compound (8) (18)

A mixture of Schiff base (2) (0.001mole) and maleic anhydride (0.002mole) was dissolved in (30mL) 1,4-dioxane. The mixture was refluxed for(30hrs) in water bath at (70 0C), the precipitate was filtered and recrystallized from ethanol.



Scheme 1. Synthesis of compounds (1-8)

Table 1. Physical properties of the derivatives (1-8)

Derivatives	Color	RF	M.P (°C)	M.Wt (g/mol)
1	Brown dark	0.34	188-190	294
2	dark	0.33	210-212	398
3	Dark	0.31	225-227	447.5
4	Brown dark	O.31	201-203	455
5	Brown dark	0.32	222-224	441
6	Dark	0.29	213-215	522
7	dark Brown	0.32	266-268	516
8	dark Brown	0.30	230-232	482

3. Results and Discussion

Derivative (1) 2-amino-4-(5,6-dichloro-1H-benzo[d]imidazol-2-yl) phenol

FT-IR showed band at 3371cm^{-1} for OH phenol, , 2916cm^{-1}, for C-H aliphatic, 3024 cm^{-1}for C-H aromatic, 3147 cm^{-1}for NH amine, 1558 cm^{-1} for C=C aromatic ,1666 cm^{-1} for C=N and 1203 cm^{-1} for C-O group ^{1}H-NMR of derivative (1) showed δ : (9.6 (S,1H,OH) phenol , 8.3 (S,1H,NH) 9.2imidazole , 6.9-8 (M,8H,Ar-H),

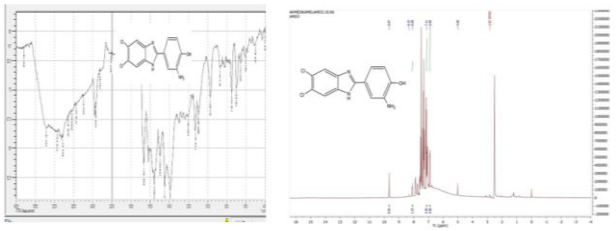


Figure (1) 1H-NMR Spectrum of The Compound (1). and FT-IR Spectrum of the Compound (1)

Derivative(2)(Z)-4-(5,6-dichloro-1H-benzo[d]imidazol-2-yl)-2-((2hydroxy benzylidene) amino) phenol.

FT-IR showed band at 3409cm-1 for OH phenol, 2977 cm-1, for C-H aliphatic, 3030 cm-1, for C-H aromatic,, 1604 cm-1 for C=C aromatic , 1681 cm-1 for C=N, 1126 cm-1 for C-O group 1H-NMR of derivative (2) showed δ : (10.6 (S,1H,OH) phenol , 10.5 (S,7H,NH) imidazole , 7.08-7.7 (M,8H,Ar-H),

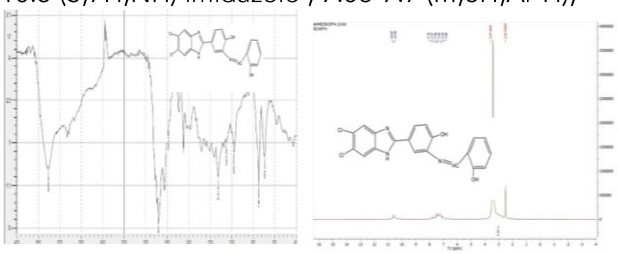


Figure (2) 1H-NMR Spectrum of The Compound (2). and FT-IR Spectrum of the Compound (2)

Derivative(3)3-chloro-1-(5-(5,6-dichloro-1H-benzo[d]imidazol-2-yl)-2-hydroxyphenyl)-4-(2-hydroxyphenyl) azetidin-2-one

FT-IR showed band at 3380cm-1 for OH phenol, , 2977 cm-1 for C-H aliphatic, 3015 cm-1 for C-H aromatic, , 1605 cm-1 for C=C aromatic , 1712 cm-1 for C=O, 1172 cm-1for C-O group 1H-NMR of derivative (3) showed δ : (10.7 (S,2H,OH) phenol , 10.6 (S,1H,NH) , 7.1-8.3 (M,9H,Ar-H), 3.03(d,1H(CH) ,1.2(d,1H(CH)

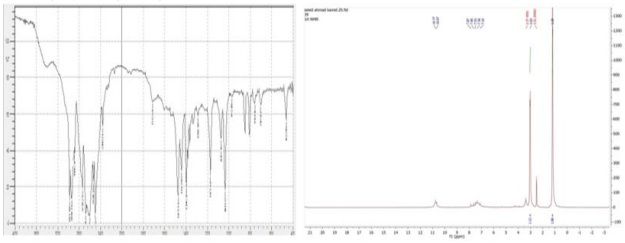


Figure (3) 1H-NMR Spectrum of The Compound (3). and FT-IR Spectrum of the Compound (3)

Derivativ (4) 3-(5-(5,6-dichloro-1H-benzo[d]imidazol-2-yl)-2-hydroxyphenyl)-2-(2-hydroxyphenyl) imidazolidin-4-one.

FT-IR showed band at 3380cm^{-1} for OH phenol, 2977 cm^{-1}for C-H aliphatic, 3042 cm^{-1} for C-H aromatic, 1604 cm-1 for C=C aromatic, 1712 cm-1for C=O group, 1180 cm-1 for C-O group. 1H-NMR of derivative (4) showed δ: 9.3 (S,2H, OH), phenol ,9.1(S,1H, NH),

imidazole, 6.9-8.3 (M,8H,Ar-H) , 5.2(S,1H,), NH imidazole , 4.3(S,1H(CH), 1.7(S,2H(CH2)

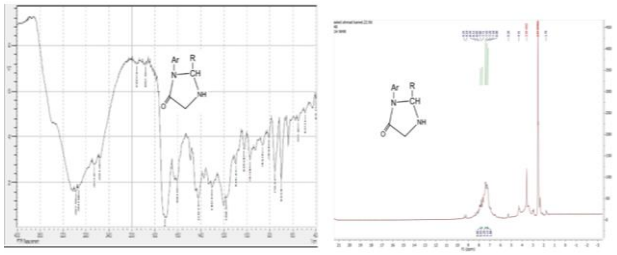


Figure (4) 1H-NMR Spectrum of The Compound (4). and FT-IR Spectrum of the Compound (4)

Derivativ (5) 4-(5,6-dichloro-1H-benzo[d]imidazol-2-yl)-2-(5-(2-hydroxyphenyl)-2,5-dihydro-1H-tetrazol-1-yl) phenol.

FT-IR showed band at 3209cm-1 for OH phenol, 2970 cm-1for C-H aliphatic, 3031 cm-1 for C-H aromatic, 1624 cm-1 for C=C aromatic, 1674 cm-1for C=N group, 1296 cm-1 for C-O group. 1H-NMR of derivative (5) showed δ: 10.4 (S,2H, OH), phenol ,9.6(S,1H,NH),imidazole, 6.5-7.8 (M,9H,Ar-H) , 5.2(S,1H,NH), tetrazol, 1.2(S,1H(CH)

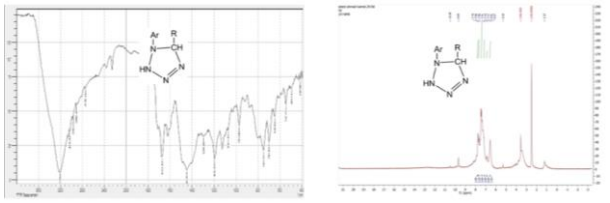


Figure (5) 1H-NMR Spectrum of The Compound (5). and FT-IR Spectrum of the Compound (5)

Derivativ (6) 3-(5-(5,6-dichloro-1H-benzo[d]imidazol-2-yl)-2-hydroxyphenyl)-2-(2-hydroxyphenyl) thiazolidin-4-one.

FT-IR showed band at 3505cm-1 for OH phenol, 2916 cm-1for C-H aliphatic, 3062 cm-1 for C-H aromatic, 1620 cm-1 for C=C aromatic, 1720 cm-1for C=O group, 1288 cm-1 for C-O group. 1H-NMR of derivative (6) showed δ: 9.34 (S,2H, OH), phenol ,9.32(S,1H, NH), 6.9-8.6 (M,9H, Ar-H), 3.6(S,1H(CH), 2.04(S,2H(CH) thiazolidine.

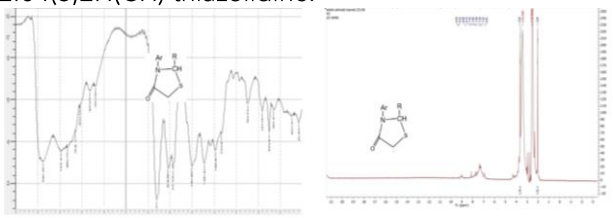


Figure (6) 1H-NMR Spectrum of The Compound (6). and FT-IR Spectrum of the Compound (6)

Derivativ (7) 3-(5-(5,6-dichloro-1H-benzo[d]imidazol-2-yl)-2-hydroxyphenyl)-2-(2-hydroxyphenyl)-2,3-dihydroquinazolin-4(1H)-one.

FT-IR showed band at 3348cm-1 for OH phenol, 2962 cm-1for C-H aliphatic, 3084 cm-1 for C-H aromatic, 1581 cm-1 for C=C aromatic, 1666 cm-1for C=O group, 1234 cm-1 for C-O group. 1H-NMR of derivative (7) showed δ: , 11.8 (S,2H,OH), phenol ,9.6(S,1H,NH),imidazole, 6.8-8.05 (M,9H,Ar-H) , 4.3(S,1H,NH),quan, 2.8(S,1H(CH)

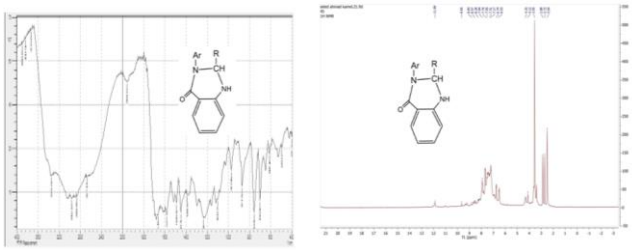


Figure (7) 1H-NMR Spectrum of The Compound (7). and FT-IR Spectrum of the Compound (7)

Derivativ (8) 1-(5-(5,6-dichloro-1H-benzo[d]imidazol-2-yl)-2-hydroxyphenyl)-7-(2-hydroxyphenyl)-6,7-dihydro-1H-azepine-2,5-dione.

FT-IR showed band at 3394cm-1 for OH phenol, 2977 cm-1for C-H aliphatic, 3042 cm-1 for C-H aromatic, 1627 cm-1 for C=C aromatic, 1720 cm-1for C=O group, 1211 cm-1 for C-O group. 1H-NMR of derivative (8) showed δ: 11.8 (S,2H, OH), phenol ,9.2(S,1H, NH), imidazole, 6.8-8.05 (M,9H, Ar-H), 3.16(S,1H(CH), 6.30(d,2H(CH), 6.36(d,2H(CH).

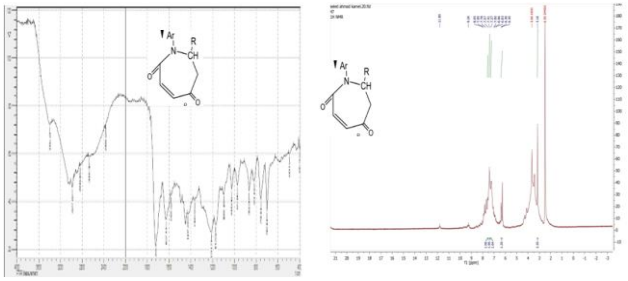


Figure (8) 1H-NMR Spectrum of The Compound (8). and FT-IR Spectrum of the Compound (8)

Biological study

The effect of (7) compound on the larynx cancer cells was performed. The study included two cell lines, the first was infected cancer cells(A549) and the second was healthy living cells (WRL68). This compound was prepared with different concentrations (400; 200; 100; 50; 25) µg\ml. when 400 µg\ml of this compound was used, it gave an inhibitory activity (57%) on A549 line, also it gave an inhibitory activity (51%) on WRL68 cells. Table (2) showed the effect of different concentration of 7 compound in different cells line. Figure (10) showed the percent of residual cells in different concentration and IC50

Table (2) showed the effect of different concentration of 7 compound in different cells line.

	A549		WRL68	
Concen.	Mean	SD	Mean	SD
400.00	43.17	3.64	49.69	3.51
200.00	58.10	2.37	74.46	0.85
100.00	75.62	3.47	92.13	1.56
50.00	88.08	3.28	96.18	1.25
25.00	94.60	2.17	96.95	1.14
12.50	95.37	1.86	94.91	2.20
6.25	95.83	1.97	94.92	0.81

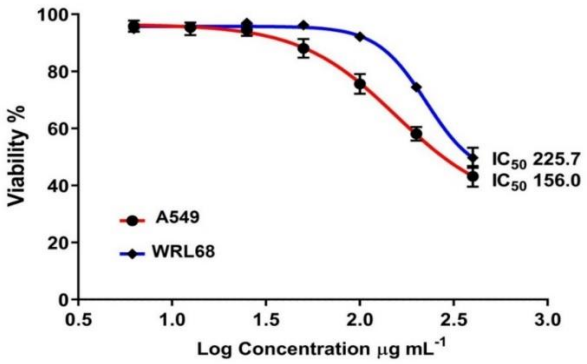


Figure (9) IC50 for comp. (7)

4. Conclusion

This research relied on the preparation of the heterocyclic derivative from 3-amino -4-hydroxy benzoic acid, which mainly led to the diagnosis of the compounds prepared on several techniques thereof (FT-IR, 1 H-NMR) and their evaluation against Ante cancer, these compounds were stable and have good biological efficacy.

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