Synthesis A New Bis Oxazine and Thiazine Derivatives and Study Their Biological Activities.

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Abstract:

Oxazine and thiazine are heterocyclic organic compounds that have a wide range of pharmacological applications. In this study, some chalcone derivatives (1–5) were synthesized based on the reaction of an equal amount of p-substituted acetophenone and terephthalaldehyde in a basic medium. Oxazine derivatives (6-10) and thiazine derivatives (11–15) are synthesized from the reactions of chalcones (1-5) with urea and thiourea, respectively, in a basic medium. The newly synthesized compounds were identified using various physical techniques like 1H-NMR and FT-IR spectra, in addition to docking analysis for some of these derivatives. Finally, these compounds were tested for their biological activity, IC50, and % of PC3 cell line viability as markers of anticancer activity.

Key words: Oxazine, Thiazine, Anticancer, Biological activity.

تخليق مشتقات جديدة ثنائية الاوكسازين والثيازين ودراسة تطبيقها البايولوجي

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الخلاصة:

الأوكسازين والثيازين هما مركبات عضوية حلقية غير متجانسة تمتاز بتطبيقها بمجال واسع في التطبيقات الدوائية. في هذه الدراسة، تم تصنيع بعض مشتقات الجالكون (1-5) بناءً على تفاعل كمية متساوية من p-substituted acetophenone و terephthalaldehyde في وسط قاعدي. ان مشتقات أوكسازين (6-10) ومشتقات الثيازين (11-15) تم تصنيعها من تفاعلات الجالكون (1-5) مع اليوريا والثيويوريا على التوالي في وسط قاعدي. تم تشخيص المركبات المخلقة باستخدام تقنيات طيفية مختلفة مثل أطياف H-NMR1 و FT-IR ، بالإضافة إلى تحليل Docking

الكلمات المفتاحية: الاوكسازين, الثيايزين, مضادات السرطان, الفعالية البايولوجية.

Introduction

Oxazine is a heterocyclic molecule that can be produced from chalcone (1). Oxazine contain in his structure heteroatom such as, nitrogen, oxygen as well as homoatoms carbon in bone structures (2). Oxazepines have numerous applications in medicine, including anticancer (3), antibiotics (4), antioxidants (5), drugs (6), and industry, including insecticidal (7) and other uses.

Thiazine is known as a heterocyclic molecule that contains 4 carbon atoms in different positions from nitrogen and oxygen atoms (8). Thiazine have been used in a big wide of applications (9- 11). A literature review identified several thiazine and oxazine compounds that are in the development stage as possible novel medications. These molecules are among the most promising sources of bioactive

compounds due to the adaptability of the thiazine and oxazine skeletons and the relative chemical simplicity and accessibility of these compounds (12).

One of the most dangerous diseases that affects people and sometimes results in death is cancer. From this point on, researchers developed and found more potent anticancer medicines, such as chemotherapy for the treatment of cancer, Prostate cancer is a cancer that occurs in the prostate. The prostate is a small, walnut-shaped gland in males that produces the seminal fluid that nourishes and transports sperm. Prostate cancer is one of the most common types of cancer. Many prostate cancers grow slowly and are confined to the prostate gland, where they may not cause serious harm. However, while some types of prostate cancer grow slowly and may need minimal or even no treatment, other types are aggressive and can spread quickly (13) or be treated with heterocyclic derivatives containing anticancer drugs (14). As a result, chemical investigations of heterocyclic compounds greatly aid in the production of a wide range of fused heterocyclic compounds with diverse biological and pharmacological properties.

Materials and Methods

Merck and BDH, from which chemicals were used.

Synthesis of Chalcone (1-5) (15)

Dissolve 20 gm of sodium hydroxide in 250 ml of distal water. In an ice bath, 50 ml of ethanol absolute was added to the solution and stirred for 15 minutes. 0.02 mmol of each para substituted acetophenone (-OH, -OCH3, -OC4H9, -Br, and -Cl) were stirred with 0.01 mmol of terephthalaldehyde for 12 hours at room temperature to become cold. These solutions were filtered and neutralized with diluted HCl until pH equaled 7, dried, and finally, recrystallized from ethanol to produce target compounds (1-5).

Synthesis of Oxazine Derivatives (6-10) (16)

After 8 hours of refluxing, 0.001 mol of each of the chalcone compounds (1-5) were added to 0.12 g (0.002 mol) of urea that had been dissolved in 50 ml EtOH absolute and 10% sodium hydroxide, then poured into 500 ml of cold H2O with continuous stirring for an hour and kept in the refrigerator for 24 hours. The solutions were filtered and washed. Finally, recrystallized these solutions by using absolute ethanol.

Synthesis of Thiazine derivatives (11-15) (17)

Refluxed for 9 hours, the mixture of each 0.001 mol of chacones compounds (1-5) with (0.152 gm, 0.002 mol) of thiourea that was dissolved in 50 ml EtOH absolute and 10% sodium hydroxide was then poured into 500 ml cold H2O with continuous stirring for an hour and then kept in the refrigerator for 24 hrs. The solutions were filtered and washed. Finally, recrystallized these solutions by using absolute ethanol.

Biological Activity Test

Anti-bacteria activity test

The test was conducted in accordance with the well-diffusion method. The synthesized compounds were tested against different types of bacteria: (*E. coli*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Psendomonas aeruginosa*).

Sensitivity assay

Using the agar-well diffusion method, the antibacterial activities of each of the derivatives (6, 7, 9, 11 and 14) were studied. Approximately 3-5 colonies of each kind of bacterial isolate were transferred to a tube containing 3 mL of normal saline and mixed well. Then the suspension was compared with the MacFarland turbidity standard (N° 0.5), which it equaled (1.5×10^6 CFU/mL). The bacterial suspension was generally applied to Mueller Hinton Agar (MHA) plates and allowed to dry at room temperature. The

diameter of six wells was punched (6 mm). A hundred microliters of the synthesized compounds in concentrated form were injected into wells. For 18–24 hours, all plates were incubated at 37°C. The antibacterial activity of synthesized compounds was determined by measuring the inhibition zone (mm), which includes the diameter of the disc that lacks bacterial growth. Finally, the inhibition diameters were measured for each pore using a ruler.

Cytotoxicity of Synthesized Thiazine derivative as anti-Anticancer

The cytotoxic effect of different compounds was performed by using MTT ready to use kit (Intron Biotech):

A . Kit Contents

1. MTT solution 3-(4,5-dimethylthiazol-2yl) 2,5diphenyl tetrazolium bromide (MW=414) 1 mL x 10 vials.
2. Solubilization solution 50 mL x 2 bottle.

B. Procedure

Follow the manufacturer's instructions for agreement with.

1- The cells (4.5 x 10^5) were cultured in 96-well plates to a final volume of 200 µL complete culture medium per each well. The plates were covered with a sterile parafilm, gently stirred and incubated for 24 hours at 37 ° C, 5% CO_2.

2- After the incubation, the medium was removed, and 200 µl of a 2- fold serial dilution of (9 and 15) derivatives (0, 20, 40, 80, 160, 320 µg/mL) was added to the wells. Triplicate was performed at each concentration and control. The plates were incubated for 48 hours at 37°C, 5% CO_2.

3- After exposure to the synthesized derivatives, 10µL of MTT solution was added to each well. The plates were further incubated for 4 hours at 37°C, 5% CO_2.

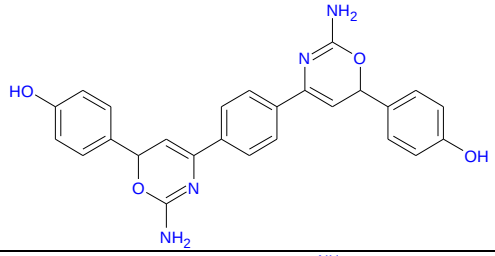
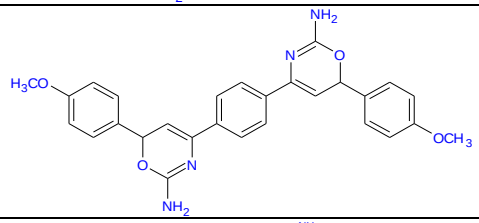
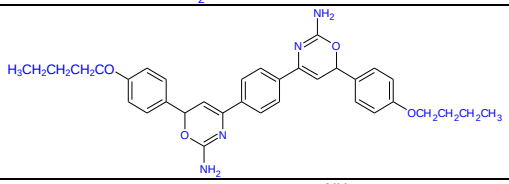
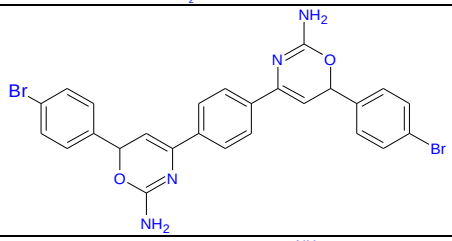
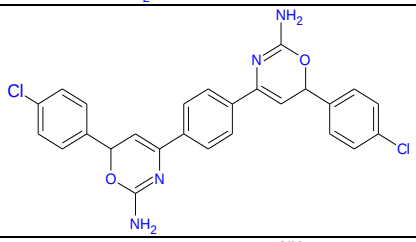
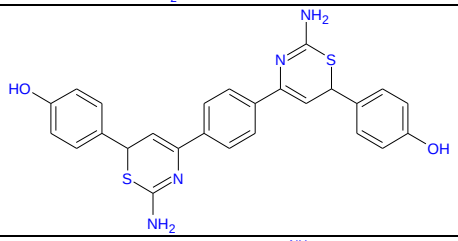
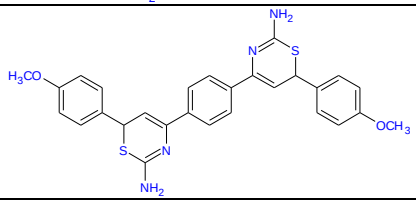
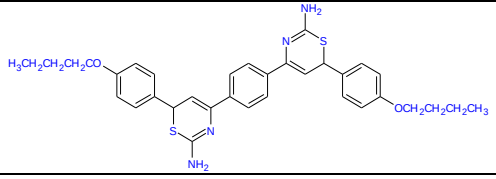
4- The medium was then carefully removed, and 100 µL of DMSO Solubilization solution was added to each well and incubated for 5 minutes.

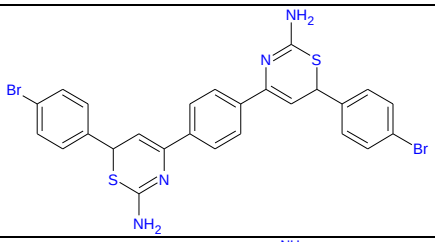
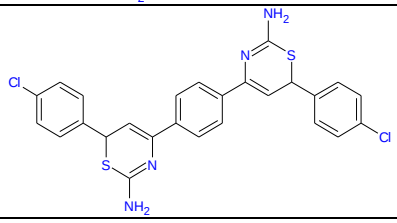
5- Absorbance was measured using an ELISA reader (Bio-rad, Germany) at a wavelength of 575nm.

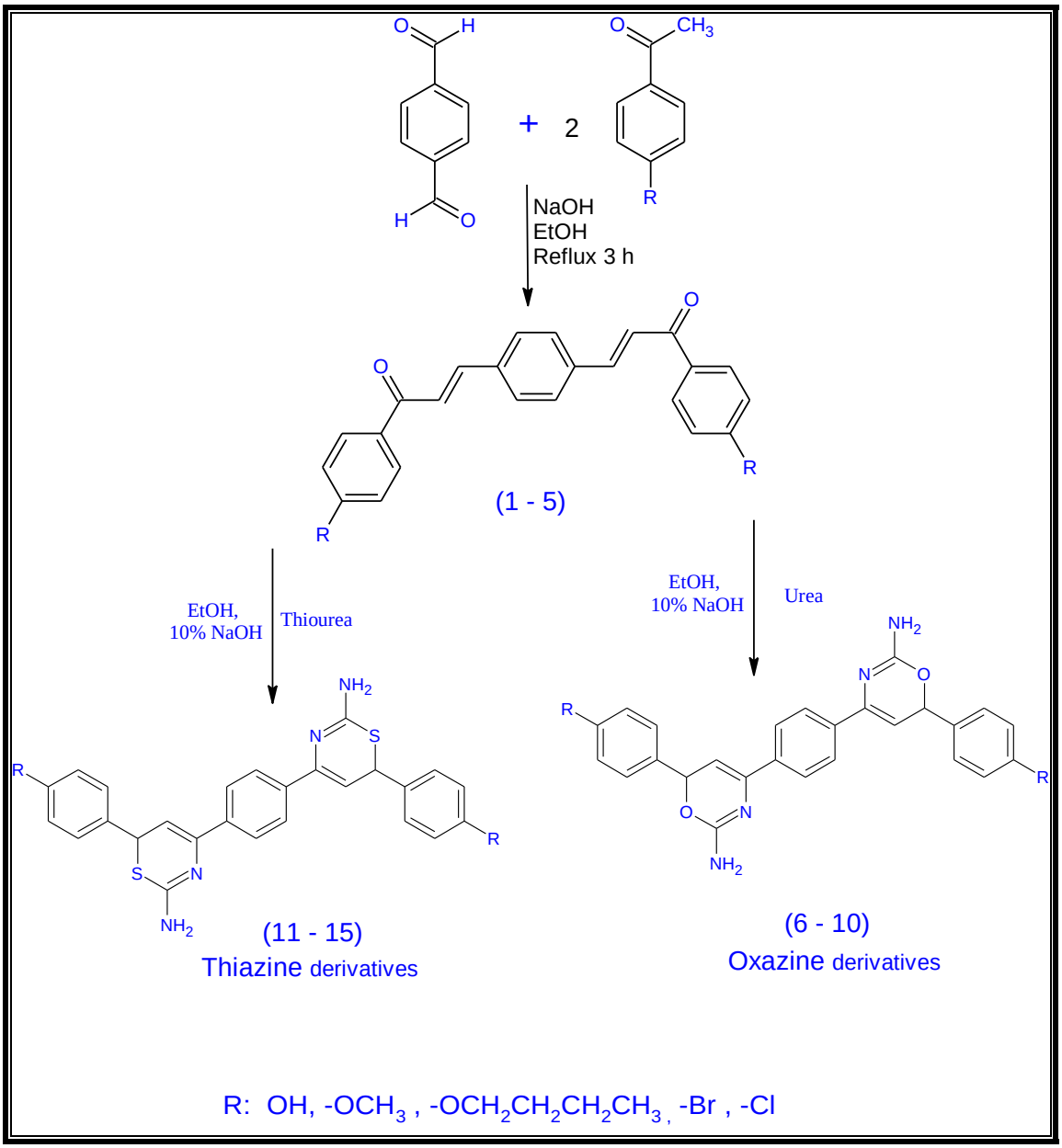
Molecular Docking

The crystallographic 3D structure of Glucosamine-6-Phosphate synthase (GP6 synthase PDB ID: 1MOQ) and Human androgen receptor (AR PDB:1E3G) were downloaded from protein data bank, the enzyme structure was subjected to energy minimization using Swiss protein viewer (version 4.1), several preparation steps were performed, the water molecules and co-crystallized ligands were removed and then the structure was corrected and polar hydrogens were added. The synthesized compounds were sketched using Chemdraw ultra (version 18.0) and saved in sdf format file and then was converted to pdb file format by Open babel software. After finish energy minimization (The MM2 force field in chem3D software was applied to the ligands in order to perform energy minimization and bond angles correction while Amber10 force field parameters in MOE software was applied to the receptors) for both of enzyme and receptor, the docking process was performed using Autodock Tools (version 1.5.6) and save them in pdbqt file format. Autodock vina was used to perform molecular docking along with AutoGrid software with grid box of size (30 x 30 x 30) and grid center (39.787 * 53.325 * 5.243) which represent the x, y and z dimensions respectively. The docking parameters were set to default values and ten conformations were generated. Discovery studio was used for generating visualization images.

Table (1): Physicochemical properties of synthesized derivatives.

Compound No.	Chemical Structure	Molecular Weight	% Yelled	Colour
6		454.47	63	Yellow
7		482.53	65	Brown - Reddish
8		493.57	61	Light Red
9		500.36	60	Orange
10		491.36	68	Red
11		486.60	71	Light Brown
12		514.66	67	Yellow
13		598.82	69	Yellow

14		612.40	65	Dark Orange
15		523.49	64	Orange



Scheme (1): Synthesis of Oxazine and Thiazine derivatives.

Result and Discussion

The derivatives that synthesized following the reactions in scheme 1. All compounds of chalcones (1-5) that evaluation by used spectroscopy such as, FT-IR and ^{1}HNMR. The reactions of terephthalaldehyde with para substituted acetophenone to produce chalcones derivatives (1-5) in presence of sodium hydroxide. In FTIR charts, all results listed in table 2. The appearance of compounds (1-5) shown by the carbonyl chalcone C=O stretching for compounds (1-5) at range 1690 - 1716 cm^{-1} (18) and C=N for compounds (6-15) at range 1642 – 1656 cm^{-1}. The C=C of alkene detected at 1607 – 1667 cm^{-1} and the C-H of aromatic ring at 3000 – 3179 cm^{-1}, the compound (1), show the broad peak at 3525 cm^{-1} for hydroxyl group, finally the compounds (2-5), C-H of aliphatic as sharp peak detects at 2860 – 2975 cm^{-1} as shown in figures (1 -5) (19, 20).

Table (2): FTIR for synthesized compounds (1-15).

Compound No.	C-H Aromatic	C-H Alifatic	C=O	C=C	O-H	$N-H_2$ Twin peak as sharp	C=N
1	3186+3079	---	1686	1607	3525	---	---
2	3041	2973+2860	1709	1646	---	---	---
3	3057+3000	2949	1716	1687	---	---	---
4	3171	---	1690	1641	---	---	---
5	3111+3034	---	1710	1616	---	---	---
6	3049	---	---	1627	3383	Masked	1652
7	3041	2971	---	1615	---	3447 and 3379	1656
8	3042	2996+2941	---	1593	---	3415 and 3346	1643
9	3033	---	---	1598	---	and 3381	1646
10	3046	---	---	1598	---	3460 and 3388	1651
11	3122+3049	---	---	1591	3363	Masked	1642
12	3070	Masked	---	1601	---	3376 and 3207	1633
13	3188+3026	2964	---	1603	---	3545 and 3485	1651
14	3064+3031	---	---	1581	---	3425 and 3370	1644
15	3164+3029	---	---	1598	---	3490 and 3466	1651

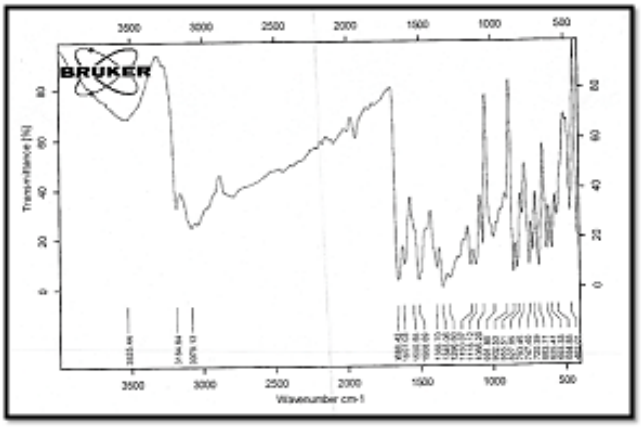


Figure (1): FTIR spectrum of Chalcone 1.

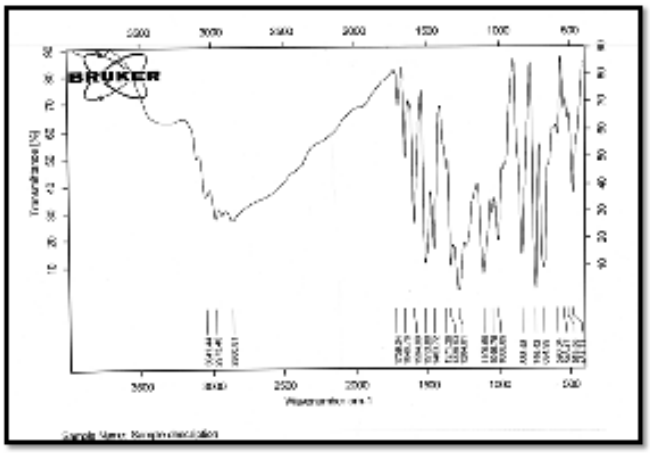


Figure (2): FTIR spectrum of Chalcone 2.

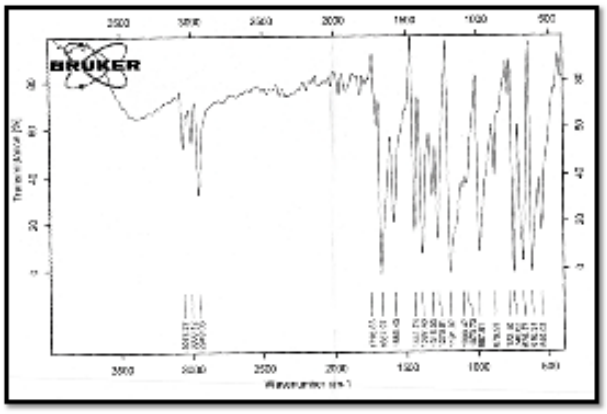


Figure (3): FTIR spectrum of Chalcone 3.

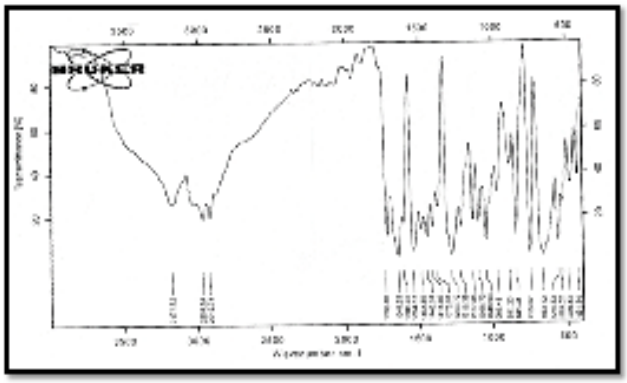


Figure (4): FTIR spectrum of Chalcone 4.

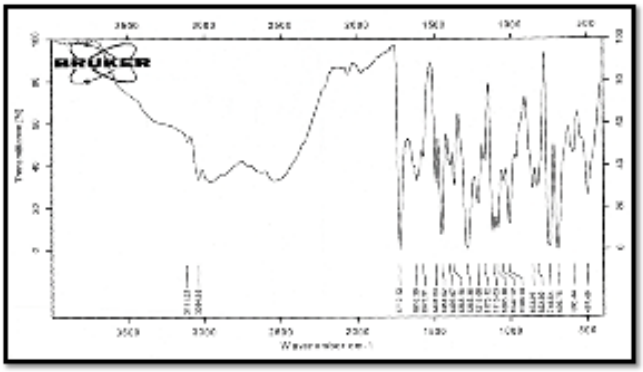


Figure (5): FTIR spectrum of Chalcone 5.

Firstly, the Oxazine derivatives (6-10) synthesized from reaction of chalcones compounds (1-5) with urea in presence sodium hydroxide. In other hand, Thiazine derivatives (11-15) synthesized from reaction of chalcones compounds (1-5) with thiourea in presence sodium hydroxide.

Secondly, in FTIR charts that shown in figures (6-15), all compounds that synthesized (6 – 15) disappeared the carbonyl group and C=C of alkene (21) and appeared a new peak of C=N that detects at range 1633 – 1656 cm^{-1} (22), C-H of aromatic ring appeared at 3026 – 3188 cm^{-1}, the C=C of aromatic ring detects at range 1581 – 1615 cm^{-1}. The compound (6) has a broad band at 3383 cm^{-1} and disappeared this band for compounds (7-10) that appeared two band at range 3368 – 3460 cm^{-1} for amino group as symmetrical and a symmetrical (23). The compound (11) has a broad band at 3363 cm^{-1} and disappeared this band for compounds (12-15) that appeared two band at range 3207–3545 cm^{-1} for amino group as symmetrical and a symmetrical (23).

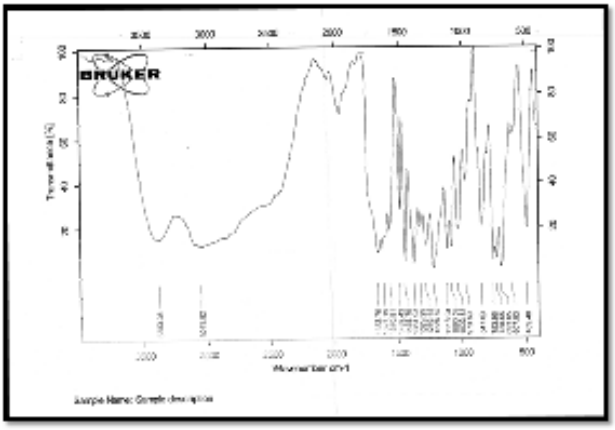


Figure (6): FTIR spectrum of Oxazine 6.

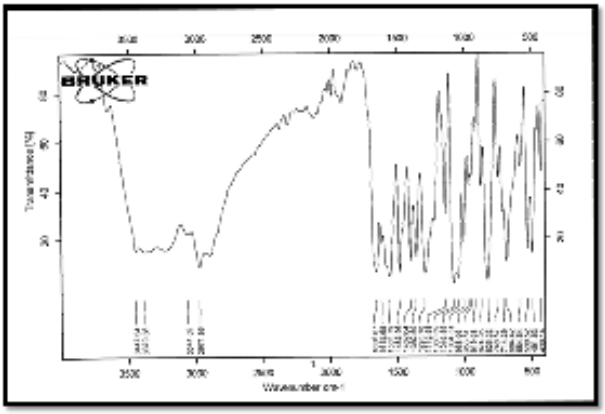


Figure (7): FTIR spectrum of Oxazine 7.

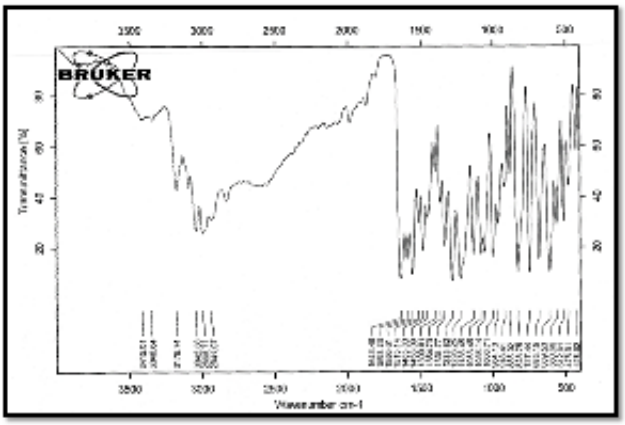


Figure (8): FTIR spectrum of Oxazine 8.

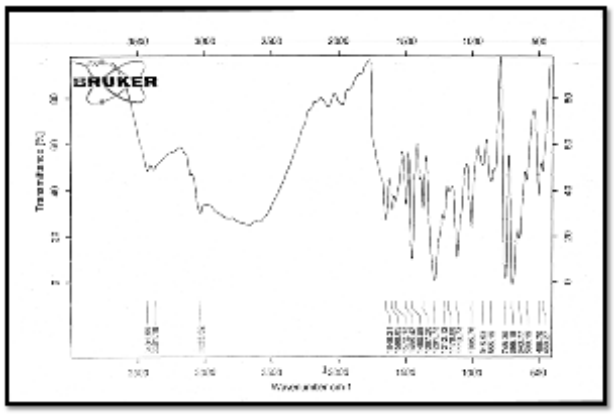


Figure (9): FTIR spectrum of Oxazine 9.

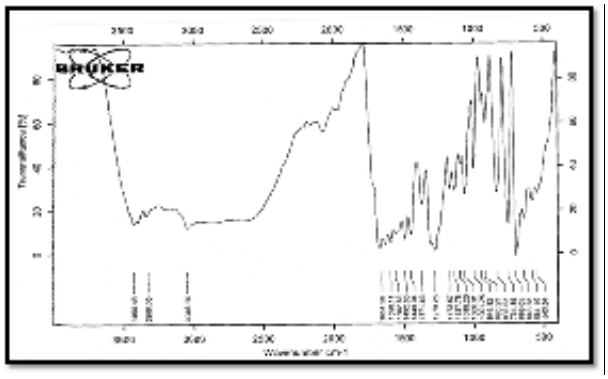


Figure (10): FTIR spectrum of Oxazine 10.

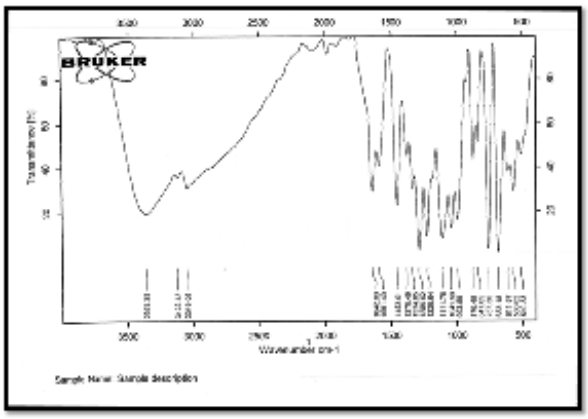


Figure (11): FTIR spectrum of Thiazine 11.

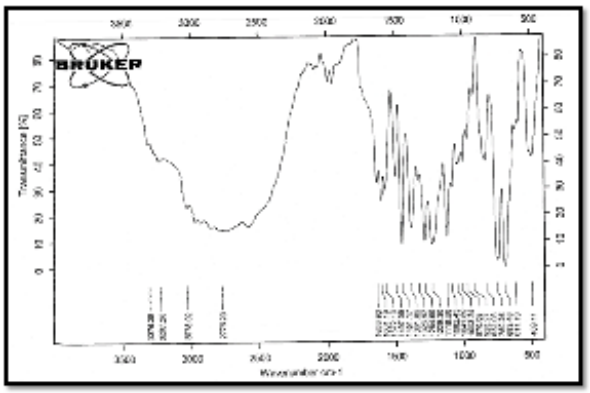


Figure (12): FTIR spectrum of Thiazine 12.

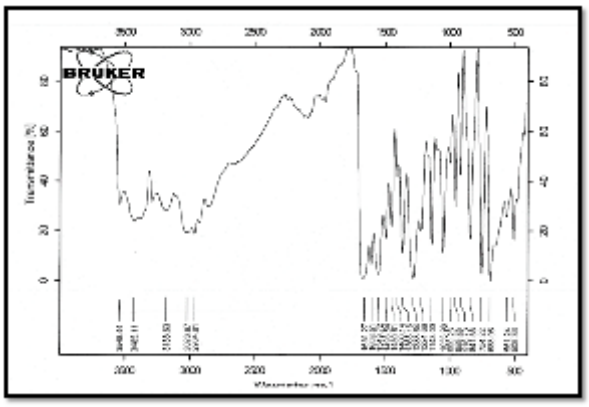


Figure (13): FTIR spectrum of Thiazine 13.

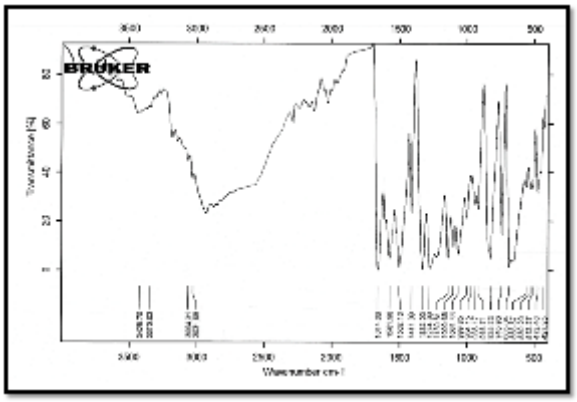


Figure (14): FTIR spectrum of Thiazine 14.

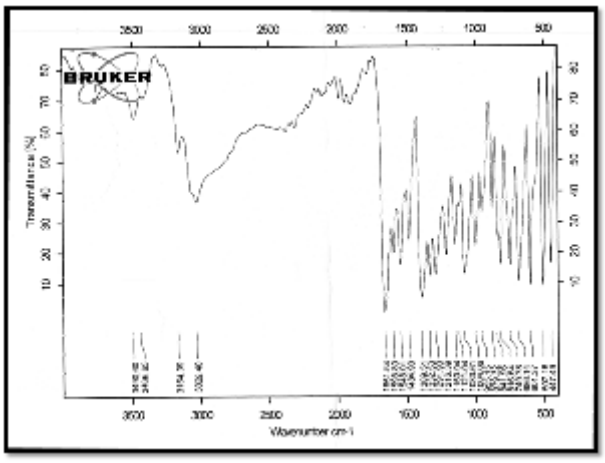


Figure (15): FTIR spectrum of Thiazine 15.

Finally, the synthesized derivatives (6–15) characterized by ^{1}HNMR that shown in figures (16 -25), all the synthesized derivatives have range bands 6.2 – 8.3 ppm for protons of aromatic rings (24) and 10.4 – 11.4 ppm for protons of amino groups (4H). The compounds (6 and 11) have multiplet bands at 10.5 and 10.7 ppm for protons of hydroxyl groups (2H). The compounds (7 and 12) have bands at 3.33 and 3.27 ppm for protons of methyl groups (6H) (25).

Table (3): ^{1}HNMR for synthesized compounds (6-15).

Compound No.	Proton of O-H	Protons of N-H	Protons of aromatic	C-H in Oxa. Or Thi ring	CH_2	CH_3
6	10.5	11.0	7.3-6.9	5.8	--	--
7	--	11.3	7.3-7.1	5.6	3.3	--
8	--	11.3-11.2	7.8-6.1	5.8	4.1-1.9	1.1
9	--	11.3	8.1-7.1	5.9	--	--
10	--	11.4	8.1-7.1	6	--	--
11	10.7	11.2	7.6-6.1	4.9	--	--
12	--	11.9-11.2	8.1-6.1	4.9	--	--
13	--	11.4	8.2-6.1	4.8	4.0-1.9	1.1
14	--	10.3	8.1-6.1	4.9	--	--
15	--	11.4	8.3-6.1	4.8	--	--

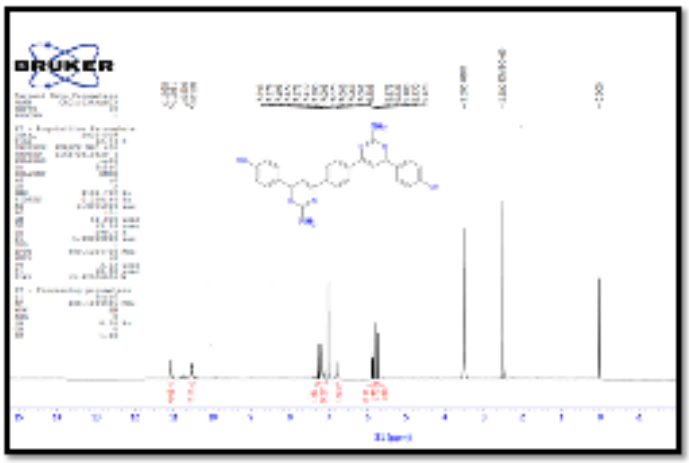


Figure (16): ^{1}HNMR spectrum of Oxazine (6).

Figure (17): ^{1}HNMR spectrum of Oxazine (7).

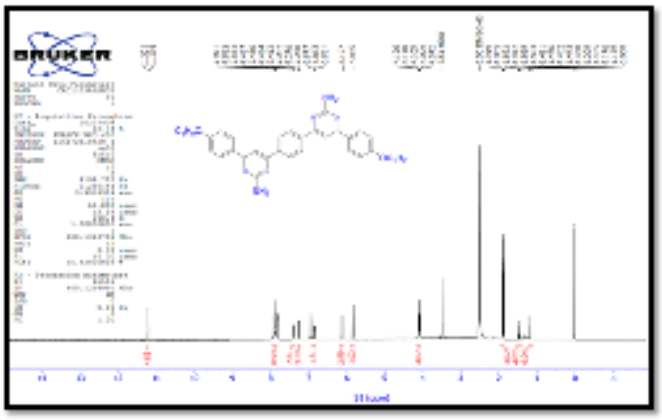


Figure (18): ^{1}HNMR spectrum of Oxazine (8).

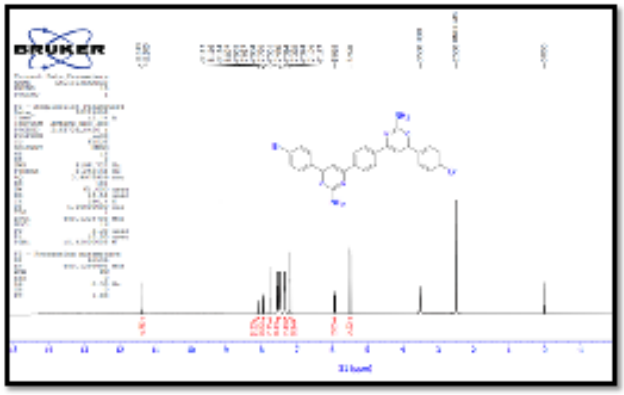


Figure (19): ^{1}HNMR spectrum of Oxazine (9).

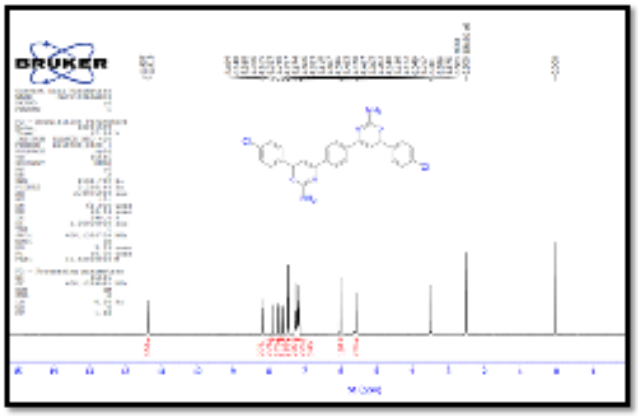


Figure (20): ^{1}HNMR spectrum of Oxazine (10).

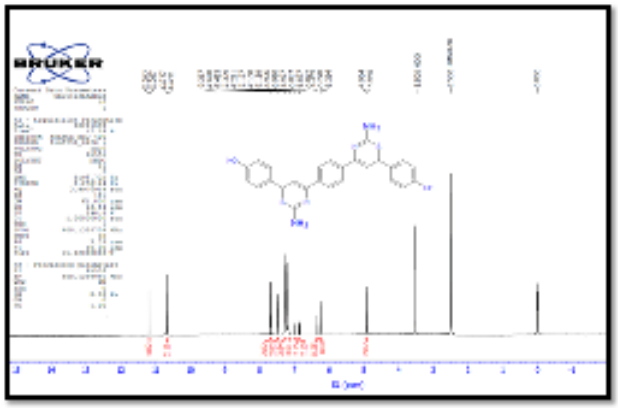


Figure (21): ^{1}HNMR spectrum of Thiazine (11).

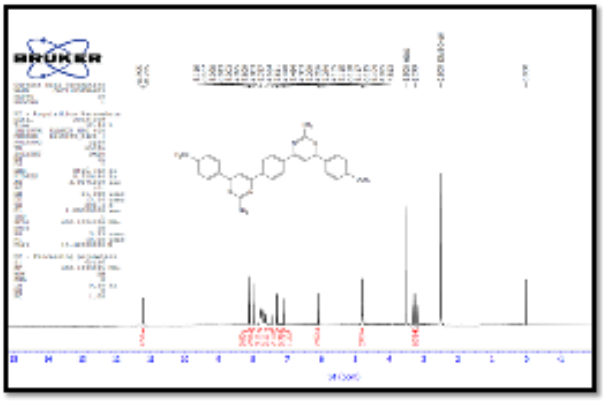


Figure (22): ^{1}HNMR spectrum of Thiazine (12).

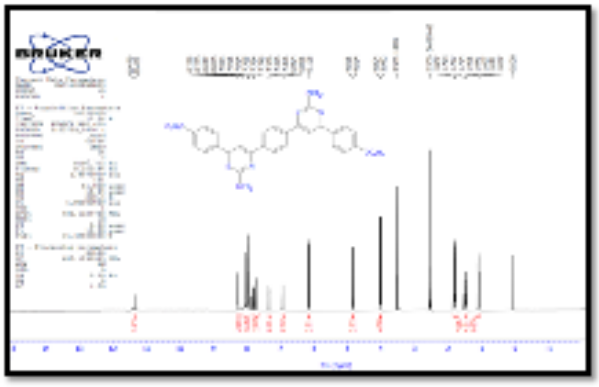


Figure (23): ^{1}HNMR spectrum of Thiazine (13).

Figure (24): ^{1}HNMR spectrum of Thiazine (14).

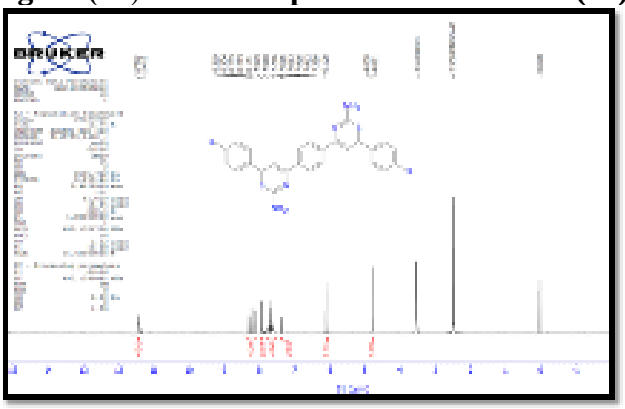


Figure (25): ^{1}HNMR spectrum of Thiazine (15).

Discussion of Docking

The docking simulations have a major role in exploring the binding modes of ligands with a target molecule. Glucosamine-6-Phosphate synthase (GP6 synthase), has attracted the interest of several researchers due to its importance in microbial cell wall synthesis [26] The enzyme catalyzes the first step in hexosamine biosynthesis and converted Fructose-6-Phosphate into GlcN-6-P (Glucosamine-6-Phosphate), which is considered a precursor of Uridine Diphosphate N-acetyl glucosamine (UDP-NAG), an essential component of the peptido-glycan layer of the microbial cell wall [27]. The synthesized thiazine derivatives show a strong binding inhibition towards the enzyme (PDB ID:1MOQ) with binding score (-9.5 and -8.0 kcal/mol) for hydroxy and chloro derivatives respectively. Their binding modes are demonstrated in figures below. For hydroxy derivative, a typical hydrogen bonding was formed by multiple amino acids in enzyme's pocket and functional groups in the ligand (ASP354 and a proton of hydroxy group & ALA602 with a proton of amine group) other residues

formed various interactions with ligand's functional groups as shown in the figures. For chloro derivative, two conventional hydrogen bonding were observed between two protons of amine group with VAL399 and ALA602 these findings proposed that the prepared thiazine derivatives could be strong candidates for antimicrobial agents [28].

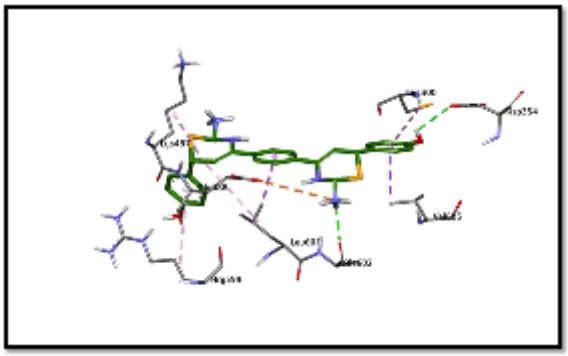


Figure (26): The docking profile of GP6 synthase (PDB ID: 1MOQ) with Thiazine-Hydroxy derivative, a) 3D binding mode.

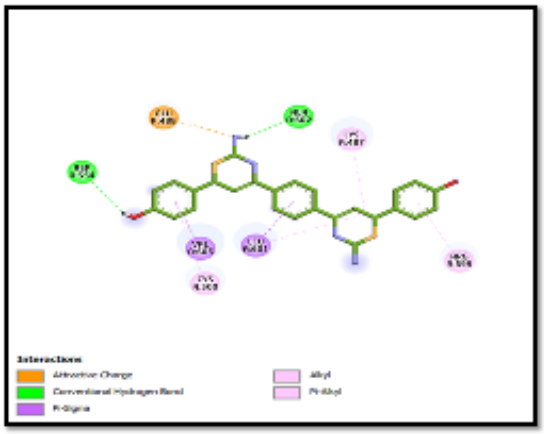


Figure (27): The docking profile of GP6 synthase (PDB ID: 1MOQ) with Thiazine-Hydroxy derivative, b) 2D diagram interactions.

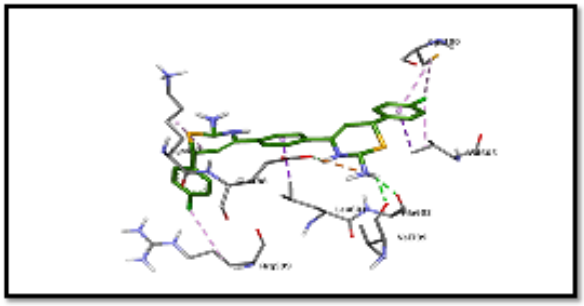


Figure (28): The docking profile of GP6 synthase (PDB ID: 1MOQ) with Thiazine-Chloro derivative, a) 3D binding mode.

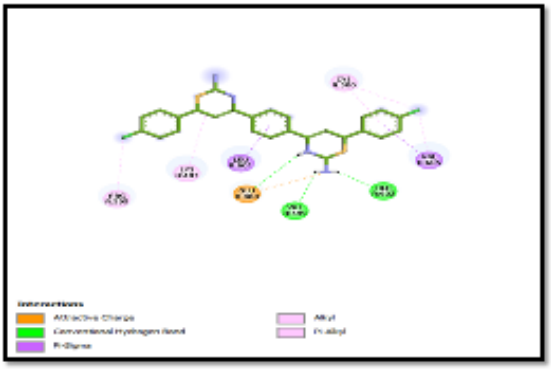


Figure (29): The docking profile of GP6 synthase (PDB ID: 1MOQ) with Thiazine-Chloro derivative, b) 2D diagram interactions.

The research also involves synthesis of some oxazine derivatives and evaluate their performance against prostate cancer's cell line (PC3). Human androgen receptor (AR) is one of main therapeutic target for prostate cancer (PC3) [29]. The synthesized oxazine derivatives exhibit a noticeable potency inhibition at AR's binding site (PDB:1E3G) with binding score (-8.8 & -8.5) kcal/mol for bromo and methoxy derivatives respectively. The figures (30 and 31) shown the interactions between the synthesized oxazine derivatives and amino acids that located at receptor's binding pocket. The bromo derivative demonstrate multiple interactions including (hydrogen bonding between PRO682 and amine group of compounds, pi-pi stacking was observed between aromatic ring of compound with TYR763). For methoxy derivative, multiple hydrogen bonds were observed (amine group with SER851, second amine group with TRP796 & GLY795) [30].

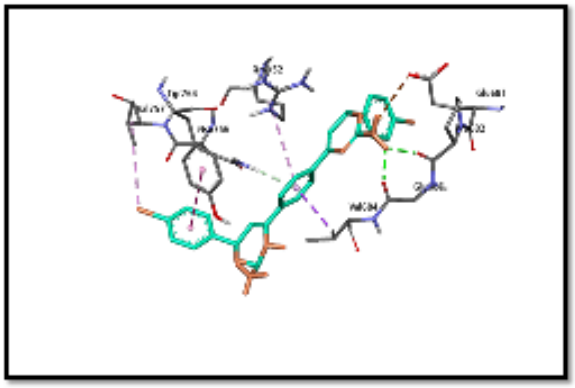


Figure (30): The docking profile of Human androgen receptor (PDB ID: 1E3G) with Oxazine-Bromo derivative, a) 3D binding mode.

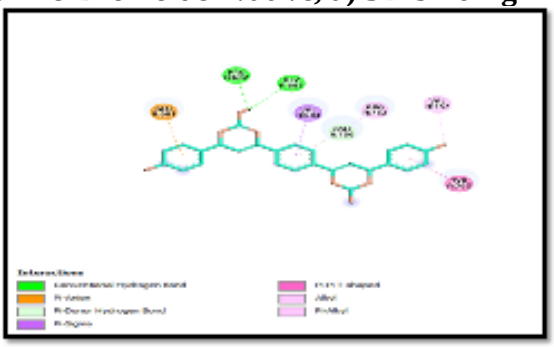


Figure (31): The docking profile of Human androgen receptor (PDB ID: 1E3G) with Oxazine-Bromo derivative, b) 2D diagram interactions.

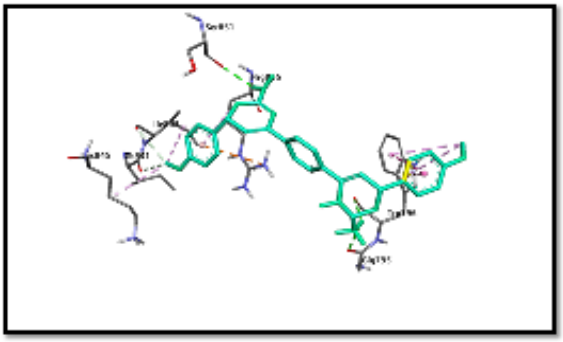


Figure (32): The docking profile of Human androgen receptor (PDB ID: 1E3G) with Oxazine-Mehtoxy derivative, a) 3D binding mode.

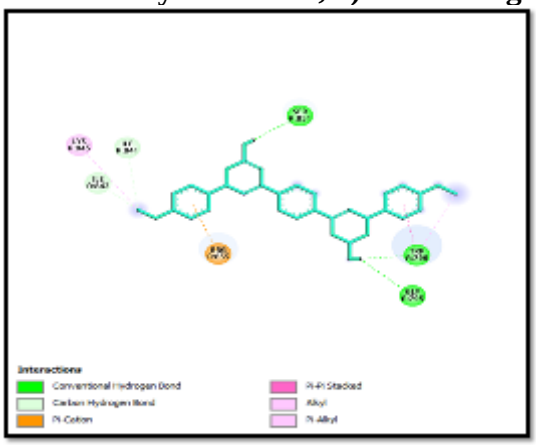


Figure (33): The docking profile of Human androgen receptor (PDB ID: 1E3G) with Oxazine-Mehtoxy derivative, b) 2D diagram interactions.

Biological activity

Each pore's inhibitory diameter was calculated using a ruler. The region of transparency that surrounds the disc is known as the zone of inhibition (31).

Against the bacterial strains, compounds 6, 7, 9, 11 and 14 have shown very good activity against E. coli. The compounds 7 and 14 were found to possess good activity against E. coli. Against the Pseudomonas aerug, the compounds 6, 7 and 11 were found no effect on zone inhibition. Remaining compounds 6, 7, 9, 11 and 14 exhibited moderate activity as anti-Staphylococcus. Generally, the compounds that were synthesized exhibited moderate activity compared with standard drugs, such as streptomycin and fluconazole (32 - 34). These derivatives (6, 7, 9, 11 and 14) were selected based on their inhibition results on GP6 synthase (PDB) and could be considered the most promising candidates as antibacterial. All results are shown in table 4.

Table (4): Biological activity of some synthesized compounds.

Compounds	Zone of inhibition (mm)			
	Staphylococcus	***Bacillus subtilis***	***Pseudomonas aerug***	***Escherichia coli***
6	+	+	-	+
7	+	++	-	++
9	+	+	++	++
11	+	+	-	+
14	+	++	+	++
Streptomycin	+	++	-	++
Flucanozole	-	-	-	-

Note: (-): no kill, (+): less 18 mm and (++): more than 17 mm.

Viability Assay by MTT dye

The cytotoxic effect of these compounds that synthesized (9 and 15) were performed via used MTT on PC3 as cell line. The Kit obtained from Intron Biotech and this experimental in Islamic Azad University, Islamic Azad University, Iran. Figure 34 shows effect of Oxazine derivative (9) on PC3 cell viability that equal (9.51 – 100) at 24 hours and (2.94 – 100) at 48 hours. The results showed action on PC3 cell line that is dose-dependent. These derivatives were selected based on their inhibition results on Human androgen receptor (PDB ID: 1E3G) and could be considered as the most promising candidates as anti-cancer agents.

The effect of Oxazine derivative (9) on the viability of PC3 cells analyzed as shown in figure 34, after 48 h, increase concentration (part per million ppm = µg/ml), decrease PC3 viability % more than 24 h. However, IC50 at 24 h equal 53.89 more than 25.50 at 48 h as shown figure 35. All result that obtained shown in table 5.

The IC50 calculate according to the following equation:

$$ability(\%) = \frac{OD - ve\ controle - OD\ sample}{ODsample}$$

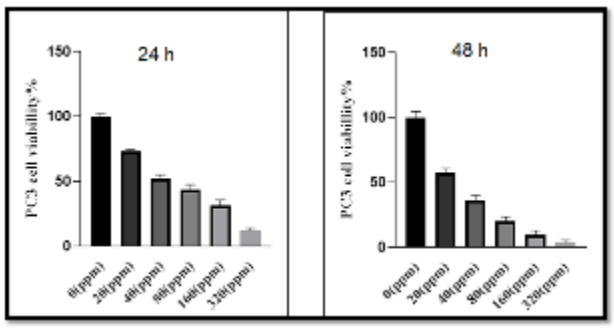


Figure (34): Effect of Oxazine derivative (9) on PC3 cell viability.
Note: the unit of concentration is (ppm = µg/ ml)

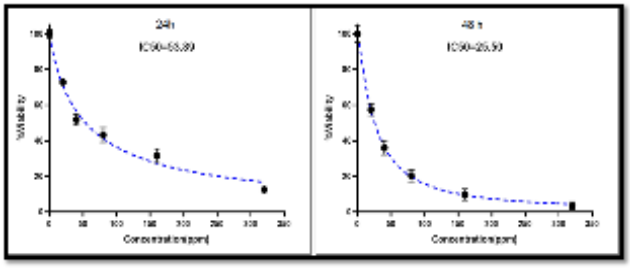


Figure (35): Dose-dependent cytotoxic effect of Oxazine (9) on PC3.

Table (5): The serum levels of electrolytes for PC3 after used Oxazine derivative (9).

Concentration (PPM)	After 24 h		After 48 h	
	Mean	SD	Mean	SD
0	100	2.216226	100	4.837271
20	72.9628	1.777783	57.5157	3.281063
40	51.8536	3.167733	36.0986	3.974472
80	43.2669	4.133425	20.3836	3.306961
160	31.6378	3.947129	9.7315	3.194306
320	12.5957	1.3591	3.5861	1.999761

The effect of Thiazine derivative (15) analyzed as shown in figure 36, after 48 h, increase concentration (ppm= µg/ml), decrease PC3 viability % more than 24 h. However, IC50 at 24 h equal 57.44 more than 17.83 at 48 h as shown figure 37. All result that obtained shown in table 6.

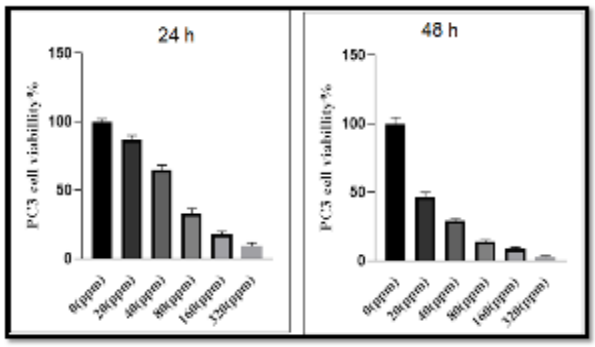


Figure (36): Effect of Thiazine derivative (15) on PC3 cell viability.

Note: the unit of concentration is (ppm = µg/ ml)

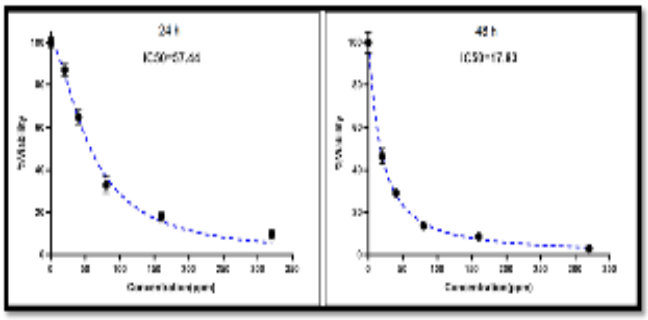


Figure (37): Dose-dependent cytotoxic effect of Thiazine (15) on PC3.

Table (6): The serum levels of electrolytes for PC3 after used Thiazine derivative (15).

Concentration (PPM)	After 24 h		After 48 h	
	Mean	SD	Mean	SD
0	100	2.216226	100	4.837271
20	87.1299	2.872745	46.4161	3.658258
40	64.9127	3.3641	29.1732	1.475255
80	32.9269	3.780147	13.6696	1.687114
160	17.9359	2.111519	8.5399	1.39553
320	9.5371	2.150265	2.9533	0.732675

Pymol molecule

Vdw (van der Waals) radii are used to show atoms in the sphere representation and, when multiplied by the ball scale factor, the ball-and-stick representation. VDW radii are also used in calculating surfaces, finding close contacts, and rendering atoms with conic and nezn (35). From Pymol, the vdw values for C, H, O and N atoms equal 1.70, 1.20, 152 and 1.55, respectively for derivate (6 and 15) in addition to S atom equal 1.80 as shown in figure 38 and 39.

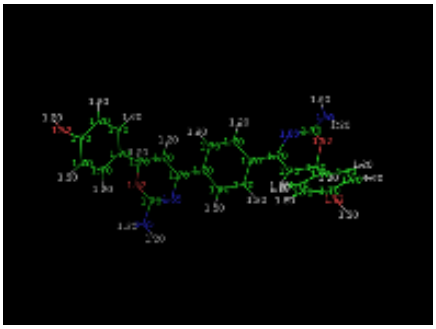


Figure (38): Vdw for derivate (6) by Pymol.

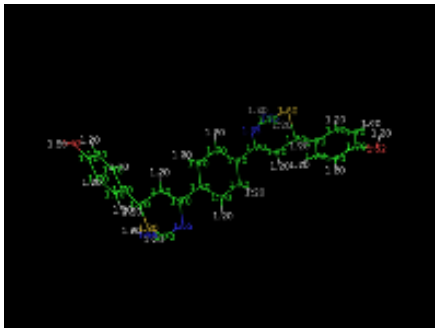


Figure (39): Vdw for derivate (15) by Pymol.

Conclusion

In conclusion, these compounds that synthesized as Oxazine derivatives (6-10) and Thiazine derivatives (11-15) from reaction of chacones compounds with urea and thiourea, respectively. This method that used to synthesized compounds show some advantages such as good yields, simple procedure and ease of workup. These compounds characterized by used some spectroscopy methods like FTIR and ^{1}HNMR, as well as docking analysis and Pymol analysis. Evaluation the biological activity of these derivatives (6, 7, 9, 11 and 14) as anti-bacteria (such as *Staphylococcus*, *Bacillus subtilis*, *Pseudomonas aerug* and *Escherichia coli*) and gives good result by inhibition of zone growth through inhibition results on GP6 synthase. Finally, the derivatives (9 and 15) tested as anti-PC3 cell line and effect on human androgen receptor via used docking analysis.

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