Microwave Assisted Synthesis, Characterization of New Heterocyclic Compounds and Evaluation as Anti Breast Cancer

Muntadher M. Al-Kaabi,* Hanan A. Rady Al-Hazam, Arwa H. M.

Department of Chemistry, College of Science, University of Basrah, Basra, Iraq

Corresponding author, E-mail: m_muntather@yahoo.com

Doi: 10.29072/basjs.202116

Abstract

A number of new heterocyclic compounds derived from vanillin dimer chalcones were prepared by Claisen–Schmidt condensation using a microwave as a heat source and a base medium as a catalyst. The structures and suggestion mechanisms of reaction of the new products were attributed to elementary and spectroscopic analysis. Additionally, the *in vitro* anticancer compounds activity of (Z1, Z2, Z3, Z7, Z8 and Z9) and all of them showed high inhibition efficiency except (Z2) were evaluated with a human breast cancer cell line (Cal51), and compared with standard anticancer drugs, according standard MTT assay. The synthesized heterocyclic compounds were characterized based on their chemical properties and spectroscopic data (FTIR, ^{1}H NMR, ^{13}C MNR and CHN-S).

Article inf.

Received: 31/12/2020

Accepted

12/2/2021

Keywords:

Heterocycle, Vanillin, Microwave, Anticancer, Cytotoxicity

1. Introduction

A heterocyclic compound is a cyclic compound that has at least two different elements atoms in its ring(s)[1]. Several of biochemical material essential to life include heterocyclic compounds. For example, nucleic acids (DNA and RNA) which carry the genetic information is include long chains of heterocyclic compounds joined each to other by different types of materials[2,3]. Many naturally substances such as vitamins, antibiotics, and pigments are heterocyclic compounds (92). The most common and important heterocycle compounds are those having five or six membered rings and containing heteroatoms of oxygen, nitrogen, and sulfur [4,5]. The development of heterocyclic chemistry recently specially which derived from chalcones have been synthesized and biologically investigated for specific target of diseases on widely range. Chalcones are used to synthesize many heterocyclic derivatives like pyrazolines and pyrimidines having different heterocyclic ring systems with have a wide range from medical applications [6-8].

Cankara Pirol et al., have been synthesized a novel series from amide derivatives of 5-(p-tolyl)-1-(quinolin-2-yl) pyrazole-3-carboxylic acid and studied against human cancer cell lines. Compound with 2-chloro-4-pyridinyl group in the amide part showed good cytotoxic activity against all cell lines [9], as show in Fig. 1.

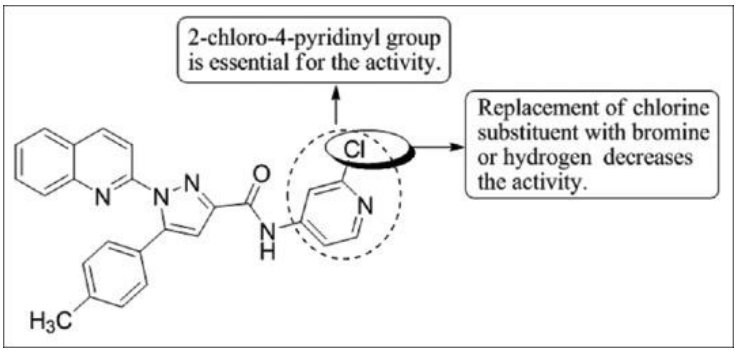


Fig. 1: Pyrazole as Anticancer

Ma et al., were designed, synthesized 1,2,3-Triazole–pyrimidine–urea derivatives and evaluated for anticancer activity. Almost all of the synthesized compounds showed powerful activity versus all the cancer cell lines [10], as shown in bellow Fig. 2.

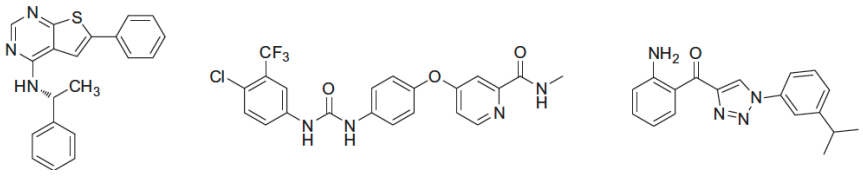


Fig. 2: Pyrazines derivative with anticancer activity

Al-Harbi et. al., synthesized a new class from poly-fused pyrazolothieno pyrimidine derivatives. All the synthesized compounds were tested for their hypoglycemic activities against standard pioglitazone and were found to have equipotent hypoglycemic activity can be used as an important anti-diabetic agent [11], as shown in Fig. 3.

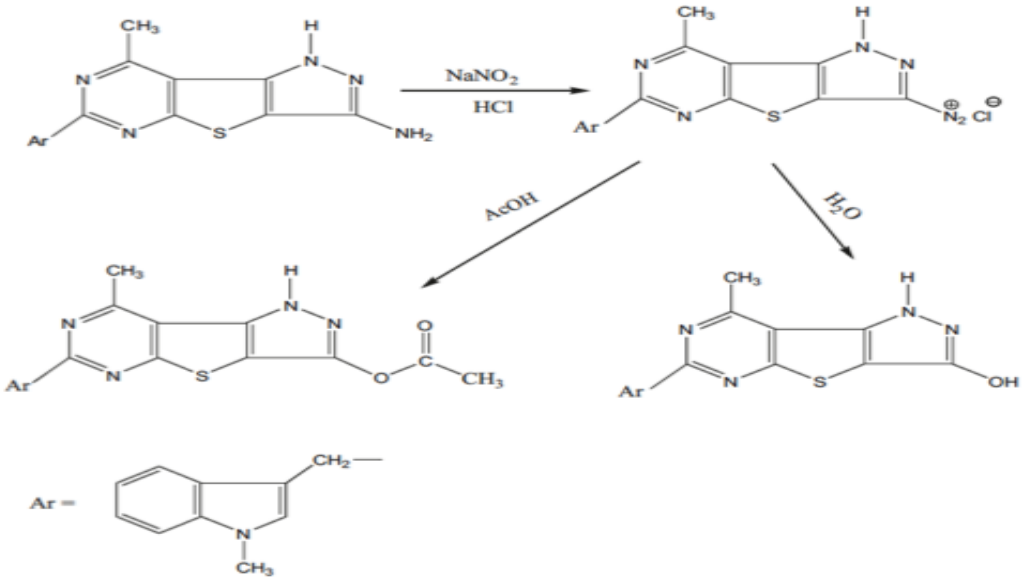


Fig. 3: Pyrazines derivative with antidiabetic activity

The aim of our study is synthesis of new heterocyclic compounds derived from chalcones assisted Microwae technique which have signeficants advandags such as reduceing the reaction time and solvents comparative with coneentional methods, and evaluated these novels compounds as anticancer and hepato-protective.

2. Experiment work

The uncorrected melting points of compounds were taken in open capillaries and recorded on melting point apparatus Buchi thermal point, The elemental analysis of all the synthesized compounds was performed by using Eager 300 for EA1112 Analyzer in University of Tehran. The FTIR spectra of all synthesized compounds were measured as KBr disc for solid sample for the region between (400-4000) cm-1 by using SHIMADZU FTIR-8400. ^{1}H NMR and ^{13}C NMR spectra for the compounds were obtained in deuterated solvent DMSO-d6 by 400 MHz for proton and 100 MHz for carbon by using Spectrometer AC-400MHz SHIMAZU Tehran University. The Microwave technique used in synthesized the compounds by microwave type Panasonic NN-SN382, (MALAYZIA) 25 L, Power (1200 W) and frequency (2450 MHz).

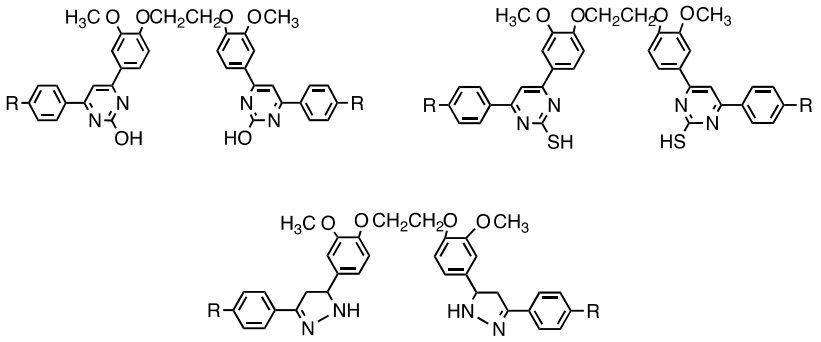
a. Synthesis of compounds

A mixture of chalcone (0.01 mole), (hydrazine hydrate, urea and thiourea) respectively (0.02 mole) and 3ml (40%) KOH in 10 ml DMF. Then the mixture irradiated in a microwave oven at 90W for 2-6 min. It was then cooled and poured in cold water acidified with dilution HCl. Then Filtered, washed and dried. The product was recrystallized from ethanol. the products yield was obtained in 67-90% [12,13]. Physical properties of chalcone compounds are displayed in Tables (1) and chemical structure are illustrated in Fig. 4.

Table1: Some Physical Data of Heterocyclic Derivative Compounds

Sym.	Name of the hetrochalcone	Color	Melting Point (^{0}C)	Yield (%)
Z1	4,4'-(5,5'-((ethane-1,2-diylbis (oxy)) bis (3-methyl-4,1-phenylene)) bis (4,5-dihydro-1*H*-pyrazole-5,3-diyl)) dianiline	Yellow	155-157	88
Z2	6,6'-((ethane-1,2-diylbis (oxy)) bis (3-methyl-4,1-phenylene)) bis (4-(4-aminophenyl) pyrimidin-2-ol)	Yellow	213-215	79
Z3	6,6'-((ethane-1,2-diylbis (oxy)) bis (3-methyl-4,1-phenylene)) bis (4-(4-aminophenyl) pyrimidine-2-thiol)	Wight Yellow	197-200	85

Z4	1,2-bis(2-methyl-4-(3-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)phenoxy) ethane	Yellow	125-127	90
Z5	6,6'-((ethane-1,2-diylbis(oxy))bis(3-methyl-4,1-phenylene))bis(4-(4-nitrophenyl)pyrimidin-2-ol)	bright yellow	217-220	80
Z6	6,6'-((ethane-1,2-diylbis (oxy)) bis (3-methyl-4,1-phenylene)) bis (4-(4-nitrophenyl) pyrimidine-2-thiol)	brown	193-195	87
Z7	1,2-bis(2-methoxy-4-(3-(p-tolyl)-4,5-dihydro-1H-pyrazol-5-yl)phenoxy)ethane	Yellow	117-119	80
Z8	6,6'-((ethane-1,2-diylbis(oxy)) bis (3-methoxy-4,1-phenylene)) bis (4-(p-tolyl)pyrimidin-2-ol)	bright yellow	191-193	67
Z9	6,6'-((ethane-1,2-diylbis(oxy)) bis (3-methoxy-4,1-phenylene)) bis (4-(p-tolyl)pyrimidine-2-thiol)	bright yellow	186-188	75



R = NH_2, NO_2, CH_3

Fig. 4: Substituents Heterocyclic Compounds.

b. Maintenance of cell cultures

Cancer cell line (CAL51) was collected from the IRAQ Biotech company Cell Bank Unit in Basrah, RPMI-1640 supplemented used in maintained with 10% Fetal bovine, penicillin 100

unit/ml and streptomycin 100 µg/ml. Trypsin-EDTA have been used in passaging Cells were reseeded at 50% confluence twice per 7 days and incubated at 37 °C and 5% CO2 [14].

C. Combination Cytotoxicity Assays

Cytotoxic effect determine throgh the [3- 4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] MTT cell viability assay was carry out on 96-well plates. Cell line CAL51 were spored at 1×10^4 cells/well. After 24 hr. monolayer was completed, Then its treated with our compounds with critical concentration (1000) µg/ml. After 72 hrs. of treatment cell viability was measured by removing the medium, adding 28 µL of 2 mg/mL solution of MTT and incubating the cells for 2 hr. at 37 °C. The crystals remaining in the holes after removing the MTT solution, then added DMSO 100 µL to solubilized it where followed by incubation at 37 °C for 15 min with shaking [15]. The absorbency was determined on a microplate reader at 620 nm (test wavelength); the assay was performed in triplicate. The inhibition rate of cell growth (the percentage of cytotoxicity) was calculated as the following equation:

Proliferation rate (PR)= B/A*100

A = is the mean optical density of untreated wells

B = is the optical density of treated wells

IR= 100- PR [16].

3. Elemental Analysis

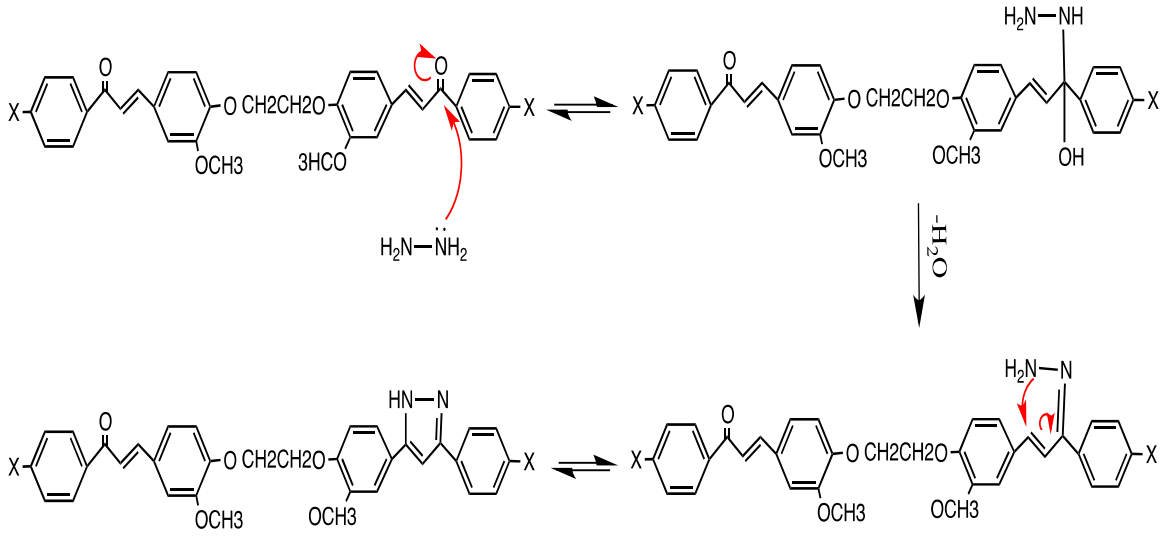
The synthesized chalcones and heterocyclic compounds were characterized by elemental analysis (CHNO-S), and their spectra were recorded by Eager 300 for EA1112 Analyzer. It was found that the calculated values of carbon, hydrogen and nitrogen elements are compatible with observed value which confirmed the validity of the suggested structure of the synthesized compounds. As shown in Tables 2.

Table 2: Elemental Analysis of Chalcone Compounds

Sym.	Molecular formula	Calculated				Observed			
		%C	% H	% N	% S	%C	% H	% N	% S
Z1	$C_{34}H_{36}N_6O_4$ 592.69	68.90	6.12	14.18	-	68.96	6.06	14.10	-
Z2	$C_{36}H_{32}N_6O_6$ 644.68	67.07	5.00	13.03	-	67.11	5.04	13.10	-
Z3	$C_{36}H_{32}N_6O_4S_2$ 676.81	63.88	4.76	12.41	9.47	63.83	4.69	12.37	9.45
Z4	$C_{34}H_{32}N_6O_8$ 652.65	62.57	4.90	12.88	-	62.59	4.84	12.85	-
Z5	$C_{36}H_{28}N_6O_{10}$ 704.64	61.36	4.00	11.93	-	61.29	4.15	11.85	-
Z6	$C_{36}H_{28}N_6O_8S_2$ 736.77	58.69	3.83	11.41	8.70	58.59	3.86	11.36	8.66
Z7	$C_{36}H_{38}N_4O_4$ 590.71	73.20	6.48	9.48	-	73.35	6.57	9.61	-
Z8	$C_{38}H_{34}N_4O_6$ 642.70	71.01	5.33	8.71	-	71.13	5.49	8.77	-
Z9	$C_{38}H_{34}N_4O_4S_2$ 674.83	67.63	5.08	8.30	9.50	67.50	5.17	8.27	9.46

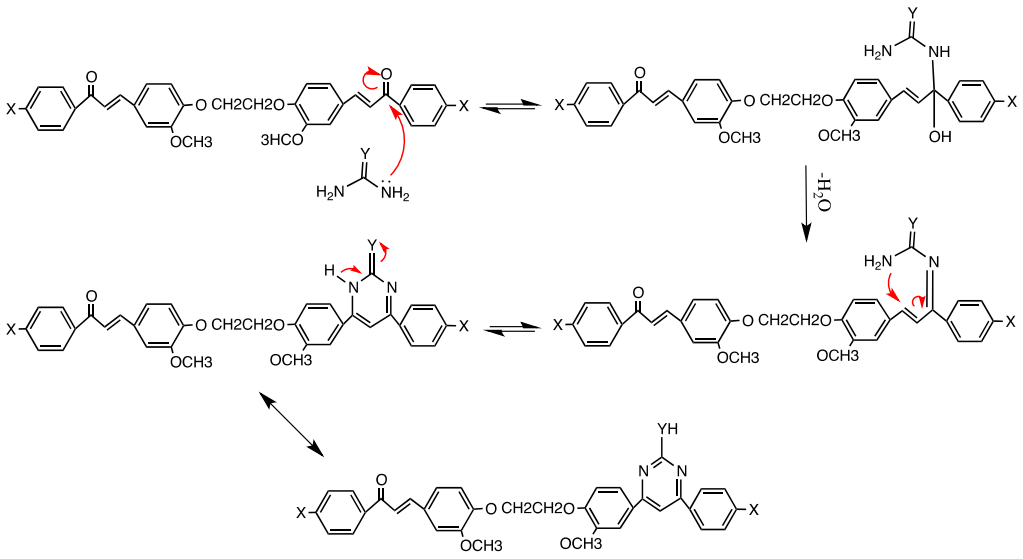
4. Result and discussion

The compounds were synthesized by the reaction of (0.02 mole) of hydrazine, urea and thiourea respectively with (0.01) mole of appropriate chalcones by using 40% KOH in DMF. Microwave irradiation was used at a different time 4-6 min. The mechanism of reactions was explained by means of nucleophilic attack of amino group related to (hydrazine, urea and thiourea) followed by cyclization, fig. 5 and 6 illustrat the mechanisem of heterocyclic compounds synthesis.



X = NH_2, NO_2, CH_3

Fig. 5: Formation of Pyrazole Compounds



X = NH_2, NO_2, CH_3, Y = O, S

Fig. 6: Formation of Thiopyrimidine and Oxopyrimidine Compounds

The IR spectra of heterocyclic compounds synthesized in this study were characterized through disappearance of the strong absorption band which was belong to the stretching (C=O) group at (1634-1684) cm^{-1} which belong to the chalcone compounds. These facts enhance the correct expected chemical structure of these compounds. While, The FTIR spectra of heterocyclic compounds in figures (3-8) - (3-16) showed strong absorption bands in the range (1647-1697) cm^{-1} due to (C=N) stretching of azomethane group. Moreover, to these bands, there was medium bands showed in the region (1450-1600) cm^{-1} which were impute to the (C=C) aromatic group. The IR spectra of compounds (Z2, Z5, and Z8) showed the strong absorption bands at region (3200-3610) cm^{-1} which belong to (O-H) group stretching in Oxopyrimidine compounds. When the compounds (Z3, Z6 and Z9) showed strong bands between the range (2511-2576) cm^{-1} due to the (S-H) group stretching in thiopyrimidines. However, all these spectra shewed absorption bands in the range (3000-3100) cm^{-1}, were belong to the aromatic (-CH) stretching and bands between the region (2916-3000) cm^{-1} attributed to the (-CH) or (CH3). Moreover, the IR spectra for compounds (Z1, Z2 and Z3) appeared in region between (3224-3369) cm^{-1} a strong absorption band which belong to NH stretching. The absorption bands data of these compounds are illustrate in table 3. These results conformed to the information in the literature [17-22].

Table 3: Data of the FT-IR Spectra of Heterocyclic Compounds

Sym.	υOH Str. cm-1	υNH_2 Str. cm-1	υC=N Ar. Str. cm-1	υC=C Ar. Str. cm-1	υNO_2 Str. cm-1	υCH Ar. Str. cm-1	υCH, CH_3 Al. Str. cm-1	υS-H Str. cm-1
Z1	-	3448s 3367	1627s	1512	-	3058w	2928w	-
Z2	3568s	3448s 3375	1678s	1593s	-	3073w	2930	-
Z3	-	3564 3448	1678	1512	-	3063w	2900	2533
Z4	-	3348m	1647s	1600s	1512	3080w	2928w	-

Z5	3387s	-	1681s	1593s	1512s	3080w	2960w	-
Z6	-	-	1681s	1589s	1512s	3190w	2947m	2533
Z7	-	3402m	1678s	1512s	-	3073w	2931w	-
Z8	3417s	-	1681	1589s	-	3069w	2939m	-
Z9	-	-	1681s	1589s	-	3073w	2960w	2532s

The synthesized heterocyclic compounds were recognized by ^{1}H NMR spectroscopy. The data of ^{1}H NMR for these compounds are illustrated in Table 4. These showed similar patterns of the heterocyclic strictures and characterized by the presence of aromatic protons. The ^{1}H NMR spectra of all heterocyclic compounds showed signals at (6.50-8.66) ppm which belong to aromatic ring [23-25]. This fact compatable with the chemical structure of these compounds. The low field singlet within the region (9.30-9.87) ppm were refered to hydroxyl group (OH) signal in the cmpounds Z2, Z5 and Z8 [26]. Moreover, all spectrum of heterocyclic compounds showed singlet signals at reagion (2.22-3.85) ppm due to the protons of methoxy beside methyl groups in Z7, Z8 and Z9. The spectra of Z1, Z4 and Z7 were characterized by the egress of the protons of Pyrazole ring [27-30]. The low field singlets in the region (9.00-9.88) ppm were referred to thiol (SH) signals in thiopyrimidine Z3, Z6 and Z9 compounds. In addition, the low field singlets in the region (9.60-9.90) ppm were assigned to primary amine signals in Z1, Z2 and Z3 compounds [26,31].

Table 4: Chemical Shift (ppm) of Heterocyclic Compounds

Sym.	Ar. CH	NH	OH	SH	CH_2	OCH_3	CH_3	NH_2
Z1	6.56-7.95	9.66	-	-	4.41	3.76	-	6.12
Z2	6.64-7.95	-	9.30	-	4.47	3.84	-	6.12
Z3	6.63-8.15	-	-	9.30	4.47	3.36	-	6.12
Z4	6.56-7.95	9.64	-	-	4.42	2.89	-	-
Z5	6.84-8.34	-	9.85	-	4.47	3.82	-	-

Z6	6.57-8.37	-	-	9.86	4.48	3.38	-	-
Z7	6.91-8.65	9.86	-	-	4.41	3.83	2.36	-
Z8	7.10-8.08	-	9.86	-	4.47	3.82	2.40	-
Z9	7.12-8.08	-	-	9.86	4.47	3.82	2.40	-

While, in ^{13}C MNR all spectra showed multi peaks, in the region (39-40) ppm due to the DMSO solvent, the most important thing which give strong evidence to support our Hetero syntheses is disappear peck at region (185-195) for C=O group in all hetero compounds spectra. Also, all ^{13}C NMR spectrum of the Heterocyclic compounds showed signals at (50 -70) ppm chemical shift due to the (OCH_3) and (OCH_2) groups, Z7, Z8, and Z9 showed single peck at (21) ppm for CH_3 group [32]. Moreover, ^{13}C NMR spectra for all prepared chalcones showed signals within region (108-150) ppm for aromatic system [33,34] ^{13}C NMR data of these compounds are summarized in Table 5 and numbering of carbon atoms in Fig. 5.

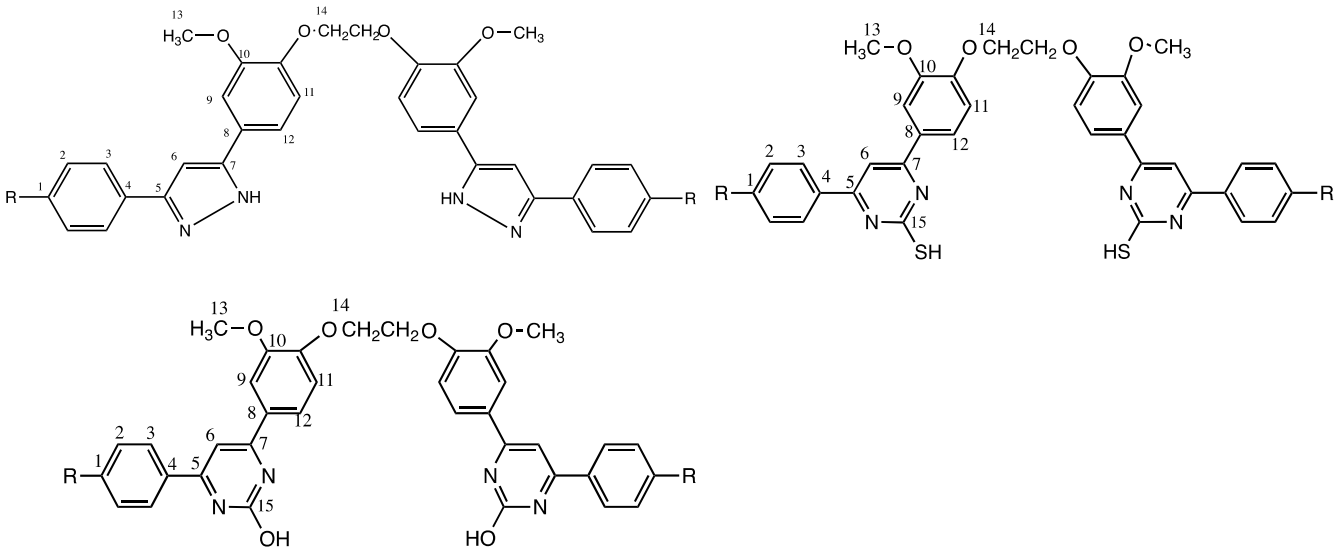


Fig. 6: Numbering Carbon Atoms of Heterocyclic Compounds

Table 5: Chemical Shift (ppm) of Hererocyclic Compounds

Sym.	Z1	Z2	Z3	Z4	Z5	Z6	Z7	Z8	Z9
C1	151.08	149.64	149.64	149.52	149.63	149.63	139.18	143.79	143.79
C2	113.16	112.86	112.86	123.89	126.37	126.37	128.50	129.06	129.05
C3	127.18	128.94	130.41	127.50	130.40	130.40	123.90	126.37	126.37
C4	123.89	126.37	126.37	139.17	135.53	137.50	129.52	130.41	130.41
C5	149.52	154.17	154.18	149.52	153.57	153.57	149.51	153.57	153.57
C6	108.13	110.26	110.26	108.13	110.24	110.26	109.86	110.26	110.26
C7	149.52	153.57	153.57	149.52	153.57	153.57	149.49	153.57	153.57
C8	127.18	130.41	131.49	127.50	130.40	130.40	125.81	129.74	129.74
C9	109.89	110.26	110.26	109.89	110.24	110.26	109.86	111.56	111.57
C10	139.17	150.07	150.07	142.27	149.63	149.63	145.55	149.63	149.64
C11	119.17	111.30	111.29	113.16	112.85	112.88	113.17	112.88	112.87
C12	123.89	120.66	123.60	119.17	126.37	126.37	119.14	124.22	124.22
C13	55.89	55.97	55.97	55.89	55.96	55.97	55.89	55.97	55.97
C14	67.60	67.65	67.64	67.60	67.64	67.65	67.58	67.65	67.65
C15	-	164.87	175.07	-	163.52	177.36	-	166.78	171.72
C16	-	-	-	-	-	-	28.38	21.65	21.64

5. Biochemical Application

The in-vitro cytotoxicity assay of prepared Heterocyclic compounds all hetero compound except (Z2) shown high inhibition rate more than 50%. Heterocycles are a good choice when designing molecules that will interact with targets and disrupt the biological pathways associated with cancer progression. Pathways related to cell growth and development are often targeted such anticancer therapies. Nitrogen based heterocyclic are particular importance in anticancer drug design because their ability to induce cell death [35], all heterocyclic compounds except (Z2) shown high inhibition rate more than 50 %, as shown in Table 6 and Fig.6.

Table 6: Rate of inhibition for heterocyclic compounds on CAL51 cell line

Compounds (1 mg/ml)	**% Inhibition**
Control	-
Z1	57.3
Z2	22.1
Z3	64.9
Z7	56.7
Z8	64.6
Z9	66.1

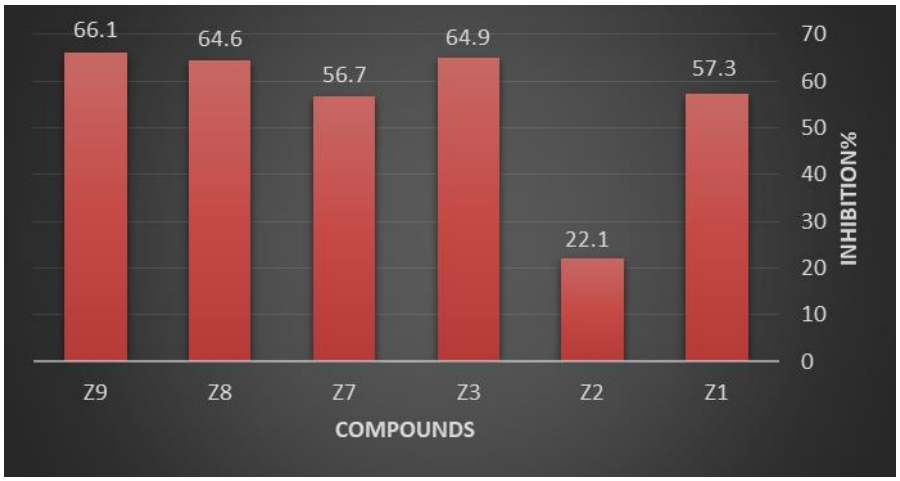


Fig. 6: Rate of inhibition for heterocyclic compounds on CAL51 cell line.

Conclusions

Obtained results confirmed that the heterocyclic compounds derivative from chalcones have high efficiency in inhibition of spread the cancer in live cells. In otherwise, the microwave assisted in chemistry synthesis very useful in reaction time with high yield and purity for the specific product compared with conventional methods.

References

[1] A. T. Biju, B. Sundararaju, Heterocyclic Chemistry, J. of Hetero. Chem., 58 (2021) 905-1033.

[2] D. Bandyopadhyay, E. Rhodes. B.K. Banik, A. green, chemoselective, practical approach toward N-(2-azetidinonyl) 2,5-disubstituted pyrroles, RSC Adv., 3 (2013) 16756-16764.

[3] A.R. Katritzky, A.F. Pozharski, Handbook of heterocyclic chemistry, Uni. Of Florida, Sec. ed., (2000) 566-552.

[4] N.M. Mahrous Hamada, E.M. Sharshira, Synthesis, Antimicrobial Evaluation of Some Heterocyclic Chalcone Derivatives, Molecules, 16 (2011) 2304-2312.

[5] A.A. Patel, A.G. Mehta, Synthesis and characterization of some pyrimidine–quinoline clubbed molecules and their microbicidal efficacy, J. of Saudi Chem. Soc., 14 (2010) 203-208.

[6] S.R. Manivannan, B.A. Kumar, Synthesis and Characterization of 2-Pyrazoline Derivatives and Their Insilico and Invitro Studies on Antimicrobial and Anticancer Activity, Pram. Res. J., 9 (2019) 2249-2976.

[7] D. Bandyopadhyay, B.K. Banik, Microwave-Induced Synthesis of Heterocycles of Medicinal Interests, Green Synthetic Approaches for Biologically Relevant Heterocycles, (2015) 517-557.

[8] Hanan A. Al- hazam, Afrodet A. Saleh, Abbas F. Abbas, Synthesis, Characterization and Antibacterial Study of 2((E) -Cinnamoyl imino) 4-methyl thiazole with Some Amino Acids, International Journal of Chemistry and Applications, 6 (2014), 7-14.

[9] S.C. Pirol, B. Çaliskan, I. Durmaz, R. Atalay, E. Banoglu, Synthesis and preliminary mechanistic evaluation of 5-(p-tolyl)-1-(quinolin-2-yl) pyrazole-3-carboxylic acid amides with potent antiproliferative activity on human cancer cell lines, Eur. J. Med. Chem., 87 (2014) 140-149.

[10] L. Ma, B. Wang, L. Pang, M. Zhang, S. Wang, Y. Zheng, Design and synthesis of novel 1,2,3-triazole–pyrimidine–urea hybrids as potential anticancer agents, Bioorg Med. Chem. Lett., 25 (2015) 1124–1128.

[11] N.O. Al-Harbi, S.A. Bahashwan, A.A. Fayed, M.S. Aboonq, A.E. Amr, Anti-parkinsonism, hypoglycemic and anti-microbial activities of new poly fused ring heterocyclic candidates, Int. J. Biol. Macromol, 57 (2013) 165–173.

[12] D. Haleshappa, A. Jayarama, R. Bairy, S. Acharya, P. S. Patilf, Second and third order nonlinear optical studies of a novel thiophene substituted chalcone derivative, Chem. Zvesti., 555 (2019) 125-132.

[13] Y. Xue, X. Gong, The conformational, electronic and spectral properties of chalcones: A density functional theory study, J. Mol. Struct. Theochem, 901 (2009) 226-231.

[14] G. Vanangamudi, M. Subramanian, P. Jayanthi, R. Arulkumaran, D. Kamalakkannan, G. Thirunarayanan, IR and NMR spectral studies of some 2-hydroxy-1-naphthylchalcones: Assessment of substituent effects, Arab J. Chem., 7 (2011) 717-727.

[15] W.P. Hayes, C. J. Timmons, The C=O and C=C fundamental and overtone stretching bands and the electronic absorption bands of some α, β-unsaturated, Sci. Direct, 24 (1968) 323-334.

[16] M.M. Ibrahima, M. Al-Refaia, R. Abu-El-Halawaa, H. Tashtousha, Alsohailib, M. Masadc, Synthesis of Some New Chalcone and 4,5-Dihydro-1H-Pyrazole Derivatives as Potential Antimicrobial Agents, Jordan J. of Chem., 7 (2012), 115-123.

[17] A. Mansour, M.M. Eid, N.S.A.M. Khalil, Synthesis and Reactions of Some New Heterocyclic Carbohydrazides and Related Compounds as Potential Anticancer Agents, Molecules, 8 (2003), 744-755.

[18] A.M. Al-Shammari, M.A. Alshami, M.A. Umran, A.A. Almukhtar, N.Y. Yaseen, K. Raad, A. A. Hussien, Establishment and characterization of a receptor-negative, hormone-nonresponsive breast cancer cell line from an Iraqi patient, Breast Cancer Targets Ther., 7 (2015) 223-230.

[19] R.I. Freshney, Culture of animal cells a manual of basic technique and specialized applications, Wiley-Blackwell**,** 6th ed. (2010)732.

[20] A.M. Al-Shammari, M.I. Salman, Y.D. Saihood, N.Y. Yaseen, K. Raed, H.K. Shaker, In vitro synergistic enhancement of Newcastle Disease Virus to 5-fluorouracil cytotoxicity against tumor cells, Biomedicines, 4 (2016) 3-11

[21] M.N. Koopaei, M.J. Assarzadeh, A. Almasirad, S.F. Ghasemi-Nirib, M. Amini, A. Kebriaeezadeh, N.N. Koopaei, M. Ghadimi, A. Tabei, Synthesis and Analgesic Activity of Novel Hydrazide and Hydrazine Derivatives, Iranian J. of Pharm. Res., 12 (2013) 721-727.

[22] G. F. Fadhil, H.A. Radhy, Al. Perjéssy, M. Šamalíková, E. Kolehmainen, Walter M.F. Fabian, K. Laihia, Z. Šusteková, Dual Substituent Parameter Modeling of Theoretical, NMR and IR Spectral Data of 5-Substituted Indole-2,3-diones, Molecules, 7 (2002) 833-839.

[23] Y. Lyu, E. Rachita, N. Pogharian, P. Froimowicz, H. Ishida, Electronic effects of asymmetric and meta-alkoxy substituents on the polymerization behavior of bis-benzoxazines, Polymer Chem., 4 (2020) 1-10.

[24] N. Abood, J.A. AL-Hilfi, Theoretical NMR investigation of pyrazole and substituted Pyrazoles, DNMR and 1H spin-lattice relaxation times, Iraqi Academic Sci. J., 1 (2013), 340-350.

[25] L.G. Wade Jr., Organic Chemistry, 6th ed., Pearson Prentice Hall, NY, (2006) 508-608.

[26] D.C.G.A. Pinto, C.M.M. Santos, A. M. S. Silva, Advanced NMR techniques for structural characterization of heterocyclic structures, Recent Res. Developments in Hetero. Chem., 2 (2007) 397-475.

[27] C.N. Beecher, C.K. Larive, ^{1}H and ^{15}N NMR Characterization of the Amine Groups of Heparan Sulfate Related Glucosamine Monosaccharides in Aqueous Solution, Anal. Chem., 87(2015) 6842-6848.

[28] A.R. Mehetre, S.R. Deshmukh, V.N. Bhosale, Synthesis and Characterization of Schiff Base and Their Chalcone Derived from 3-Amino Acetophenone, Intern. J. for Res. in Applied Sci. & Eng. Tech., 6 (2018) 2478-2481.

[29] N.J.P. Subhashini, T.T. Shivaraj, Synthesis characterization and anti-bacterial activity of novel chalcone derivatives of indole, Der. Pharma. Chemica., 7 (2015) 38-45.

[30] B. Ahmed, Z. Naturforsch, T.A. Al-Howiriny, Two New Hydroxy Chalcone Derivatives from Thymus cilicicus, Zeitschrift für Naturforschung, 62 (2007) 121-124.

[31] W. Hu, H. Wang, Y. Hou, Y. Hao, D. Liu, Trimethylsilyl reporter groups for NMR studies of conformational changes in G protein-coupled receptors, FEBS Letters, 593 (2019) 1113-1121.

[32] U. Groselj, D. Kralj, J. Wagger, G. Dahmann, B. Stanovnik, J. Svete, Synthesis of 3-(2-aminoethyl)-5-hydroxy-1H-pyrazole derivatives, Arkivoc, iii (2012) 49-65.

[33] S. Pundir, S.K. Mehta, S.M. Mobin, K.K. Bhasin, Synthesis and characterization of some symmetrical substituted 1-(2-chloroethyl) pyrazole-based chalcogenides, Ind. J. of Heter. Chem., 27 (2017) 1-7.

[34] P.A. Beckmann, C.W. Mallory, F.B. Mallory, A.L. Rheingold, X. Wang, Methoxy and Methyl Group Rotation: Solid-State NMR (1) H Spin-Lattice Relaxation, Electronic Structure Calculations, X-ray Diffractometry, and Scanning Electron Microscopy, Chemphyschem., 16 (2015) 1509-1519.

[35] P. Martins, J. Jesus, S. Santos, L.R. Raposo, C. Roma-Rodrigues, P.V. Baptista, A.R. Fernandes, Heterocyclic anticancer compounds: Recent advances and the paradigm shift towards the use of nanomedicine´s toll box, Molecules., 20 (2015) 16852-16891.

المستخلص

تم تحضير عدد من المركبات الحلقية غير المتجانسة الجديدة المشتقة من الجالكونات المشتقة من ثنائي الفانيلين بواسطة تكاثف Claisen-Schmidt باستخدام الميكروويف كمصدر للحرارة في الوسط القاعدي. تم تاكيد التركيب الكيميائي وآليات التفاعلات المقترحة بواسطة مطيافية تحليل العناصر والتحليل الطيفي. بالإضافة إلى ذلك ، تم تقييم نشاط المركبات كمضادات للسرطان (Z1، Z2، Z3، Z7، Z8، Z9)وجميعها أظهرت كفاءة عالية في التثبيط ما عدا (Z2)مع خط خلايا سرطان الثدي البشري(Cal51)وفقًا لفحص MTT القياسي. تم تشخيص المركبات الحلقية غير المتجانسة بناءً على الخصائص الكيميائية والفيزيائية وبيانات التحليل الطيفي (CHN-S, ^{13}C NMR, ^{1}H NMR, FT-IR).