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Microwave Assisted Synthesis, Characterization and Biological Study of Some Chalcone Compounds Derived from Phenyl Isothiocyanate

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Abstract
Chalcones are synthesized by Claisen-Schmidt condensation, which involves cross-aldol condensation of appropriate aldehydes and ketones by base catalyzed reaction, the new chalcone derivatives synthesized by the reaction aldehyde with their compounds. By microwave assisted synthesis, a considerable increase in the reaction rate has been observed and that too, with better yields. M.P., TLC, CHN, FTIR, NMR and MS spectroscopy has characterized all the synthesized compounds. The biological screening data of the synthesized compounds were also studied.
Keywords: microwave, chalcone, antibacterial.
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Introduction

Microwave dielectric heating uses the ability of some liquids and solids to transform electromagnetic radiation into heat to drive chemical reactions. The entry of microwave ovens possible to carry out many transformations with greater efficiency and ease of workup [Hoz et al, 2005, Gedye et al,1998, Nuchter et al,2000] the use of microwave has becomes very attractive in the field of medical sciences [Chattree et al, 2013]. Microwave-induced organic reaction enhancement (MORE) chemistry [Syam et al, 2012 and Modzelewska et al, 2006] is gaining popularity as a non-conventional technique for rapid organic synthesis. Important features of this technique are easy access to very high temperature, good control over energy input in a reaction, higher yields and rapid synthesis of organic compounds.

Chalcones are 1,3-diphenyl-urea derivatives in which three aromatic rings are linked by a three carbon α, β-unsaturated carbonyl system. These are abundant in edible plants and are considered to be the precursors of flavonoids and isoflavonoids [Hassan et al, 2007]. Chalcones are synthesized by Claisen-Schmidt condensation, which involves cross-aldol condensation of appropriate aldehydes and ketones by base catalyzed or acid catalyzed reaction followed by dehydration. Chalcone is a common natural pigment and one of the important intermediate in the biosynthesis of flavonoids. Synthetic and naturally occurring chalcones have been extensively studied and developed as one of the pharmaceutically important molecules. Chalcone derivatives are screened for their anti-inflammatory activity [Herenciaa et al, 1998], chemo preventive activity [Ahmad et al, 2016], cardiovascular disease [Tiellas,etal,2016], anticancer activity[Das et al, 2016], cytotoxic activity [Kotha1et al, 2017], antiprolifirative activity [Mellado, et al, 2018], antimalarial activity [Yadav et al, 2012], antiviral activity [Gan et al, 2017] and anti–HIV activity [Al-Hazam et al, 2017]. Therefore, in the present investigation, it has been considered worthwhile to synthesize some new chalcone derivatives by conventional and microwave irradiation methods and a comparison has been made between two methods.

Experimental Work

Melting point were determined in Buchi thermal point apparatus and were uncorrected, Elemental analysis (CHN) were recorded in Costech ESC4010 CHNSO in University of Tehran in Iran. FT-IR Spectra were recorded on Shimadzu FT-IR 8400 Fourier Transformer infrared as KBr disk in the range 40-4000cm^{-1}. ^{1}HNMR and ^{13}CNMR spectra were recorded on Brucker spctrospin ultra shield magnets 400MHz instrument using tetramethyl silane (TMS) as an internal standard and DMSO-d_6 as a solvent in university of university of Tehran. The compounds were synthesized by microwave type Panasonic microwave instrument (Malaysia), NN-SN382, compact 20L, power1200 Watt and frequency 2450 MHz, by using turntable system with different powers between 90-300W. Thin layer chromatography were performed on pre-coated sheets with 0.25 mm layer of Silica Gel GF254 of the Merck Company.

Synthesis of Compounds

1- Synthesis 1-(4-Acetylphenyl)-3-phenylthiourea

A mixture of 4-aminoacetophenone (1.4gm, 0.01mole) and phenyl thiocyanate (1.35gm, 0.01mol) in 50ml dry acetone, then irradiated inside microwave oven 270W for 4min. The reaction was monitored by TLC using eluent

n-hexane: ethyl acetate (3:7), the obtained product white crystals was filter off and recrystallized from ethanol to give 1-(4-Acetylphenyl)-3-phenylthiourea (m.p. 160-162ºC).

2- Synthesis of Chalcone (a-h)

A mixture of (0.27gm, 0.01 mole) of 1-(4-Acetylphenyl)-3-phenylthiourea, (0.01mole) of substituted benzaldehydes were dissolved in 3ml of ethanol and 1ml (40%) KOH then irradiated inside microwave oven 90W for 4min. The reaction was monitored by TLC using eluent n-hexane: ethyl acetate (3:7), then it was poured in to crushed ice and acidified with HCl. The solid separated was filtered and recrystallized from ethanol.

(a): yield 83%. Melting point 200-202ºC, CHN analysis that formula **$C_{22}H_{17}BrN_2OS$** calculated C, 60.422 H, 3.925 N, 3.925 S, 7.335; Found C, 60.366 H, 3.884 N, 6.385, S, 7.258. FT-IR spectra νmax 3224, 3012, 1678, 1546, 1338, 698 cm^{-1}. ^{1}HNMR spectra δppm, (9.89, 1H) s, (9.61, 1H) s (6.51, 1H) s and (6.00, 3H) t. ^{13}CNMR spectra δppm, 93.5, 121.7, 126.7, 128.1, 134.9, 135.3, 131.3, 128.1 128.2, 128.8, 128.5, 180.5, 161.3, 130.6, 131.3 and 134.9. MS spectra (m/z),436, 228, 211, 135,138, 157,93,77and51

(b): yield 80%. Melting point 160-162ºC, CHN analysis that formula **$C_{23}H_{20}N_2OS$** calculated C, 74.160 H, 5.413 N, 7.522 S, 8.611; Found C, 74.100 H, 5.389 N, 7.447, S, 8.521. FT-IR spectra νmax 3375, 3018, 2978, 1730, 1683, 1595cm^{-1}. ^{1}HNMR spectra δppm, (9.63,1H)s, (9.38,1H)s (6.51,1H)s , (6.00,3H)t and (2.2,3H) .^{13}CNMR spectra δppm, 99.6, 110.6, 121.7, 136.3, 135.4, 141.7, 163,9, 126.8, 127.5, 127.8, 160.0, 174.3, 163.9, 128.7, 128.8, 132.4 and 23.2. . MS spectra (m/z),372, 288, 146, 135, 118, 92, 93, 77 and 51

(c): yield 85%. Melting point 179-181ºC, CHN analysis that formula **$C_{22}H_{17}ClN_2OS$** calculated C, 67.259 H, 4.366 N, 7.133 S, 8.186; Found C, 67.212 H, 4.228 N, 7.088 S, 8.004. FT-IR spectra νmax 3215, 3028, 2916, 1658, 1600, 1330, 813cm^{-1}. ^{1}HNMR spectra δppm, (9.69,1H)s, (9.31,1H)s (7.71,1H)s and (4.94,3H)t. .^{13}CNMR spectra δppm, 119.4, 111.5, 115.5, 121.5, 135.4, 146.8. 165.5, 126.3, 126.5, 127.5, 147.5, 173.9, 161.9, 127.6, 127.8 and 133.7. . MS spectra (m/z), 392, 228, 166, 135, 138, 112, 93, 77 and 51.

(d): yield 84%. Melting point 180-182ºC, CHN analysis that formula **$C_{22}H_{17}FN_2OS$** calculated C, 70.196 H, 4.552 N, 7.448, S, 8.528; Found C, 70.012 H, 4.465 N, 7.333 S, 8.449. FT-IR spectra νmax 3272, 2962, 1631, 1257, 825 cm^{-1}. ^{1}HNMR spectra δppm, (9.72,1H)s, (9.04,1H)s (7.17,1H)s and (4.95,3H)t..^{13}CNMR spectra δppm, 99.5, 110.9, 15.3, 115.5, 129.9, 135.4, 162.9, 121.7, 126.3, 126.7, 139.1, 174, 2, 152.5, 127.5, 127.8, and 128.9. . MS spectra (m/z), 376, 228, 150, 135, 122, 96, 93, 77 and 51.

(e): yield 78%. Melting point 176-178ºC, CHN analysis that formula **$C_{22}H_{16}N_2OS$** calculated C, 73.723 H, 5.068 N, 7.822 S, 8.948; Found C, 73.623 H, 4.886 N, 7.695 S, 8.747.. FT-IR spectra νmax 3240, 3055, 1643, 1573, 1319 cm^{-1}. ^{1}HNMR spectra δppm, (9.79,1H)s, (9.41,1H)s (6.42,1H)s and (6.00,3H)t..^{13}CNMR spectra δppm, 98.4, 111.1, 121.6, 126.2, 135.3, 142.8, 137.7, 126.6, 126.9, 127.5, 161.5, 180.2, 165.5, 127.7, 127.8 and 128.6. . MS spectra (m/z), 358, 228, 132, 135,104, 93, 77 and 51.

(f): yield 80%. Melting point 146-148ºC, CHN analysis that formula **$C_{24}H_{23}N_3OS$** calculated C, 71.795 H, 5.778 N, 10.475 S, 7.985; Found C, 71.722 H, 5.622 N, 10.255, S, 7.895. FT-IR spectra νmax 3331, 3053, 2924, 1681, 1527.1315cm^{-1}. ^{1}HNMR spectra δppm, (9.54,1H)s, (9.28,1H)s (6.42,1H)s, (6.00,3H)t and (3.64,3H).^{13}CNMR spectra δppm, 97.6, 110.1, 111.5, 121.4, 133.5, 137.0, 138.2, 126.7, 128.1, 128.5, 135.5, 131.6, 137.5, 127.7, 128.9, 131.4 and 61.8. MS spectra (m/z), 401, 228, 175, 135, 147, 121, 93, 77 and 51.

(g): yield 88%. Melting point 228-230ºC, CHN analysis that formula **$C_{22}H_{17}N_3O_3S$** calculated C, 65.495 H, 4.254 N, 10.422 S, 7.956; Found C, 65.344 H, 4.005 N, 10.235, S, 7.775. FT-IR spectra νmax 3340, 2926, 1674, 1600, 1346cm^{-1}. ^{1}HNMR spectra δppm, (9.53,1H)s, (9.21,1H)s (6.84,1H)s and (6.4,3H)t..^{13}CNMR spectra δppm, 40, 45, 53, 87, 117, 118,120, 123, 127, 128, 129, 135, 138,141,144, 148, 158, 161, 171, 174,177, 181. MS spectra (m/z), 403, 228, 177, 135, 149, 123, 93, 77 and 51.

(h): yield 79%. Melting point 155-157ºC, CHN analysis that formula **$C_{23}H_{20}N_2O_2S$** calculated C, 71.114 H, 5.195 N, 7.213 S, 8.254; Found C, 70.865H, 5.004 N, 7.119 S, 8.154. FT-IR spectra νmax 3361, 3061, 1681, 1599, 1267 cm^{-1}. ^{1}HNMR spectra δppm, (9.61,1H)s, (9.05,1H)s (6.92,1H)s and (4.86,3H)t and (3.74,3H).^{13}CNMR spectra δppm, 99.0, 111.6, 115.3, 121.5, 133.3, 135.3, 163.1, 126.3, 126.3, 127.5, 132.3, 173.8, 157.1, 127.6, 127.8, 128.5 and 55.1. MS spectra (m/z), 388, 228, 162, 1354, 134, 108, 93, 77 and51.

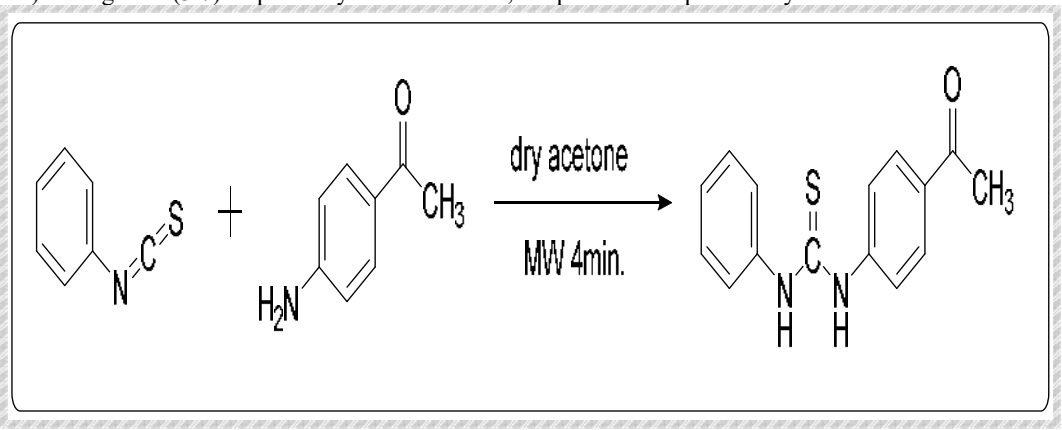
(i): yield 75%. Melting point 216-218ºC, CHN analysis that formula **$C_{22}H_{18}N_2O_2S$** calculated C, 70.575 H, 4.854 N, 7.485 S, 8.567; Found C, 70.325 H, 4.625 N, 7.309 S, 8.493. FT-IR spectra νmax 3417, 3240, 1643, 1615, 1597, 1230cm^{-1}. ^{1}HNMR spectra δppm, (9.62,1H)s, (9.47,1H)s, (8.93,1H)s (6.74,1H)s and (4.82,3H)t..^{13}CNMR spectra δppm, 99.1, 119.5, 121.2, 126.7, 134.9, 135.5, 148.6, 126.9, 128.1, 128.5, 138.6, 131.1, 147.9, 128.8, 131.1 and 131.5. MS spectra (m/z), 374, 228, 148, 135, 120, 92, 93, 77 and 51.

(j): yield 70%. Melting point 178-180ºC, CHN analysis that formula **$C_{23}H_{20}N_2O_3S$** calculated C, 68.302 H, 4.985 N, 6.935 S, 7.933; Found C, 68.025 H, 4.863 N, 6.778 S, 7.798. FT-IR spectra νmax 3488, 3329, 3053, 3100, 1658, 1597, 1342 cm^{-1}. ^{1}HNMR spectra δppm, (9.65,1H)s, (8.97,1H)s, (7.67,1H)s (6.82,1H)s, (4.88,3H)t and (3.76,3H)s .^{13}CNMR spectra δppm, 111.0, 111.3, 111.9, 119.0, 135.2, 135.4, 131.7, 121.6, 126.3, 126.6, 148.3, 174.0, 148.7, 127.5, 127.7, 127.7 and 58.1. MS spectra (m/z), 404, 228, 178, 135, 150, 124, 108, 93, 77 and 51.

RESULT AND DISCUSSION

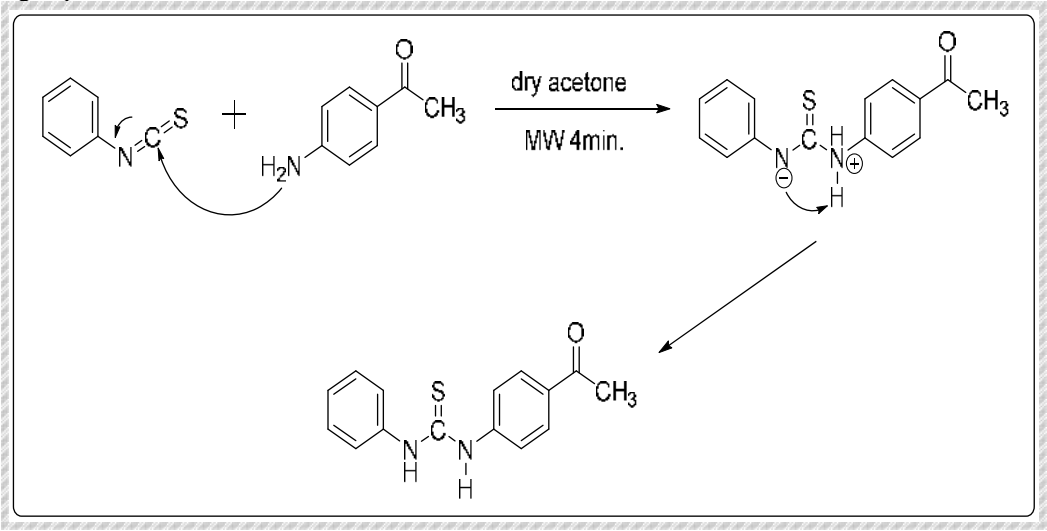
Chalcone derivatives form a group of generally less investigated compounds. However, recently growing efforts are made to synthesize and characterized these compounds. Many chalcone derivatives possess very promising properties regarding biological activities as shown in literature survey. In the present research, project the conventional methods to prepare some chalcones compounds with expected biological activity.

The Purification of *1-(4-Acetylphenyl)-3-phenylthiourea* compound was tested first by thin layer chromatography (TLC) using different eluents. The best separation was obtained in mixture of (n-hexane: ethyl acetate) having ratio (3:7) respectively as eluent. Then, the product was purified by absolute ethanol.



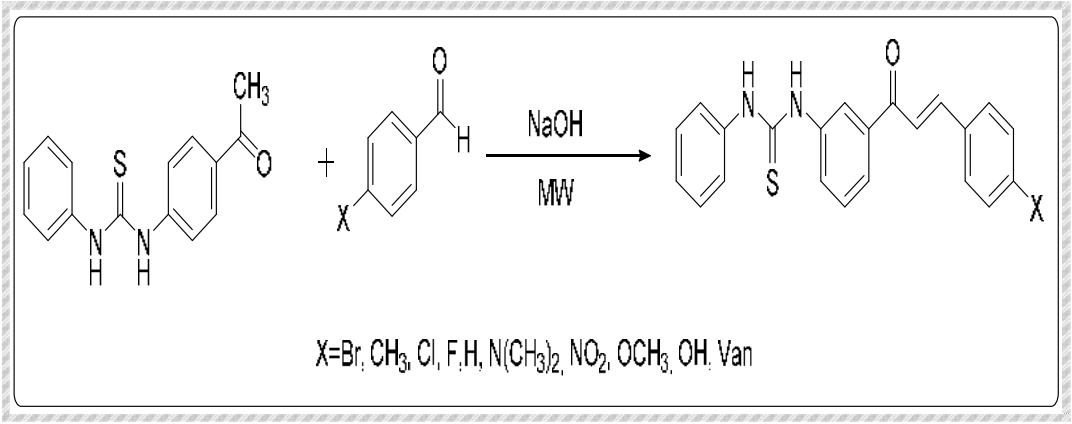
Scheme (1),

The mechanism of reaction can be explained in scheme (2), which first showed the formation of thiourea derivatives then nucleophilic attack of amine group of 4-amino acetophenone at the carbon atom of phenylisothiocyanate, the second nucleophilic attack of amine of thiourea toward active hydrogen of the other amine group.



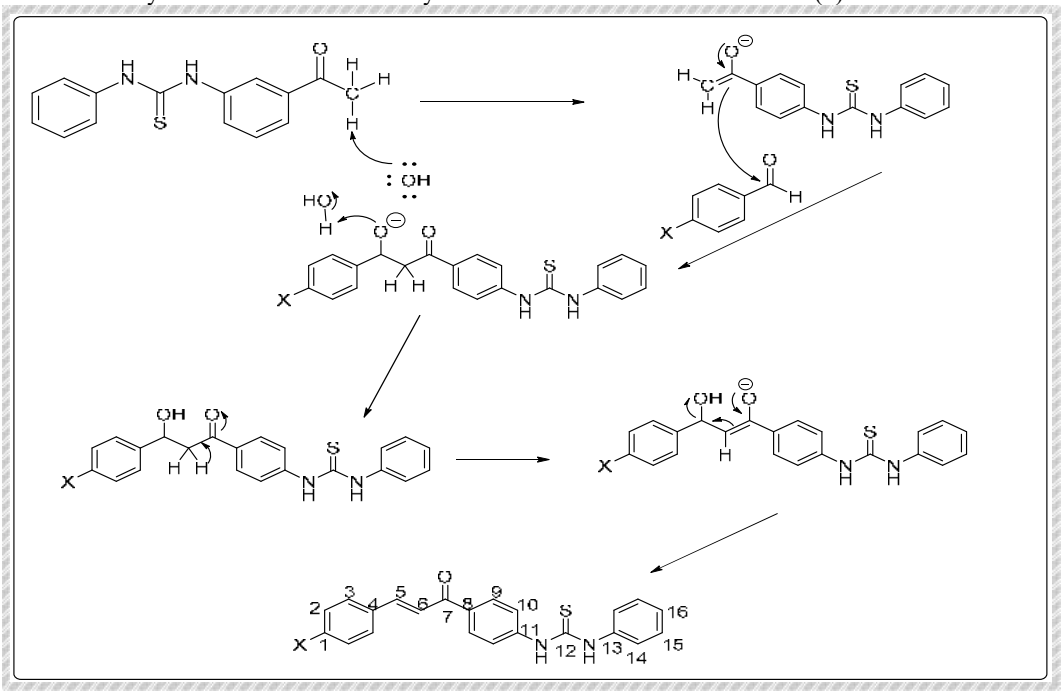
Scheme (2)

A series of chalcones were prepared according to Claisen Schmidt condensation [Claisen et al, 1881] and [Schmidt, 1881]. Variously substituted aromatic aldehydes with *1-(4-Acetylphenyl)-3-phenylthiourea* by using base catalyzed, under microwave irradiation for (1-6) min. depending on substituent's of benzaldehyde to give corresponding chalcones. The reactions were monitored for their completion by TLC, shown in Scheme (3).



Scheme (3)

The Synthesized chalcones showed different yield depending on the substituent groups, as they were electron with drawing group or electron donating group. Aldehydes with electron donating groups led to increase the electron density on the carbon atom of carbonyl group, results in enhancing their electronic properties and hence decreasing yield of products. In contrasting, those with electron withdrawing groups caused in increasing yield as the electron density on carbon atom of carbonyl were decreased as shown in scheme (4).



Scheme (4)

The structures of the synthesized compounds (a-j) were confirmed by their elemental analysis, IR, NMR and MS. CHN were situated within the range which confirmed the validity of the suggested structure of the prepared compounds. The purification compounds were tested by thin layer chromatography (TLC) using different eluents. The best separation was obtained in mixture of (benzene: methanol) (3:7) respectively as eluent. Then, the compounds were purified by using ethanol. The structures of synthesized compounds were determined on the basis of their FTIR [Al-Juburi, 2012], The spectra of all substituent chalcones compounds were characterized by the appearance of the absorption band that was attributed to the (C=O) stretching which appeared at (1631-1681) cm^{-1}.

The infrared spectra of the synthesized substituent chalcones compounds in this study were measured. The IR spectra of these compounds showed a strong infrared absorption band in the region between (3215-3375) cm^{-1} due to NH stretching. Other strong bands appeared in the region (1546-1600) cm^{-1} which were characteristic of all chalcones compounds and were due to the (C=C) stretching. Also, medium absorption bands appeared between the region (1258-1338) cm^{-1} due to (C=S) stretching. Moreover, all these spectra showed medium absorption bands due to (C-H) aromatic stretching in the region (3018-3112) cm^{-1}. However, the IR spectra of compounds (b, c, d

and g) showed that weak absorption bands appeared in the region (2916-2978) cm^{-1} due to stretching of (-CH) and (CH_3) aliphatic group. While the compounds (i) and (j) showed that strong absorption bands appeared in the region (3448-3471) cm^{-1} due to stretching of (-OH) group. Strong absorption bands appeared between the region (698-815) cm^{-1} due to (C-X) stretching [Xue et al, 2009],[Vanangamudi et al, 2011] and [Hayes et al,1968].

^{1}HNMR [Rudrapal et al, 2013, Al-Hazam, 2014]. The ^{1}HNMR spectra of (a-j) substituent chalconecompounds showed multiplet signal within the region (6.4-7.1) ppm due to aromatic ring system. Moreover, one proton of (C=CH) [Wade, 2006] which was interfere with the protons of aromatic ring. The second proton of (C=CH) at (4.8-6.4) ppm.

All these spectra showed a peak at the region (8.7-9.9) ppm, which was due to the two-proton equivalent two secondary amino group [Yoon et al, 2014]. In addition, the ^{1}HNMR spectrum of (b, f and h) compounds showed singlet signals at the chemical shift (2.2-3.7) ppm due to the three and six proton equivalent of methoxy and methyl groups [Abood et al, 2013]. The low field singlet's at the region (7.6-8.9) ppm were assigned to hydroxyl group signal in the compounds (i and j).

The ^{13}CNMR [Kurtev, et al, 1985] and [Mehetre et al, 2018] spectra of substituent chalcone compounds showed (16-17) signal according to the carbon atoms exist in the structure, the signals in the region (93-165) ppm due to C_1, C_2, C_3, C_4, C_8, C_9, C_{10}, C_{11}, C_{13}, C_{14}, C_{15} and C_{16} for aromatic ring system including the compounds (a-j). While the signals of double bond appearance in the region (129-146) ppm due to C_5 and C_6 for these compounds. Also C_7 and C_{12} showed the signals in the region (137-165) and (161-180) come back to the (C=O) and (C=S) respectively. In addition, the ^{13}CNMR spectrum of the compounds (b, f and h) showed signals at the chemical shift (23 -61) ppm due to from the methyl, N-N-dimethyl and methoxy groups.

All synthesized substituent chalcone compounds had similar fragment mechanisms [Sande et al, 1972]. The suggested analysis mechanisms of (a-h) compound include seven steps; the first step was concerned with the formation of the fragment ion (2) and (3) by cleavage the bond between chalcone molecules and diphenylthiourea, the second step includes formation of the fragment ion (4) by losing fragment anilinium ion (7) which appeared at (m/z =135) for all spectra. While the third step in the analysis mechanism includes the formation of the fragment ion (5) by losing carbonyl molecules which appeared at deferent (m/z) of these compounds. The fourth step includes formation of the fragment ion (6) by losing substituent groups atom for all compounds exception X10 carry out by two step , The fifth step includes formation of the fragment ion (8) by losing acetylene molecule atom which appeared at (m/z =77) for all spectra. The final step include formation of the fragment ion (9) by losing acetylene molecule atom which appeared at (m/z =51).

The mass spectra of (a and c) compounds showed an additional peak at (m/z=438) and (m/z=378), these peaks may be attributed to the molecular ion [M+2] which contains the second isotope bromine (Br^{81}) and (Cl^{37}) respectively.

The antibacterial [Al-Shamkhani and Al-Hazam, 2015] activities of the series [a-h] have been carried out against some strain of bacteria. The result [Table 1] showed that prepared compounds are toxic against the bacteria. The compounds (a-d) were found more active against the above microbes. The comparison of the antibacterial activity of these compounds with Streptomycin shows that these compounds have almost similar activity. The bacterial cultures for *S. aurous* and *E. coli* were obtained from Department of biology University of Basrah. Iraq. The bacterial cultures were incubated at 30°C for 24 hours by inoculation into nutrient agar. chalcones were stored dry at room temperature and dissolved 20mg/ml in dimethyl sulfoxide [DMSO]. Antibacterial activities of each compound were evaluated by the agar disc-diffusion method. Mueller Hinton Agar Media [15 cm^3] kept at 45°C was poured in the petridishes and allowed to solidify. Poured Petri plates [9 cm] were incubated with 50µL of normal saline solution of above culture media [105-106 bacteria per ml]. Discs injected with prepared chalcones [50µL] were applied on the solid agar medium by pressing tightly. The Petri plates were placed at 37°C for 24 hours. At the end of period, the inhibition zones formed on media were measured with a zone reader in millimeters.

Table (1): Inhibition Zones (mm) of The Synthesis chalcone and Heterocyclic Compounds

Code	*E. Coli	*S. aureus
a	8	13
b	8	10
c	10	10
d	zero	zero
e	10	12
f	15	25
g	zero	10
h	15	20
i	15	15
j	30	30
Streptomycin	9	9

*Staphylococcus aureus, *Escherichia coli,

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