Journal of Engineering and Applied Sciences 14 (Special Issue 8): 10472-10481, 2019
ISSN: 1816-949X

Synthesis, Characterization with Studing Anti Convulsant Activity of Some New Resins by Free Radical Polymerization Starting from Chalcone Derivatives

Iman Mehdi Mohammed Hasan
Department of Chemistry, College of Science for Women, University of Baghdad, Baghdad, Iraq

Abstract: A new series of chalcone derivatives was synthesized then polymerized theirs due to resins. Starting from (E)-3-(benzo[d] [1, 3] dioxol-5-yl)-1-(4-hydroxyphenyl) prop-2-en-1-one [1] which reacts with di bromo ethan preperated [C_2] then reacted with secondary amines(piperidine, morpholine, piperazine, 4-methyl piperidine) to prepare [C_3-C_6] as monomers which polymerized using AIBN initiator due to resins [C_7-C_{10}]. All proposed structure were supported by FTIR, some derivatives evaluated by H^1-NMR, elemental analysis, thermal analysis (TGA, DSC) and evaluated for anticonvulsant activity by MES method, most of derivatives were found to be more or comparable potent than the reference standard drug.

Key words: Chalcons derivatives, Claisen schmidt reaction, free radical polymerization, comparable, drug, anticonvulsant activity

INTRODUCTION

Chalcones are well known inter mediates for synthesizing various heterocyclic compounds (Pasquale *et al*., 2012). The compounds with be back bone of chalcones have been reported to posses various biological activities (Asiri and Khan, 2012) such as anti-inflammatory (Muralidharan *et al*., 2018), antiplatelet (Asiri and Khan, 2012), antimalarial (Yadav *et al*., 2012), antioxidant (Lahsasni *et al*., 2014), anticonvulsant (Beyhan *et al*., 2017), anticancer, inhibition (El-Messery *et al*., 2018) of chemical mediators release, inhibition of leukotriene (B_4), inhibition of tyrosin as and inhibition of aldose reductase activitys (Zhuang *et al*., 2017), the discovery of derivatives was also based on the rational considerations of pathophysiological mechanism of epileptic syndrome. Hence, the endeavor of the century is to develop antiepileptic drugs with 100% efficiency, safety and tolerability.

MATERIALS AND METHODS

General: Melting points were determined on Gallen kamp, melting point apparatus and were uncorrected. FTIR spectra of the compounds were recorded on a (SHIMADZU) FTIR. 8300 Spectrometer as KBR-disc, ^{1}H-NMR spectra were recorded at 200.13-50.32 MHz, respectively using Tetra Methyl Silane (TMS) as an internal standard, DMSO as a solvent. Elemental analysis were run using a Perkin-Elmer RE 2400 (CHN) analyzer, thermal stability (TGA&DSC), MES method.

All analysis were performed in: University of Baghdad College of Education for Pure Sciences Ibn-Al-Haitham Central Service Laboratory and College of Pharmacy Department of Pharmacognosy.

All the chemical used were supplied by (Merk, Fluka and BDH) chemicals, the solvents purified by distillation and dried with calcium chloride.

Measurement and techniques: The purity of products were investigated by (TLC) technique by using a mixture of benzene-ethanol (5:5 v/v) as elute and iodine chamber for spot location.

Differential scanning calorimetry and thermal gravemetric:
Analysis: Differential Scanning Calorimetry (DSC) and Thermal Gravemetric Analysis (TGA) was carried out using LINSEIS (DSC), equipped with an internal cooler 2P-cooling accessory and some of them were performed in Chemistry Department, College of Education for Pure Sciences\Ibn AL-Haitham [The Central Service Laboratory].

Synthesis of (E)-1-(4-hydroxyphenyl)-3-(2, 3, 4a, 8a-tetrahydrobenzo [b] [1, 4] dioxine-2-yl) prop-2-en-1-one [C_1] (Mohammed, 2015): A mixture of benzo [d] [1, 3] dioxole-5-carbaldehyde (0.035 mol) with 1-(4-hydroxy phenyl) ethanone (0.045) in 10 mL absolute ethanol of 20% NaOH was stirred on ice water bath at 3 h. The mixture kept stirred at room temperature over night then poured on to ice cold water and acidified with dilute HCL, filterered, crystallized from ethanol, m.p (225-227°C), yield 90%, color pale brown.

Table 1: Dapcited physical properties for [1-10]

Comp No.	Molecular formula	MP (°C)	Colour	Yield (%)	Purification solvent
1	$C_{16}H_{12}O_4$	225-227	Pale brown	90	Ethanol
2	$C_{18}H_{15}O_4Br$	229-231	Brown	85	Ethanol
3	$C_{23}H_{25}O_4N$	119-121	Brown	85	Acetone
4	$C_{22}H_{23}O_5N$	115-117	Brown	80	Acetone
5	$C_{22}H_{23}O_4N_2$	109-111	Brown	80	Acetone
6	$C_{23}H_{26}O_4N$	105-107	Brown	75	Acetone
7	$C_{23}H_{25}O_4N$	Oily	Brown	65	DMF
8	$C_{22}H_{23}O_5N$	Oily	Brown	60	DMF
9	$C_{22}H_{23}O_4N_2$	oily	Brown	70	DMF
10	$C_{23}H_{26}O_4N$	oily	Brown	72	DMF

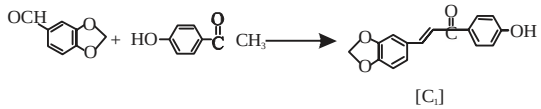
Synthesis of (E)-3-(benzo [d] [1, 3] dioxol-5-yl)-1-(4-bromoethoxy) phenyl) prop-2-en-1-one [C_2] (Ohkubo *et al.*, 2016): Sodium hydroxide (0.7 g) was dissolved in warm absolute ethanol (14 mL), the solution stirred for (1 h), [C_1] (1.7 g, 0.01 mol) dissolved in absolute ethanol (10 mL) then the first prepared solution is add to second solution drop wise, the mixture was stirred for (15 min), (0.05 mol) from dibromo ethan add to that mixtures which refluxed for (6 h), completion of the reaction confirmed by TLC, cooled, filter, dried and purified by recrystallization from absolute ethanol, mp (229-231°C), yield 85%, color brown in Table 1.

General synthesis of monomers [C_3-C_6] (Chen *et al.*, 2018): A 250 mL necks mixture of [C_2] with (30 mL) mixture of (acetone with DMF) (v:v/1:1) and [piperidine, morpholine, piperazine, 4-methyl piperidine) which add, the reaction refluxed for (4 h) confirmed by (TLC) the mixture cooled and purified by recrystallization from acetone, mp (219-221°C), yield 85% for [C_3], mp (115-117°C), yield 80% for [C_4], mp (109-111°C), yield 80% for [C_5], mp (105-107°C), yield 75% for [C_6], respectively in Table 1.

General synthesis of resins [C_7-C_{10}] (Victoria-Valenzuela *et al.*, 2018): The polymerization of these monomers was carried out in by using AIBN as initiator. A solution of the monomers (0.01 mol) in DMF (25 mL) and (5 g) of initiater were mixed in round bottle. The mixture was heated in oil bath (50-70°C). After (2 h) the contents in flask were poured into a large amount of (DMF) to precipitate the resins and evaporated under vacume, purity by TLC in Table 1.

RESULTS AND DISCUSSION

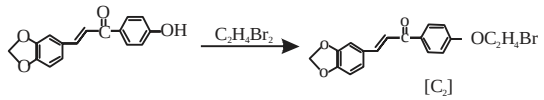
Considerable interest have been expressed in synthesis of chalcone compound in recent year due to their industrial and biological importance, starting from [C_1]



[C_1]

Scheme-1-Synthesis of chalcone [C_1]

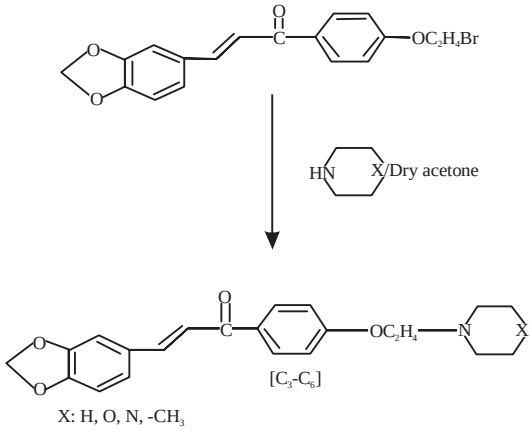
The FTIR spectrum Williams and Felming (1986) [C_1] showed the strong streaching (3454-3302 cm^{-1}) due to (OH) groups, (1693 cm^{-1}) for (C = O), (1260-1045 cm^{-1}) for (C-O-C), (830 cm^{-1}) for (1,4-disubst), (3072 cm^{-1}) for (Ar-H), (1420 cm^{-1}); for (C-N); ^{1}H-NMR (DMSO-d6) δ: (7.4-7.9 ppm) due to (Ar-H), (10.3 ppm) due to (H, OH), (2.4-3.4 ppm) for (H, CH_2), elemental analysis (CHN) for compound [1] were fitted according to Table 3. Therefore, [C_2] prepared by the condensation of the corresponding [C_1] with dibromo ethane in refluxing ethanol.



[C_2]

Scheme-2-Synthesis of [C_2]

The FTIR, Williams and Felming (1986) spectrum [C_2] showed the strong bands (2839 cm^{-1}) for (CH_2) combined with disappearance of stretching bands strong bands (3454-3302 cm^{-1}) for (OH), (1693 cm^{-1}) due to (C=O) and (740 cm^{-1}) absorption bands for (Br); ^{1}H-NMR (Williams and Felming, 1986) (DMSO-d6) δ: (7.5-8.48 ppm) for (Ar-H), (2.3-4.3 ppm) (H, CH_2). Elemental analysis for [C_2] were fitted according to the Table 3.



Scheme-3-Synthesis of [C_3-C_6]

Table 2: FTIR spectral data of [1-10]

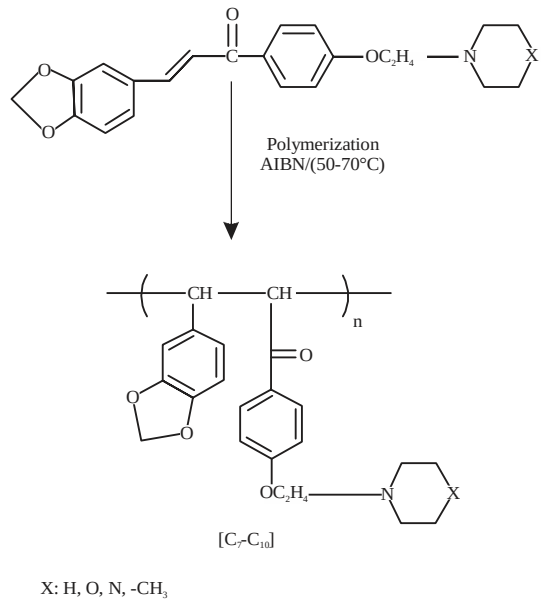
Comp No.	VCH_2	VC-O-C	VC=O	Others
1	2990-2855	1260-1045	1693	V (OH): 3454-3302, V (=C) (= =CH): 3072
2	2839	1200-1212	1635	V (Br): 740; VC=C (1597), V (=CH): 3028
3	2982-2854	1192-1100	1700	V (=CH) (3061)
4	2980-2975	1226-1168	1691	V (=CH) (3055)
5	2958-2834	1202	1689	V (=CH) (3065)
6	-	1221	1702	V (=CH)(3097)
7	2931-2873	1201-1205	1691	V (=CH) (3095)
8	2980-2870	1228-1222	1735	V (=CH) (3049)
9	2935-2870	1235-1228	1699	V (=CH) (3009)
10	2918-2850	1268-1238	1683	V (=CH) (3037)

Table 3: ^{1}H-NMR spectral data for some compound

Comp. No	H-NMR/ppm
1	Ar-H (δ = 7.4-7.9 ppm), (2.4-3.4 ppm) for (H,CH_2), (10.3 ppm) for (H,OH)
2	Ar-H(7.5-8.4 ppm), (2.3-4.3 ppm) for(H,CH_2)
6	Ar-H (δ: 7.03 ppm), (2.4-3.5 ppm) for (H,CH)
10	Ar-H (6.7-7.7 ppm), (2.07-3.37 ppm) for (H,CH_2)

FTIR, Williams and Felming (1986) spectrum [C_3] of stretching vibration is more bands at (2982-2854 cm^{-1}) for (CH_2) and strong vibration at (1226-1168 cm^{-1}) for (C-O-C), (3061 cm^{-1}) for (Ar-H), (1700 cm^{-1}) for (C=O), elemental analysis for [C_3] were fitted according to Table 2 and 3.

FTIR (Williams and Felming, 1986) spectrum [C_6] showed the bands of (3061 cm^{-1}) for (Ar-H) and (1702 cm^{-1}) for (C=O), H-NMR (DMSO-d_6) δ: (2.4-3.5 ppm) for (H-CH_2), (7.03 ppm) due to (Ar-H), elemental analysis for [C_6] were fitted according to Table 3. Therefor, [C_3-C_6] using as monomers which polymerization by AIBN initaitors in (50-70)°C due to [C_7-C_{10}] resins:



X: H, O, N, -CH_3

Scheme-4-Synthesis of [C_7-C_{10}]

Table 4: Depacited elemental analysis (CHN) for some compounds

	(CHN) analysis calculated (found)		
Comp No.	C (%)	H (%)	N (%)
1	76 (77.5)	4.76 (5.91)	-
2	57.6-59.0	4-5.5	-
3	39.70-40.5	5.59 (6.60)	21.05-22.5
8	69.29 (70.5)	6.04 (6.96)	3.67 (4 .45)
9	69.65 (70.55)	6.06 (7.11)	7.39 (8.8)
10	72.63 (73.88)	6.84 (7.91)	3.68 (4.77)

The FTIR spectrum [C_8] showed the bands (3049 cm^{-1}) for (Ar-H), (2980-2870 cm^{-1}) for (CH_2) and (1735 cm^{-1}) due to (C=O), FTIR spectrum for [C_8] obtained (3037 cm^{-1}) for (Ar-H), (1683 cm^{-1}) due to (C=O), H-NMR (DMSO-d_6) δ: (6.7-7.7 ppm) for (Ar-H), (2.07-3.37 ppm) for (H, CH), element analysis for [C_{10}] were fitted according to Table 3.

All these steps were summarized in Schemes (1-4) physical properties of all mentioned and other details [FTIR, elemental analysis, anticonvulsant activity (TGA &DSC) analysis, ^{1}H-NMR, all data are listed in Table 1-6, respectively, curing thermal stability of some compounds were evaluated by using (TGA&DSC) Table 4 are clearly show the temperature rate belong to different type dissociated for derivatives (Fig. 1-14).

Acute toxicity study: The tested compounds were administered intra peritoneally at different dose levels in separate groups of after (24 h) of the drug administration of the percent mortality in each group was observed, Approximate Lethal Dose (ALD_{50}) was calculated by karbers method (>300 $mgkg^{-1}$).

Anti convulsant activity: Animal were weighted and numbered then divided in two groups each consisting of (2-3) mices, one group were used as control and the other for sample compound treatment.

The comeal electrodes were placed on the comea of animal and the prescribed current were applied. The reading of different stages of convulsant. The sample compound were injected intra peritoneally to group (2-3) mices.

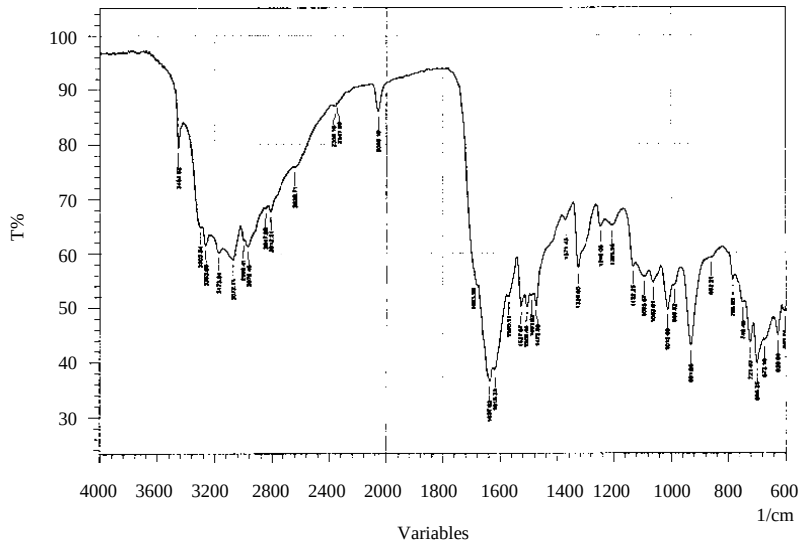


Fig. 1: FT-IR of [C_1]

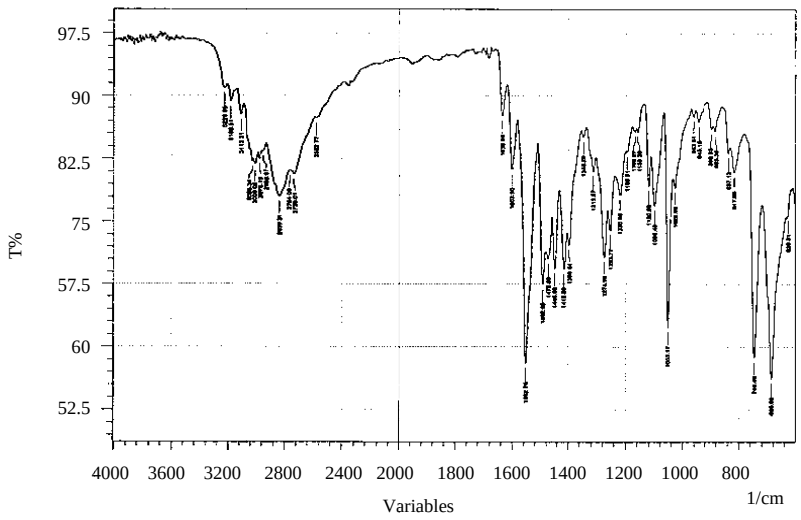


Fig. 2: FT-IR of [C_2]

Table 5: Thermal behavior data for synthesized resins [C_7-C_{10}]

Comp No.	On set point	T_g	Off set point	Char (%)
7	298.2	304.1	310.2	82
8	51.9, 106.7, 321.1	58.4, 112.8, 325.5	78.9, 123.9, 328.9	84
9	139.6	290.4	525.6	80
10	44.9, 269.7	47.7, 272.7	64.1, 295.0	80

On set temperature recorded by TGA, DSC; The midpoint temperature of the base line shift on the subsequent TGA and DSC trace (as heating rate 10°C/min) was defined asTg; Residual weight percentage at 600°C under nitrogen flow

Table 6: Extensor phase duration of systhesized title resins (sec)

Comp. No	Dose: mg/kg	Mean±SEM	Protection (%)
Control (DMSO)	-	8.700±0.07	-
Phenytion (STD)	24	1.600±0.05	85
C_7	28	2.015	75
C_8	29	1.900	87
C_9	30	2.980	77
C_{10}	30	1.600	85

The data were calculated and expressed as mean extensor phase duration in sec followed by % protection and % potency in comparison with the standard using the following formula:

$$\%protection = (MEPD_{nc} - MEPD_{sample} / MEPD) \times 100$$

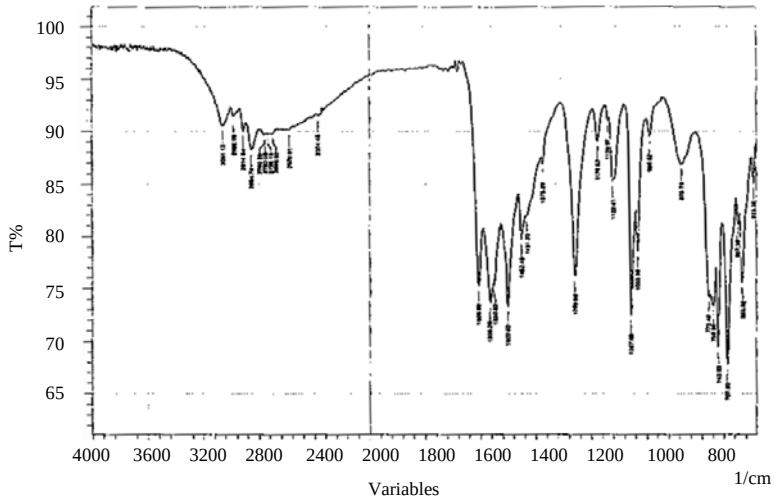


Fig. 3: FT-IR of [C_3]

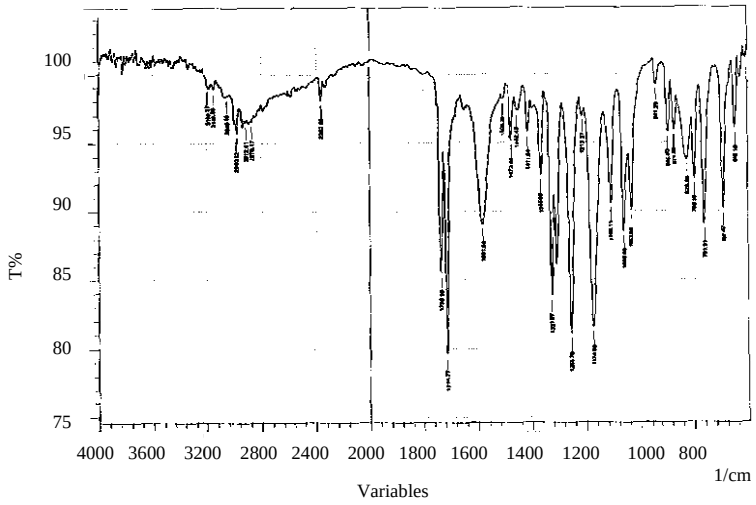


Fig. 4: FT-IR of [C_6]

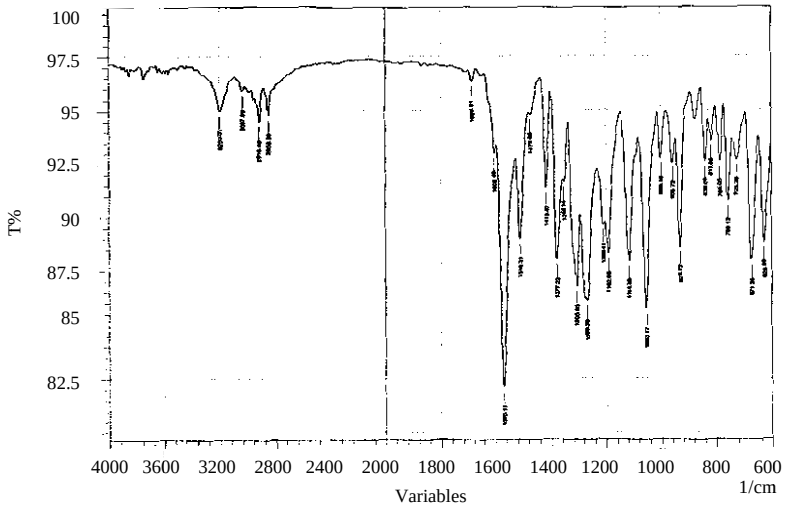


Fig. 5: FT-IR of [C_8]

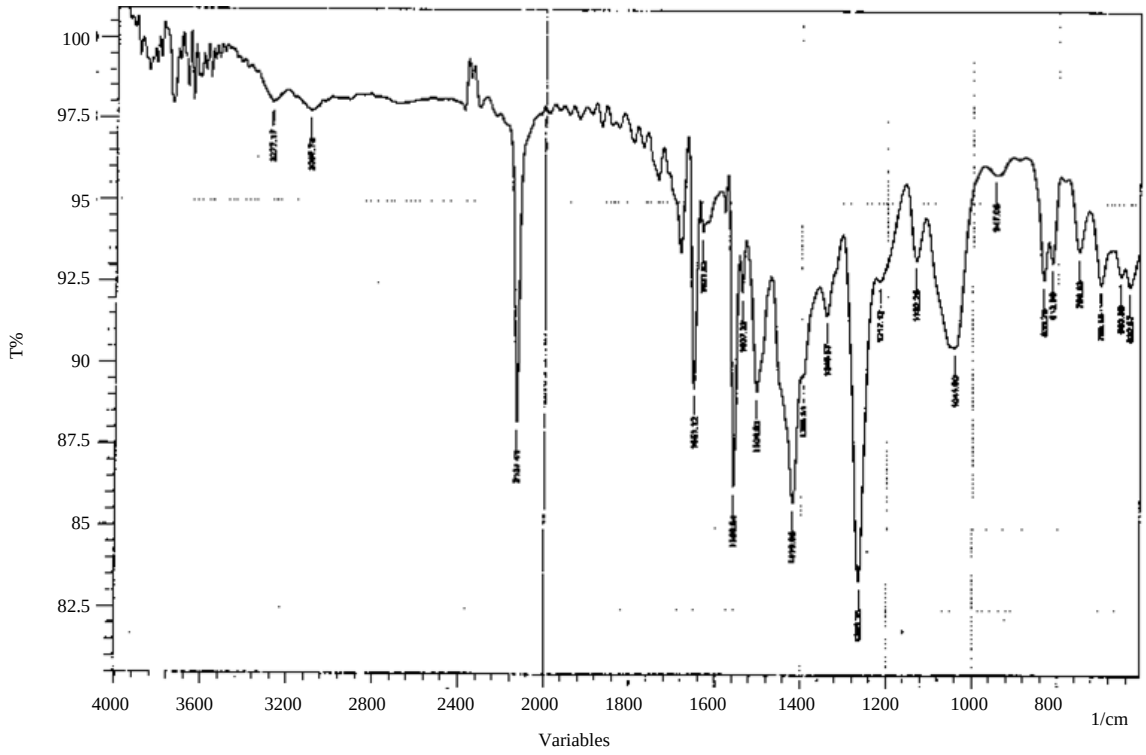


Fig. 6: FT-IR of [C_{10}]

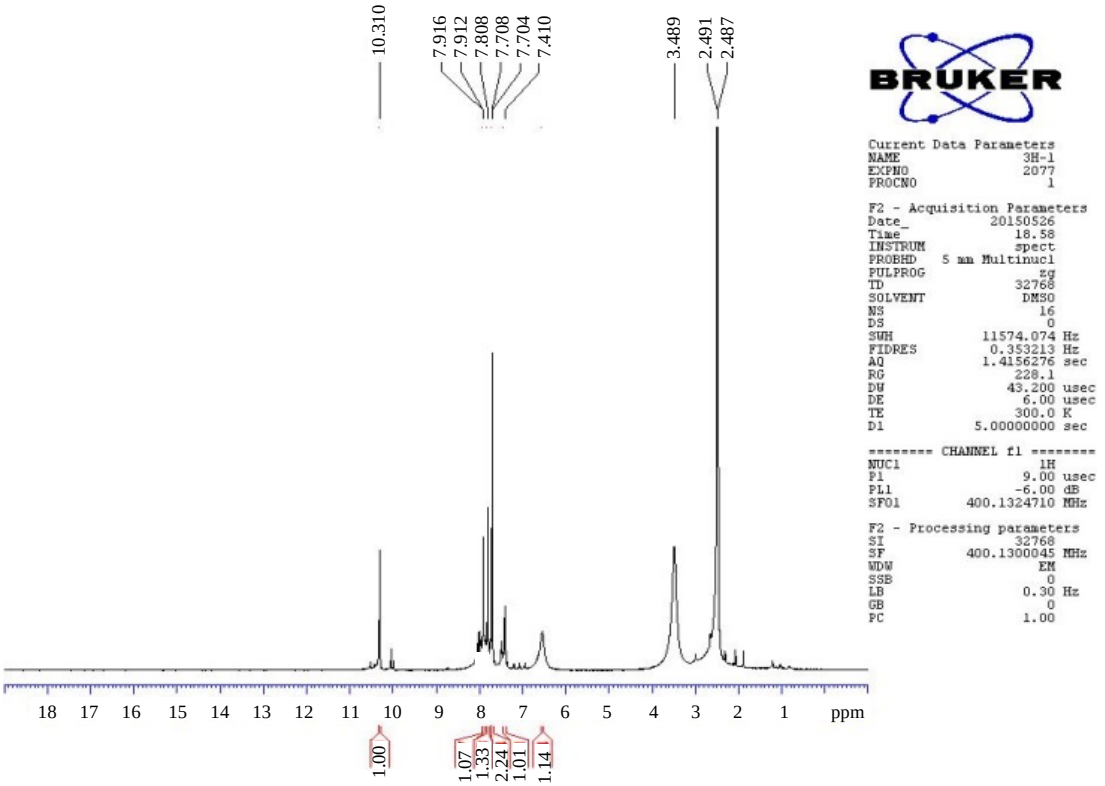


Fig. 7: H-NMR spectrum of [C_1]

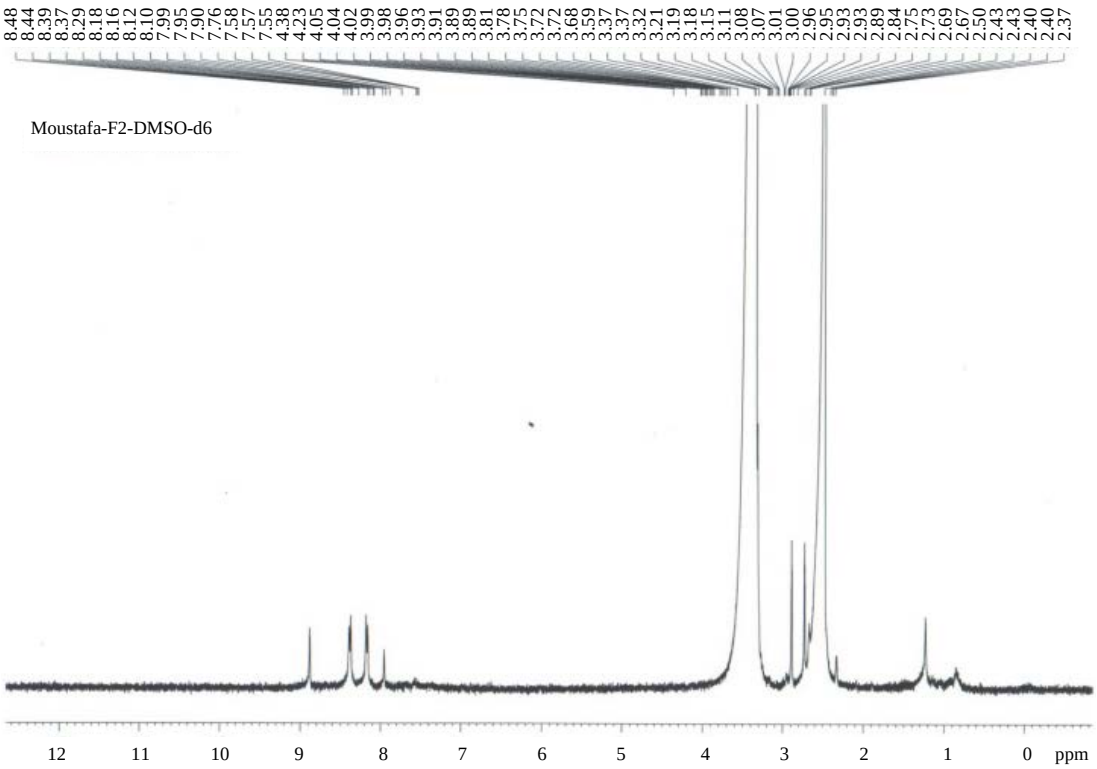


Fig. 8: H-NMR spectrum of [C_2]

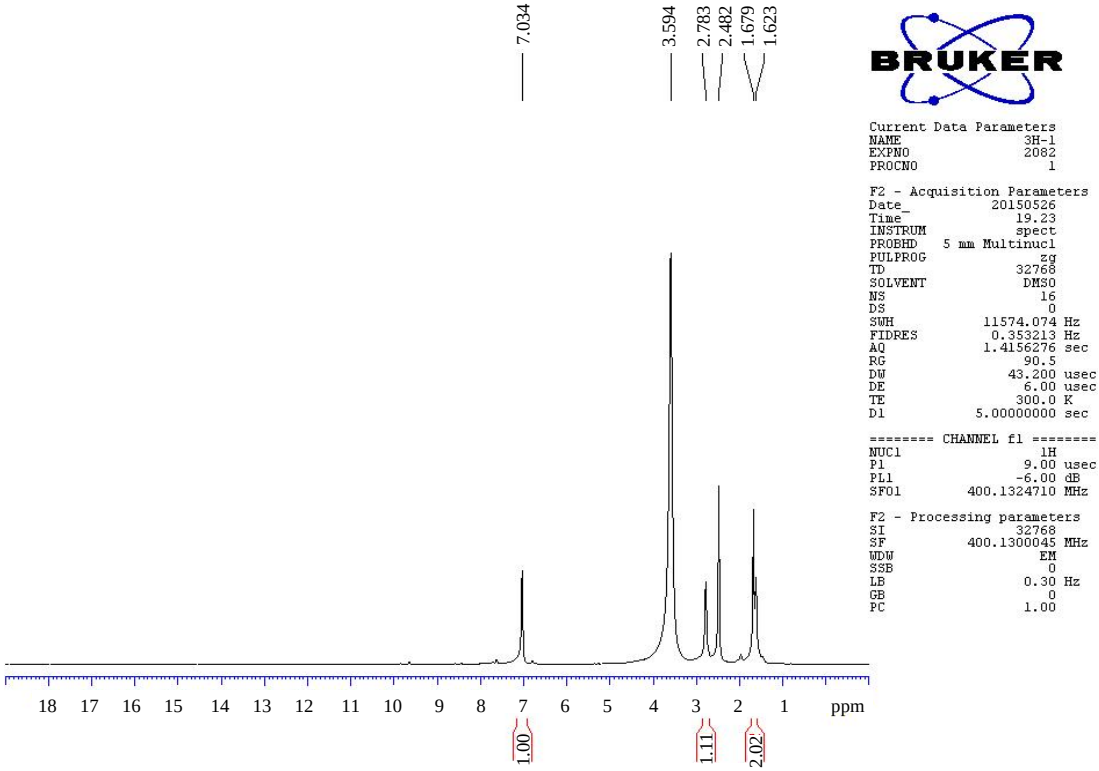


Fig. 9: H-NMR spectrum of [C_6]

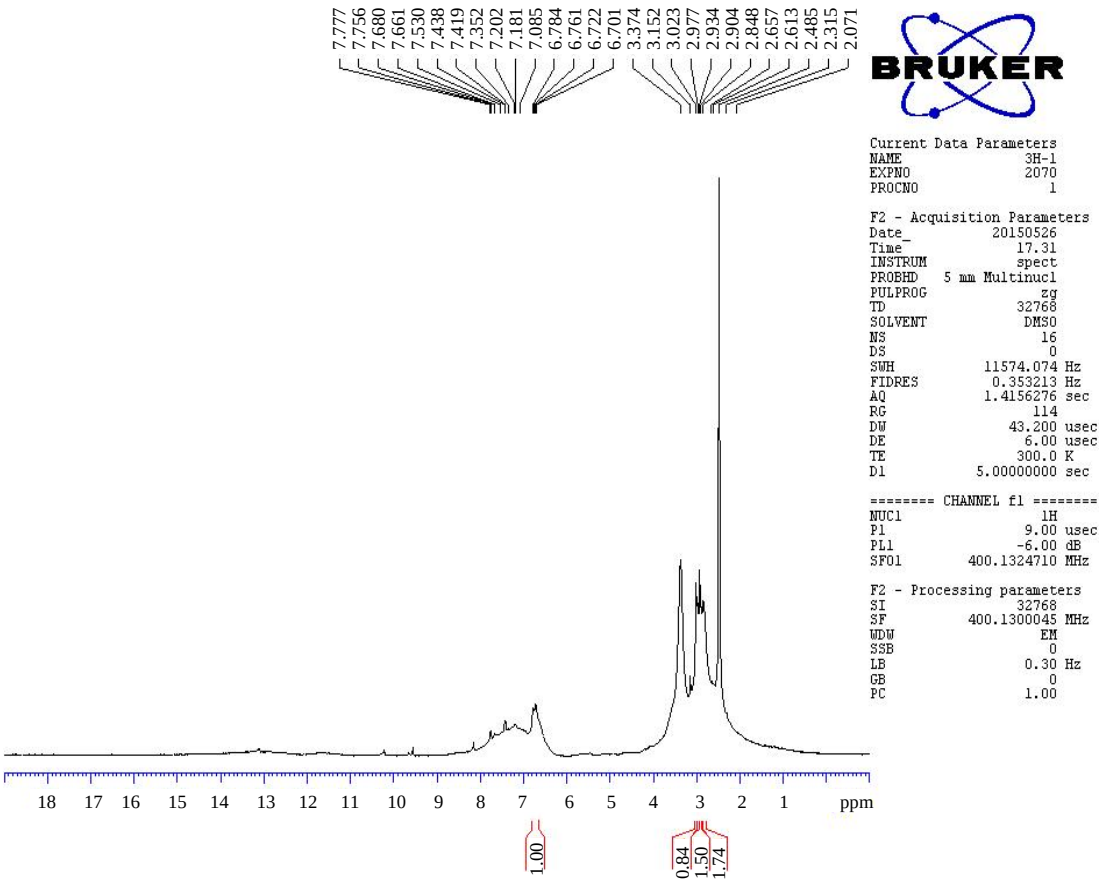


Fig. 10: H-NMR spectrum of [C_{10}]

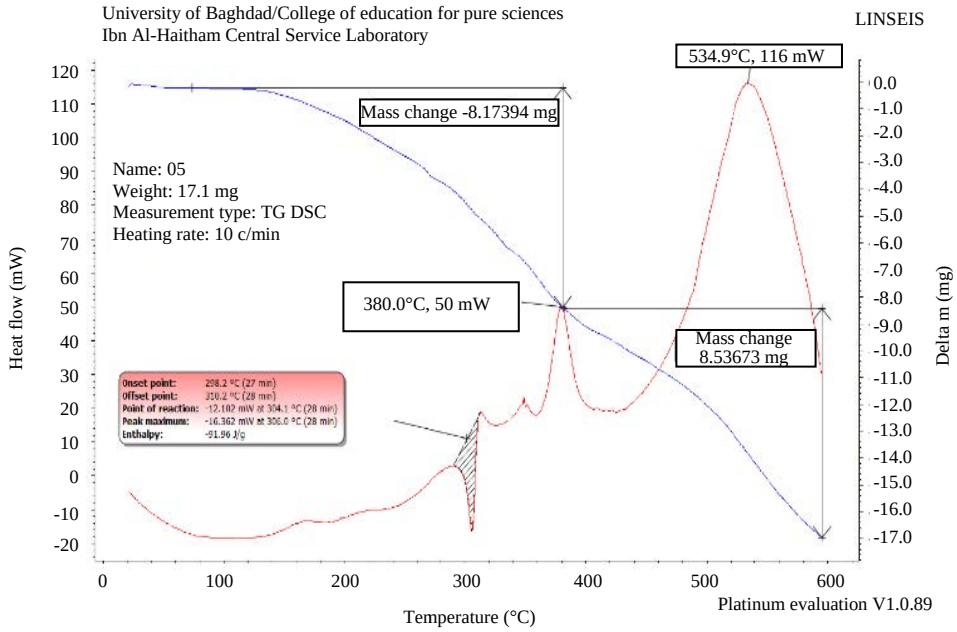


Fig. 11: TGA and DSC thermo gram of resin [C_7]

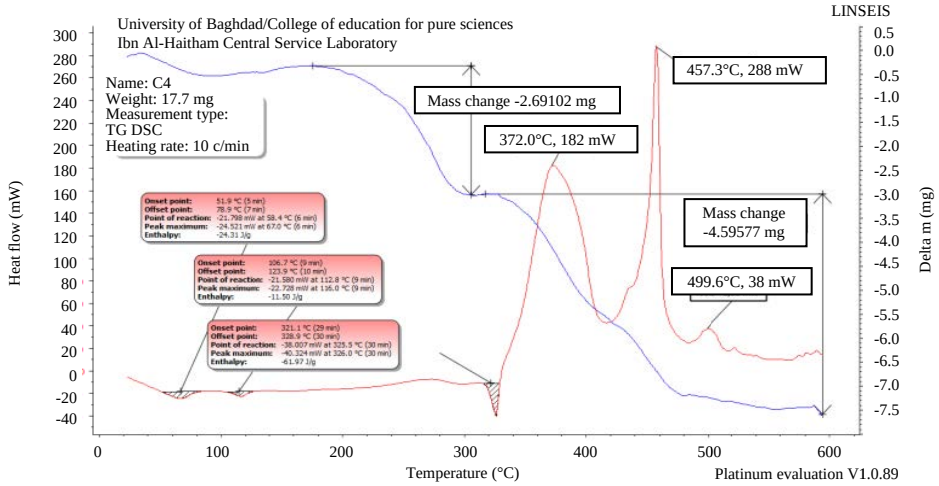


Fig. 12: TGA and DSC thermo gram of resin [C_8]

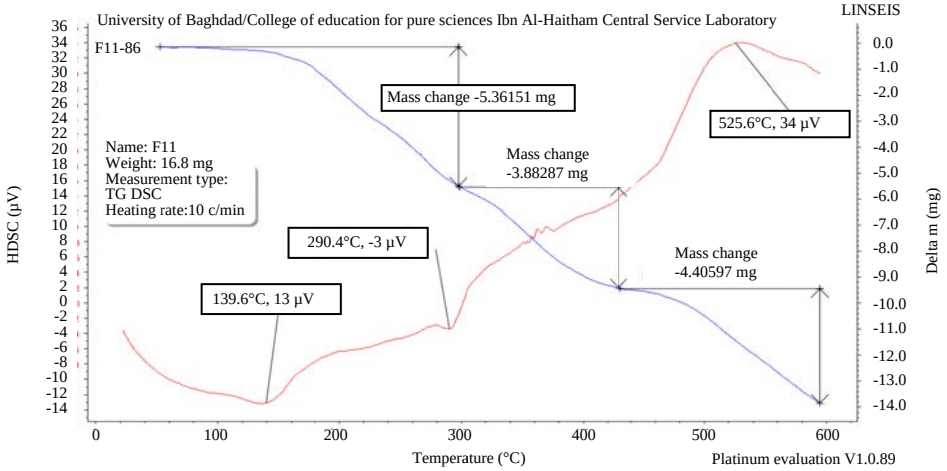


Fig. 13: TGA and DSC thermo gram of resin [C_9]

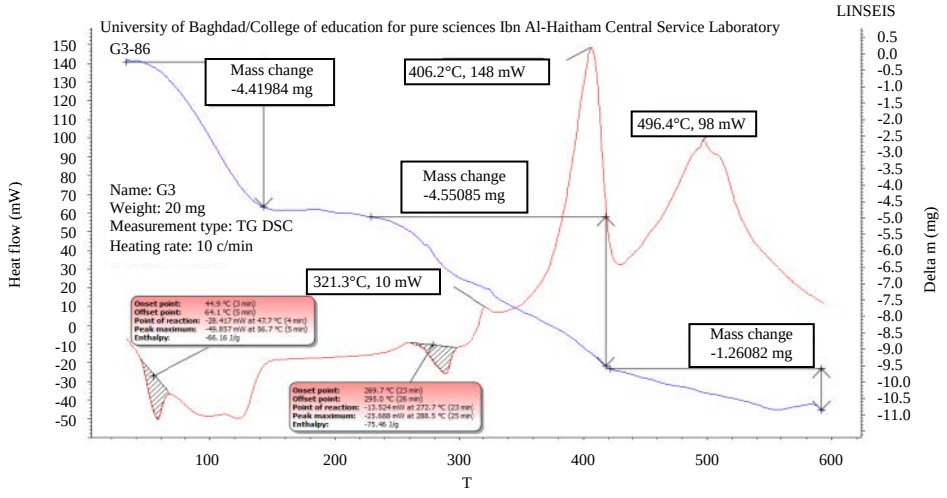


Fig. 14: TGA and DSC thermo gram of resin [C_{10}]

Where:

$MEPD_{nc}$: Meaning extensor phase duration of normal control in sec

MEPD : Extensor phase duration of sample or standard (sec)

The synthesis of title compounds were started with when subsitituted aldehyde was reacted with various ketones to yield chalcones derivatives via. Claisen schmidt reaction.

Compounds have shown significant protection as (75-87), respectively. Where as [C_8, C_{10}] have more protection which was even more against seizures as compound to be standard drug phenytion sodium used (80%).

CONCLUSION

Most of the synthesized chalcone derivatives were potential lead for anticonvulsant, antioxidant, anti biological activity, respectively on the basis of observed results, it may be concluded that the substitution favors the activity. The anticonvulsant potential of chalcone derivatives is known to be influenced to a great extent by two aryl structure, i.e.

Substituent on two aryl rings of chalcone molecular and their substitution pattern. Especially, the hydroxyle substitutent is one of the key group of enhance greatly the anticonvulsant activity of chalcone derivatives mainly due to its easy conversion of phenoxy radical through the hydrogen atom transfer mechanism.

In fact the substituent are wide spread among chalcone from synthetic source there by a number of structurally diverse chalcone including phenolic have been prepared and evaluated for anti convulsant activity.

REFERENCES

Asiri, A.M. and S.A. Khan, 2012. Synthesis, characterization and *In vitro* antibacterial activities of macromolecules derived from Bis Chalcone. J. Heterocycl. Chem., 49: 1434-1438.

Beyhan, N., B. Kocyigit-Kaymakcioglu, S. Gumru and F. Aricioglu, 2017. Synthesis and anticonvulsant activity of some 2-pyrazolines derived from chalcones. Arabian J. Chem., 10: S2073-S2081.

Chen, W., L. Ma, A. Paul and D. Seidel, 2018. Direct α-C-H bond functionalization of unprotected cyclic amines. Nat. Chem., 10: 165-169.

El-Messery, S.M., E.S.E. Habib, S.T. Al-Rashood and G.S. Hassan, 2018. Synthesis, antimicrobial, anti-biofilm evaluation and molecular modelling study of new chalcone linked amines derivatives. J. Enzyme Inhib. Med. Chem., 33: 818-832.

Lahsasni, S.A., F.H. Al Korbi and N.A.A. Aljaber, 2014. Synthesis, characterization and evaluation of antioxidant activities of some novel chalcones analogues. Chem. Centr. J., 8: 1-10.

Mohammed, E.Y., 2015. Synthesis and characterization of new heterocyclic monomers and polymers vitality with studing biological activity. PhD Thesis, University of Badhdad, Badhdad, Iraq.

Muralidharan, V., A.C. Deepti and S. Raja, 2018. A review anti-inflammatory potential of substituted pyrazoline derivative synthesized from chalcones. Intl. J. Pharm. Pharm. Sci., 10: 9-14.

Ohkubo, K., K. Hirose and S. Fukuzumi, 2016. Solvent free photooxidation of alkanes by dioxygen with 2,3 dichloro 5, 6 dicyano p benzoquinone via photoinduced electron transfer. Chem. Asian J., 11: 2255-2259.

Pasquale, G., G.P. Romanelli, J.C. Autino, J. Garcia and E.V. Ortiz *et al*., 2012. Quantitative structure-activity relationships of mosquito larvicidal chalcone derivatives. J. Agric. Food Chem., 60: 692-697.

Victoria Valenzuela, D., J. Herrera Ordonez, C.L.A. Ricardo and M. Estevez, 2018. Autoacceleration in bulk free radical polymerization: Effect of Chain transfer. Macromol. Chem. Phys., Vol. 219, 10.1002/macp.201700434

Williams, D.H. and Felming, 1986. Spectroscopic Methods in Organic Chemistry. 1st Edn., University of Baghdad, Baghdad, Iraq,.

Yadav, N., S.K. Dixit, A. Bhattacharya, L.C. Mishra and M. Sharma *et al*., 2012. Antimalarial activity of newly synthesized chalcone derivatives *In vitro*. Chem. Bio. Drug Des., 80: 340-347.

Zhuang, C., W. Zhang, C. Sheng, W. Zhang and C. Xing *et al*., 2017. Chalcone: A privileged structure in medicinal chemistry. Chem. Rev., 117: 7762-7810.