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Address:
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Box(190)

www.Edu_girl.Kuiraq.com

E-mail:Edu_grils@kuiraq.com

Ethyl Aceto Acetate as starting material for preparation pyrazol ring Derivatives

Ahmed Ali younis Alhasan[1] Radhiyah Abdul Baqi Aldujaili[2]

Department of Chemistry, College of Education for Girls / Kufa university, Iraq.

ahmed76aliyonis@gmail.com , radhiyah.aldujaili@uokufa.edu.iq

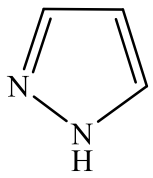
ABSTRACT :

The current study includes organic synthesis of some new pyrazol derivatives from 2-amino thiazole by prepare diazonium salt from it with Ethyl Aceto Acetate as coupling compound to form Azo compound (B). From this azo compound, pyrazol Derivatives are prepared by closing the Aceto and Aster groups via hydrazine and phenyl hydrazine under Microwave irradiation respectively . The other step is the preparation of Chalcone derivative(CH) from Azo compound (B) with p-N,N-di methyl amino banzaldehyde. also pyrazol Derivative was prepared by reaction the Chalcone derivative with hydrazine hydrate in acidic and basic medium . These compounds are identified and confirmed by FT- IR, ^{1}HNMR, ^{13}CNMR.

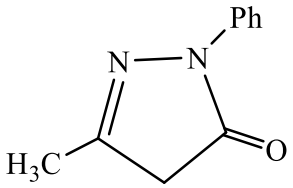
Key words :Thiazole , Pyrazole , Microwave irradiation, Ethyl aceto acetate.

INTRODUCTION

Pyrazole derivatives are the subject of many researches due to their widespread potential biological activities such as analgesic [1,2], antidiabetic [3], anticonvulsant [4], antimicrobial [5], anti-inflammatory [6], antiviral [7], and anticancer activities [8]. 1,5-Diarylpyrazole derivatives have been reported as non nucleoside HIV-1 reverse transcriptase inhibitory activity [9,10]**.** The pyrazole system (1) consists of a doubly unsaturated five membered ring with two adjacent nitrogen atoms. first synthesized compounds containing this system by Knorr [11] in 1883 via the reaction of ethyl acetoacetate with phenyl hydrazine, which yielded 1-phenyl-3- methyl-5-pyrazolone (2). Knorr introduced the name pyrazole for these compounds to denote that the nucleus was derived from pyrrole by the replacement of a carbon by nitrogen. They synthesized many members of this class and systematically investigated their properties. Also the Pyrazole ring can be found in many industrial fields[12]**.** Pyrazoles are one of the most studied groups of compounds among the azole family[13] **.**



(1)



(2)

Materials and Methods:

Chemistry

All chemicals were of the highest purity, supplied by Fluka and Merck -company. Measurements of the melting points were recorded by using electro- thermal 9300," melting point engineering LTD , U.K". Thin Layer Chromatography (T.L.C) was performed on silica gel, and spots were visualized by Iodine vapors." FT-IR" spectra, Fourier transform infrared shimadzu (8400)using potassium bromide (KBr pellets) (where by the values are expressed in cm^{-1}), ^{1}H-NMR & ^{13}C-NMR-spectra in (ppm) unit were operating in *DMSO -d6* as solvent using (**Agilent Varian 500 MHz**)-Tehran university /Iran.

Synthesis of Azo Compound (B) ethyl 3-oxo-2-(thiazol-2-yldiazenyl)butanoate [14]:

2-amino Thiazole (0.01 mole , 1g)was dissolved in (4 ml) of concentrated hydrochloric acid and (15 ml) of distilled water. The mixture was cooled at (0-5) ^{0}C in ice-water bath. Then a solution of sodium nitrite (0.01 mole, 0.69 g) was dissolved in (10 ml) of distilled water then it was cooled at(0-5 ^{0}C). This solution was added drop-wise to the mixture with stirring at the same temperature. The diazonum salt solution was added portion-wise to a solution of (0.01 mol, 1.3g) Ethyl Aceto Acetate in Ethanol with 5ml sodium hydroxide (10%) . The basicity was neutralized by adding drops of (HCl) until the pH became (7)and temperature was maintained at (0-5) ^{0}C .The mixture was stirred for 30 minutes and left overnight. The product was precipitated, filtered, washed well with distilled water and re-crystallized from absolute ethanol.

General procedure for Synthesis of Pyrazole derivatives[15] :

(B1): **5-methyl-2-phenyl-4-(thiazol-2-yldiazenyl)-2,4-dihydro-3H-pyrazol-3-one**

(B2) 5-methyl-4-(thiazol-2-yldiazenyl)-2,4-dihydro-3H-pyrazol-3-one

A mixture of Azo comp.(B) (0.01 mol, 2. 41 gm) with (0.02 mol, 2. 2gm) from Phenyl hydrazine , (0.02 mol, 1gm)from hydrazine hydrate respectively in absolute Ethanol 3 ml were added in ceramic crucible. The contents were subjected to microwave irradiation at 120 W about 3 min. for (B1) , 2 min. for (B2). Progress of the reaction was monitored by TLC. After the completion of the reaction, solid product was obtained in reaction mixture which re crystallized with absolute Ethanol. re crystallization provides the title compounds as solid crystals.

Synthesis of Chalcone derivative (Ch)[16]:

The Azo compound B (0.01 mol, 2.41 gm) with(1.5gm,0.01 mol)p-N,N-Di methyl benzaldehyde were dissolved in absolute Ethanol (30 ml). Sodium hydroxide solution 10% (5 ml) was added gradually and the mixture was stirred for(10) hrs. at room temperature. The reaction was monitored by Thin Layer Chromatography. The solvent was evaporated and the yield was re-crystallized from absolute Ethanol.

Synthesis of Pyrazole derivatives (Cha) in acidic medium and (Chb) in base medium from Chalcone derivative (Ch)[17]:

(Cha)2-(5-(4-(dimethylamino)phenyl)-4,5-dihydro-1H-pyrazol-3-yl)-2-(thiazol-2-yldiazenyl)acetohydrazide.

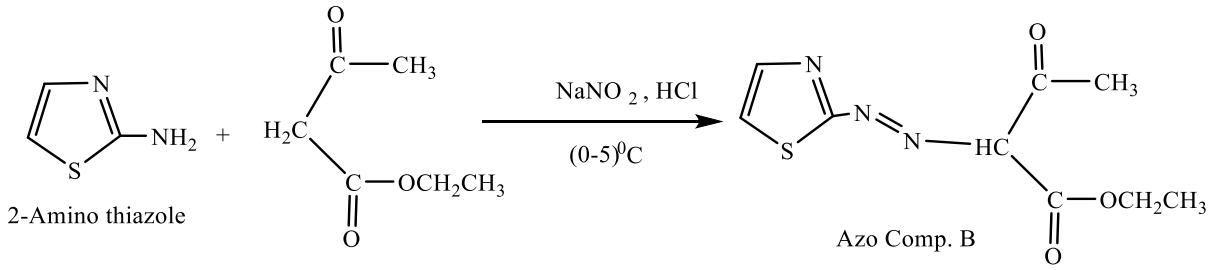
To the Chalcone derivative (Ch) (0.001 mole,0.37gm)in absolute ethanol (25ml) added glacial acetic acid(2 ml) and hydrazine hydrate 99% (0.002mole,0.1gm). Refluxed with stirring at 80 C^0 for 11 hrs . The reaction was monitored by T.L.C and The solvent was evaporated and the precipitation was re-crystallized from absolute EtOH to give comp.(Cha).

(Chb) 2-(5-(4-(dimethylamino)phenyl)-4,5-dihydro-1H-pyrazol-3-yl)-2-(thiazol-2-yldiazenyl)acetohydrazide [18].

A mixture of chalcone derivative(Ch) (0.001mole,0.37gm), hydrazine hydrate (0.002mmole,0.1gm) and alcoholic sodium hydroxide 4% (1mL) in ethanol (15mL) was refluxed with stirring for appropriate time until about 11 hrs . completion the reaction which was monitored by T.L.C and The solvent was evaporated and the precipitation was re-crystallized from absolute EtOH to give comp.(Chb).

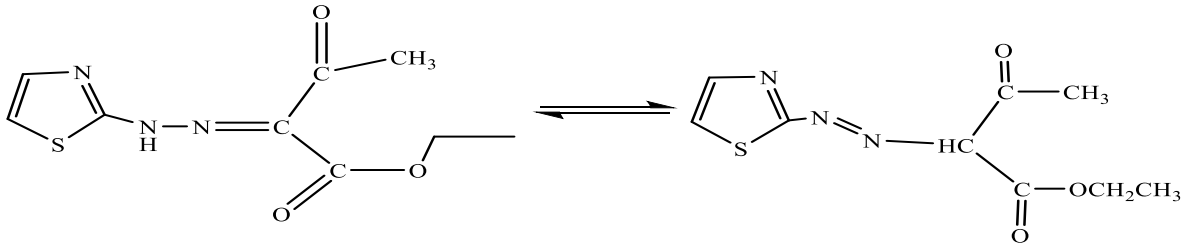
RESULTS AND DICUSSION:

The study includes preparation of Azo compound B by diazotization reaction between 2-Amino Thiazole and Ethyl Aceto Acetate as in Equation 1.



Equation 1

By FT-IR Spectrum Figure (1) can characterized the Azo comp. through the appearance of Absorption band at 3415 Cm $^{-1}$ that which due to NH group this is as a result of the Tautomerism between Azo group (N=N) and (-CH-) [19].



Structure (3) Tautomerism in Azo Comp.B

The absorption band at (2924-2856) Cm $^{-1}$back to Aliphatic (C-H) .The Carbonyl of Ester was interference with Keto Carbonyl that which appeared at 1683 Cm $^{-1}$,The band at 1633 Cm $^{-1}$ due to (C=N)endocyclic in Thiazole ring And it interfered with it(C=N) Exocyclic. Aromatic (C=C) was appeared weak at 1541 Cm $^{-1}$, the band of Azo group is showed at (1458-1431) Cm $^{-1}$, C-O band in (-OEt)is appeared at 1056 Cm $^{-1}$,Finally ,the band at 873 Cm $^{-1}$due to (C-S) in Thiazole ring.

In addition to FT-IR Spectrum, the compound B also identified by ^{1}H-NMR Spectrum Figure (2) through appearance the signals (ppm),(s,H,NH) from the Tautomerism at(10.66), (s,3H,O=C-CH_3) at (2.35),(t,3H, CH_3)acetate at(1.29),(t,2H,OOC-CH_2) acetate at (3.75),(1H, OOC-CH-N=N) at (6.55),(m, 4H, Thiazole rings) [20] Structures of Tautomerismat (7.1-8.1),The signal at 3.27 due to the water in the solvent DMSO(Di methyl sulfoxide) And that the signal appeared at(2.5).By ^{13}C-NMR spectrum Figure (3) ,the Azo comp. identified through the appearance of the following signals in (ppm),C(C=O)Keto group at 208.9, C(O=C-O)Ester at 171.3, C(CH-N=N) at 72.7, C(CH_3)ester group at 14.2, C(CH_2-O-C=O)at 62.2, C(CH_3)Keto group at 25, C(S-C-N)Thiazole ring at 163.6, C (Thiazole ring)at 112.5-142.7.

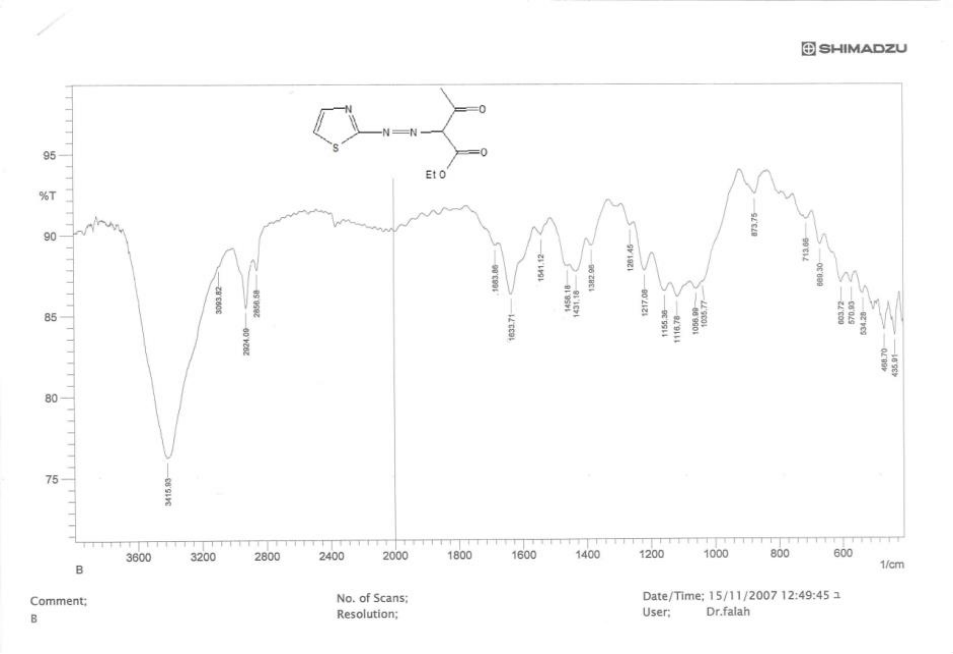


Figure (1)FT-IR Spectrum for Azo comp. B

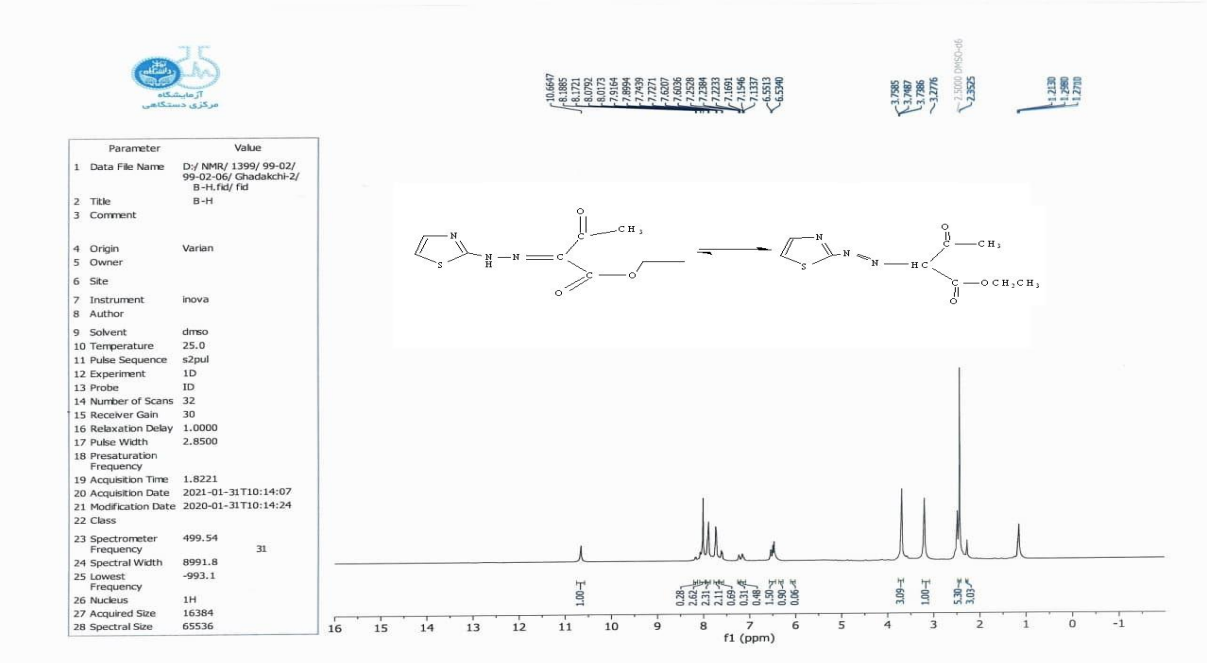


Figure (2)1H-NMR spectrum for Azo comp. B

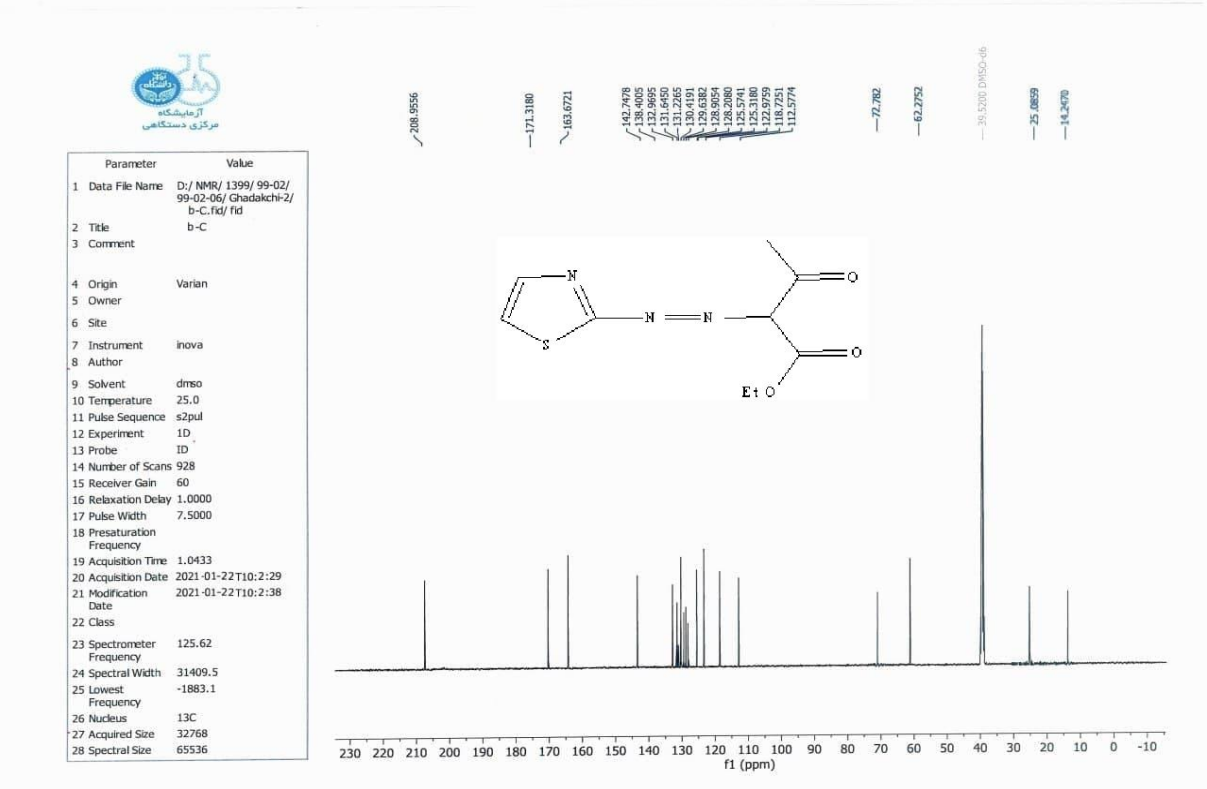
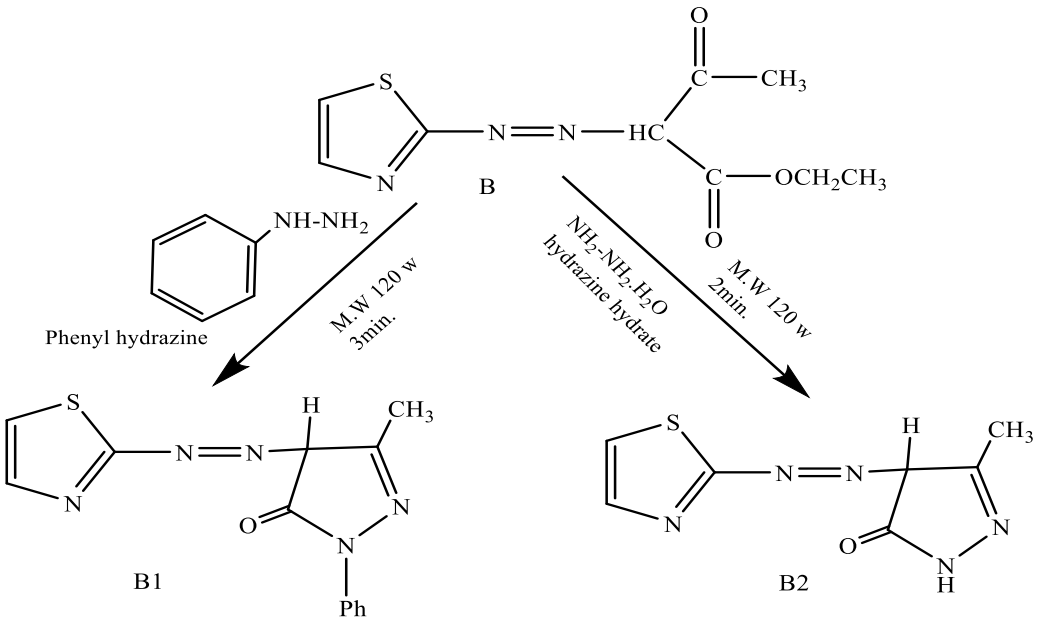
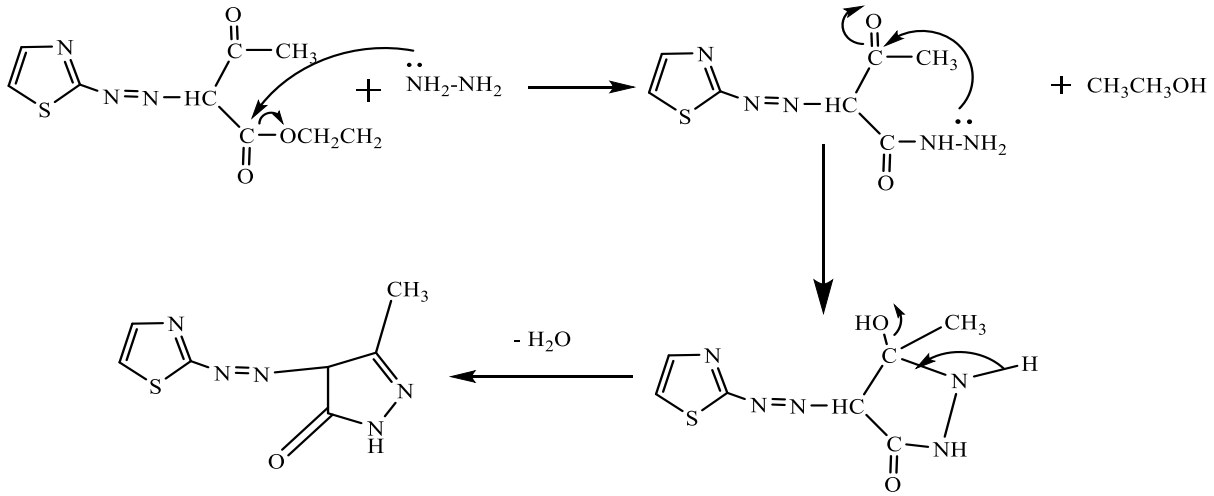


Figure (3)13C-NMR spectrum for Azo comp. B

From Azo comp. B was prepared the pyrazole-3-one rings by reaction it with hydrazine and phenyl hydrazine respectively via Microwave irradiation, Scheme(1).



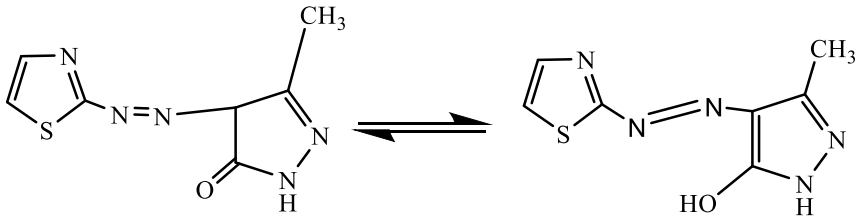
Scheme(1) preparation of pyrazole-3-one rings



Scheme(2) The proposed mechanism for preparation of pyrazole-5-one ring [21]

The derivatives B1, B2 were identified through FT-IR Spectra Figures (4),(5) by The absorption bands for The Carbonyl of pyrazole ring appeared clearly at (1685 ,1660)Cm $^{-1}$,The bands at 1629 Cm $^{-1}$ sharp in B1 and weak in B2 due to (C=N)endocyclic in Thiazole

ring And it interfered with it(C=N) Exo cyclic. Aromatic (C=C) were appeared sharp clearly in B1 at 1558 Cm $^{-1}$ and weak in B2 at 1514 Cm $^{-1}$, the weak bands of Azo group is showed at (1485-1433) ,(1458-1433)Cm $^{-1}$, the bands at (835, 958) Cm $^{-1}$due to (C-S) in Thiazole ring in each derivative. The bands of NH resulting from the Tautomerism in B1 and B2 appeared at (3176, 3197) Cm $^{-1}$ respectively and the band at 3325 Cm $^{-1}$ in the derivative B2 due to vibration of NH Pyrazole ring. Other Tautomerism was occurred between (-C=O)in Pyrazole ring with (CH-N=N-)in the same ring and characterized by appear the bands of hydroxyl(OH) groups in the derivatives (B1,B2) at (3414,3425) Cm $^{-1}$ respectively.



Structure (4) Tautomerism in B1, B2

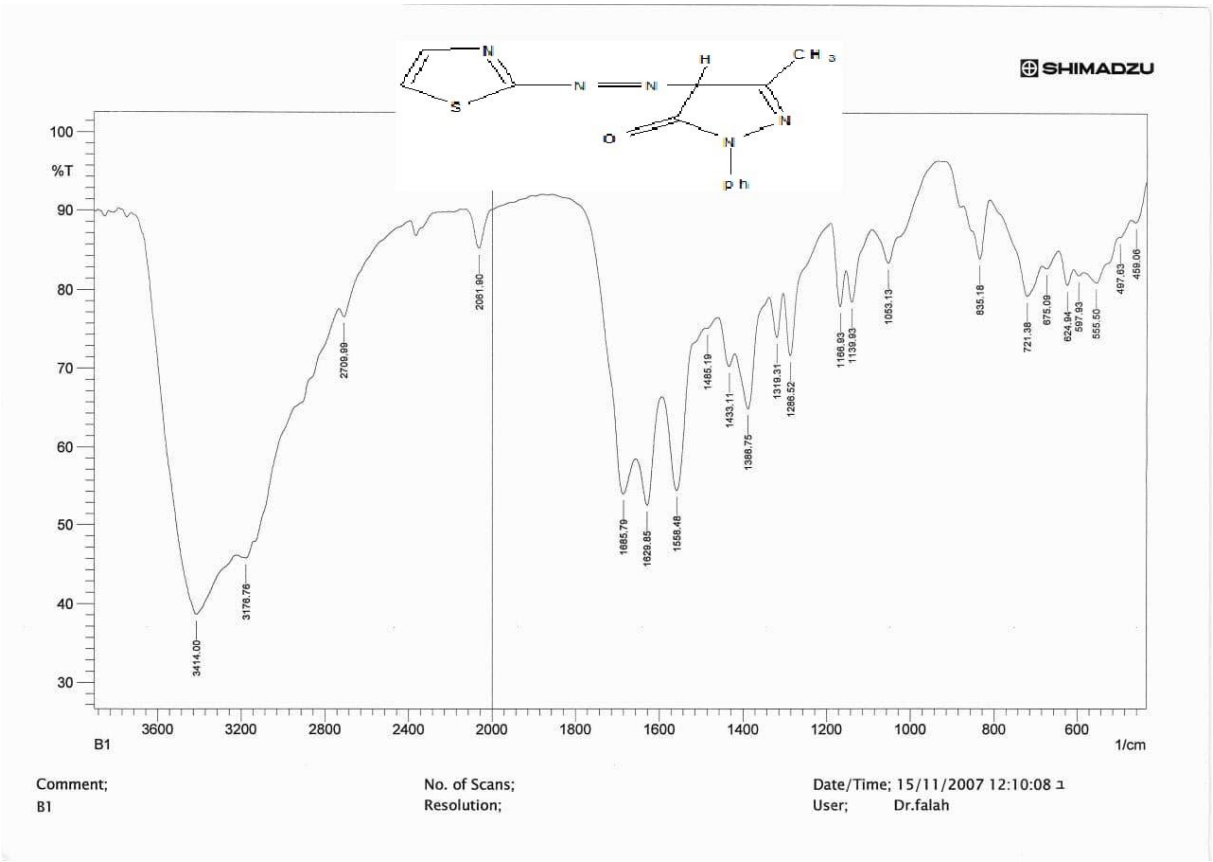


Figure (4)FT-IR Spectrum for B1

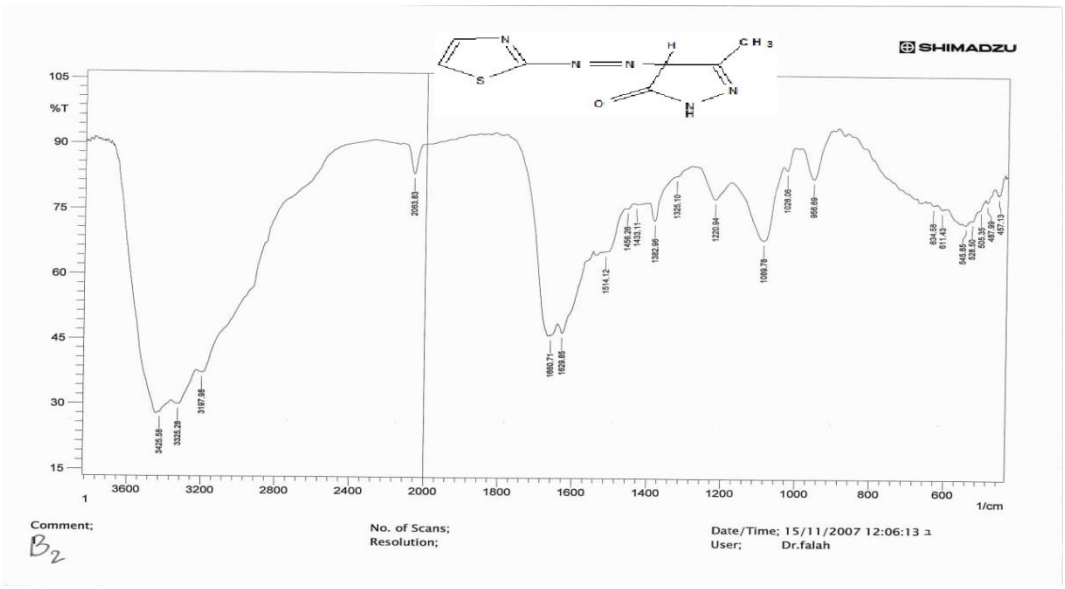
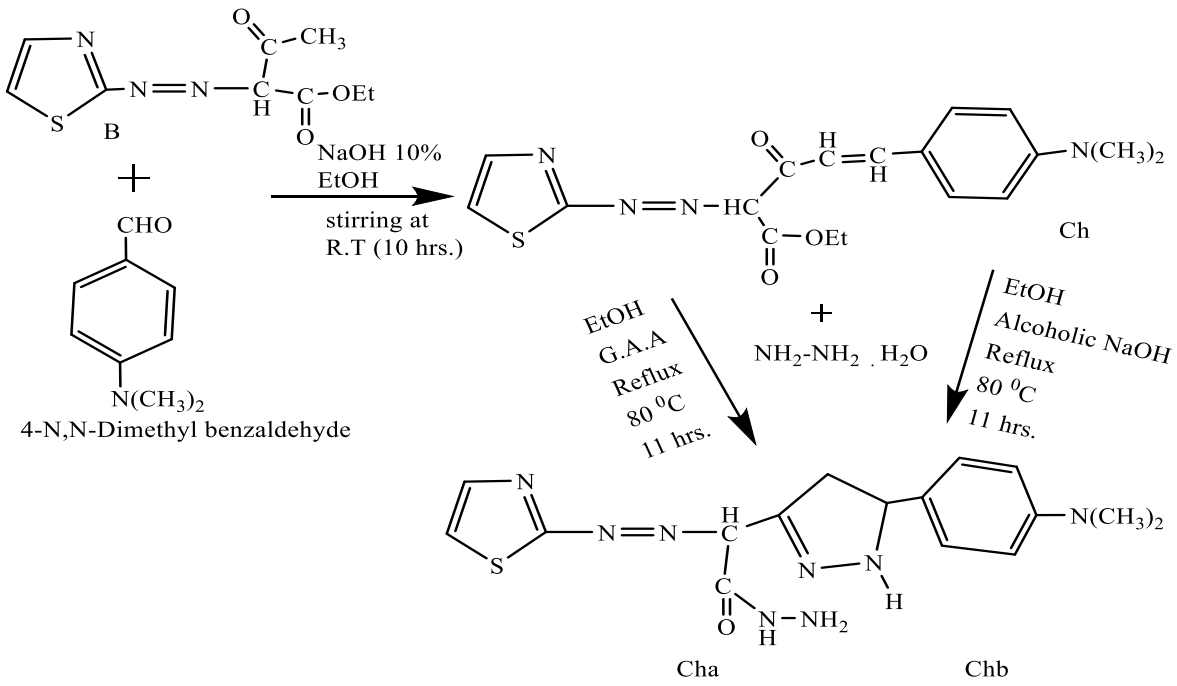
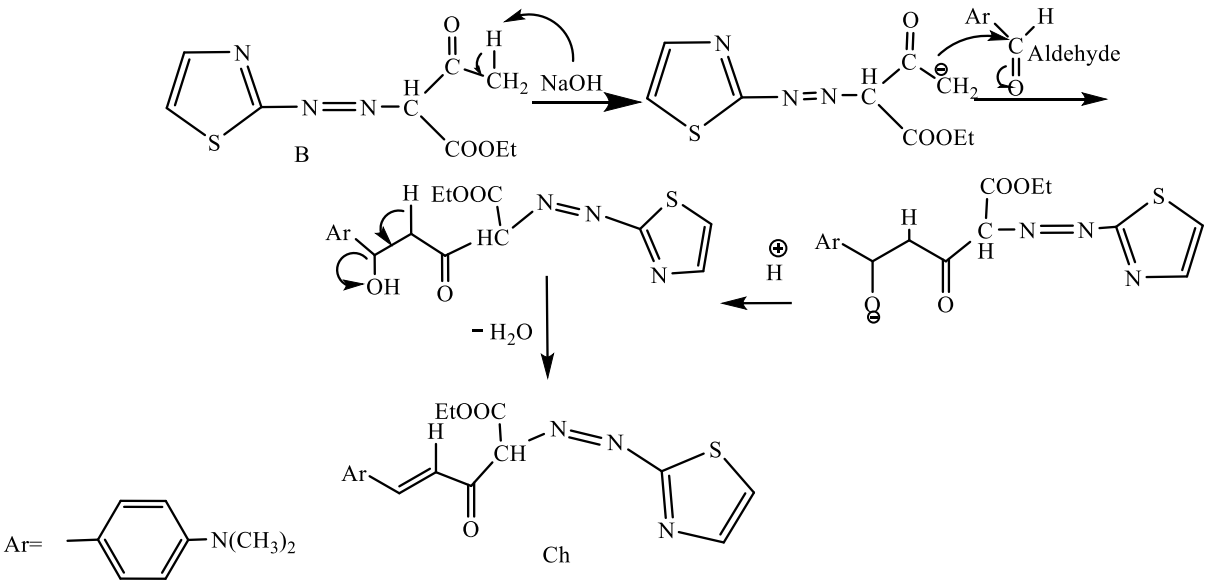


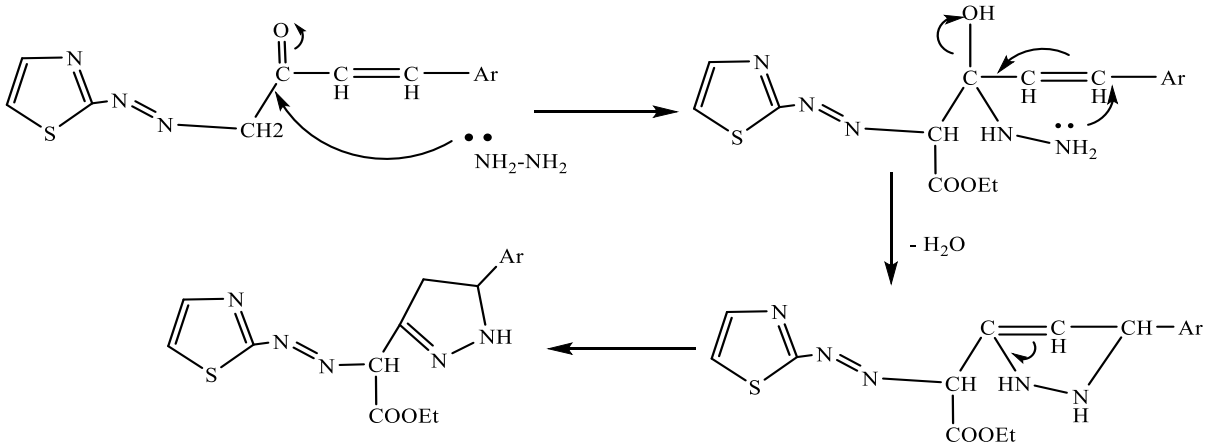
Figure (5)FT-IR Spectrum for B2



Scheme(3) preparation of Chalcon and its derivatives



Scheme(4) The proposed Mechanism for preparation of Chalcon



Scheme(5) The proposed Mechanism for preparation of Pyrazole derivatives

The Chalcon derivative(Ch) in FT-IR, Figure(6),was identified through the appearance of stretching band of (NH) resulting from the Tautomerism at (3435) cm^{-1}, (C-H) Aliphatic at (2924-2854) cm^{-1}, (C-H) Aromatic at (3088-3045) cm^{-1} , Carbonyl group(-C=O) ester at (1716) cm^{-1} , Carbonyl group(-C=O) of Chalcon group at (1668) cm^{-1}, (C=N) endo cyclic ring Thiazole at (1598) cm^{-1}, (C=C)Alkene (1573) cm^{-1}, and (C=C)Aromatic at(1558-1543)cm^{-1} in addition to the stretching band (C-S) at (835) cm^{-1}.The Azo group (N=N) at (1523-1473) cm^{-1}.

The derivatives Cha, Chb are the same structure but prepared in different conditions ,the first one was prepared in acidic catalyst that which glacial acetic acid but the other was prepared in basic catalyst that which Ethanolic sodium hydroxide. The Pyrazole derivatives (Cha, Chb) in FT-IR, Figures(7,8),was identified through the appearance of stretching bands of all (NH) groups and Primary aliphatic amine (NH_2) at (3417-3448),(3448) cm^{-1}, (C-H) Aliphatic at (2964-2944) ,(2918-2862)cm^{-1} respectively, , Carbonyl group(-C=O) amide is it Shoulder and interfered with (C=N) endo cyclic at (1598),(1604) cm^{-1} , and (C=C)Aromatic in(Chb) at(1566)cm^{-1} in addition to the stretching bands (C-S) appeared weak in Cha at (810) $cm^{-1}$and

sharp in (Chb)at(813) cm^{-1} .The Azo groups (N=N) in Cha and Chb at (1417) , (1479-1413) cm^{-1} respectively .

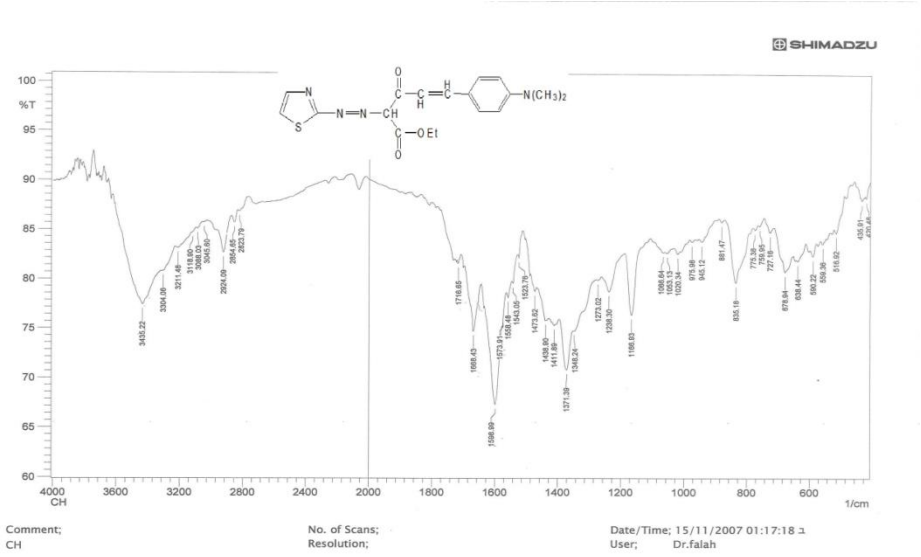


Figure (6)FT-IR Spectrum for Ch derivative

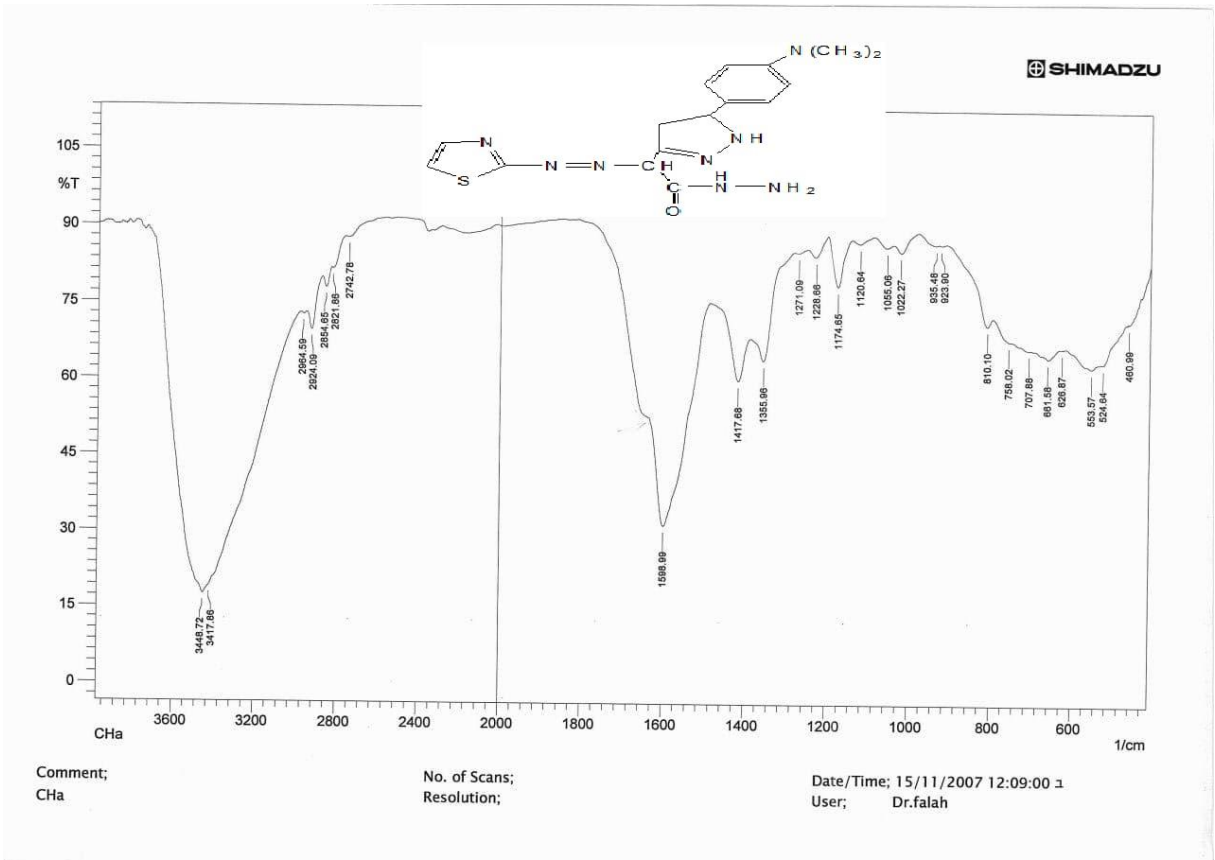


Figure (7)FT-IR Spectrum for the derivative Cha

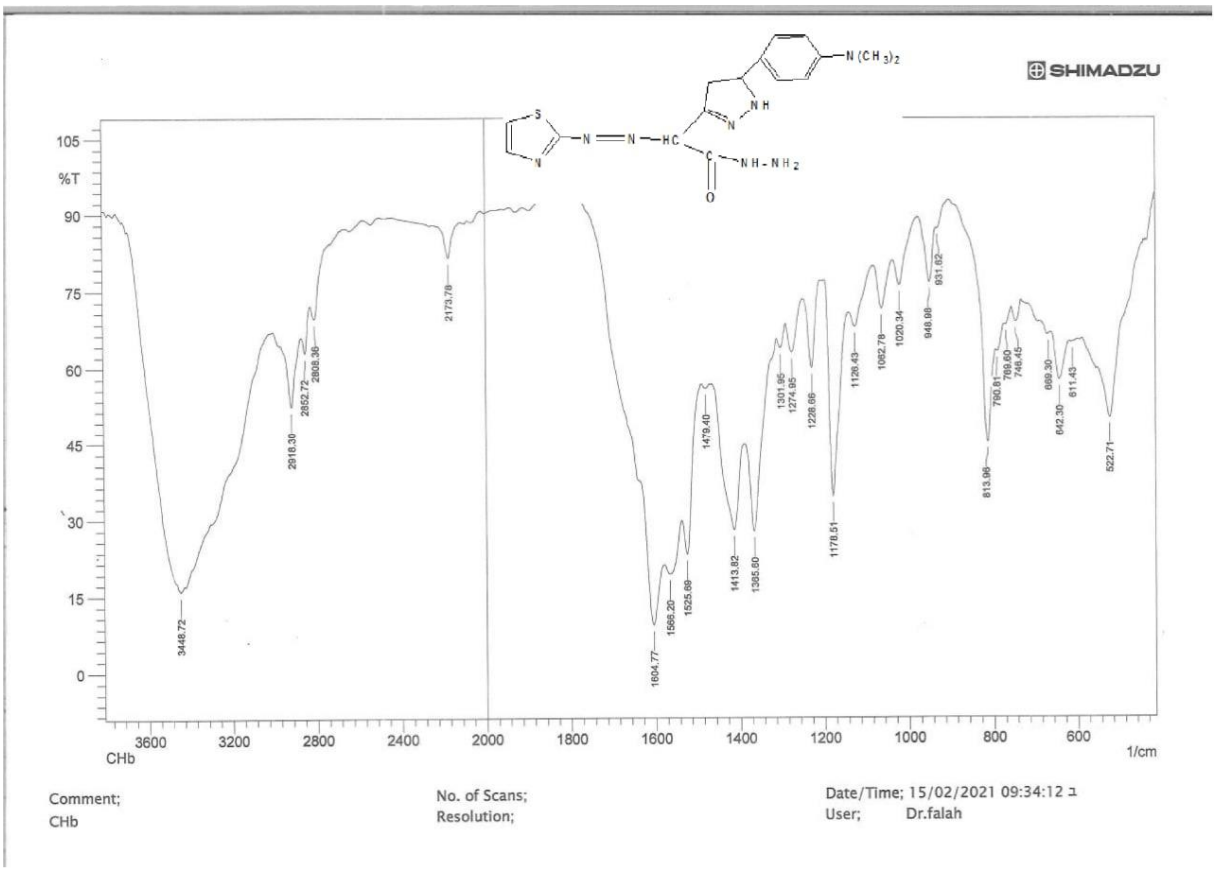


Figure (8)FT-IR Spectrum for the derivative Chb

Table (1) The physical properties for prepared derivatives

Comp No.	m.P° C	Yield %	Color	M. F	M. Wt	R_f
B	Decompose 270	58	Black	$C_9H_{11}O_3N_3S$	241	0.8 Chloroform: MeOH 2 5 : 2.5
B_1	Oil	41.4	Brown	$C_{13}H_{11}N_50S$	285	0.8 Chlorofor : MeOH 2.5 : 2.5
B_2	Oil	51.5	Dark Yellow	$C_7H_7N_5OS$	209	0.7 Chloroform: MeOH

						2.5 : 2.5
CH	**97-99**	**60**	**Dark brown**	**$C_{18}H_{20}N_4O_3S$**	**372**	**0.75 Chloroform:MeOH 2 : 3**
CHa	**Oil**	**53**	**Light Earthy**	**$C_{16}H_{19}N_8OS$**	**371**	**0.9 Benzene : MeOH 2 : 3**
CHb	**156-158**	**51**	**Light Earthy**	**$C_{16}H_{19}N_8OS$**	**371**	**0.8 Benzene : MeOH 2 : 3**

CONCLUSION

In this study, synthesis of many new pyrazole ring derivatives from 2-Amino Thiazole and Ethyl aceto acetate was reported. The work included preparation of Azo compound as the first step. these derivatives were found to be stable at room temperature. some of them are posses high melting points. Whereas other of these derivatives is oily. All of these derivatives were confirmed by spectral data analysis: FTIR and ^{1}H-NMR ,^{13}C-NMR for the starting material that which Azo compound. When preparing the derivatives(Cha , Chb), we noticed that the derivative prepared with the base medium (Chb) is the best because it is a solid with a high melting point that is easy to deal with, unlike the other derivative(Cha) that was oily .

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