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Synthesis and Characterization of Indazol-3-one and Thioxo Pyrimidines Derivatives from Mono and Twin Chalcones

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Abstract

This work involved synthesis and characterization of new mono and twin fused pyrazolone(indazol-3-one) $(IV)_{a-d}$ and thioxo pyrimidine $(III)_{a-d}$ derivatives from Chalcones (mono$(I)_{a,b}$ and twin$(I)_{c,d}$) The synthesis of mono chalcones $(I)_{a,b}$ includes the reaction of (p-methoxy or p- methyl) benzaldehyde with 4-amino acetophenone while the twin acetophenone with p- methoxy benzaldehyde to produce twin chalcones $(I)_{c,d}$, then converted it by Robinson annulations reaction to form the corresponding derivatives $(II)_{a-d}$ afterward reflux the cyclohexenones with hydrazine and some drops of GAA lead to form indazole derivatives $(IV)_{a-d}$. Pyrimidines were synthesized via the reaction of chalcones with thiourea in NaOH and 80% ethanol. All these compounds are characterized by FT-IR spectroscopy and some of them by ^{1}HNMR spectroscopy.

keywords: Chalcones , Heterocyclic , cyclohexenone , pyrimidine , indazole .

تحضير و تشخيص مشتقات اندازول-3-اون و ثايواوكسوبيرميدين من الجالكونات الاحادية و الثنائية

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الخلاصة

تضمن البحث تحضير و تشخيص مركبات الثايواوكسوبيريميدين و الاندازول-3-اون الاحادية والثنائية الجديدة والمحضرة من الجالكونات الاحادية و الثنائية و ذلك من تفاعل بارا- امينواسيتوفينون مع بارا-ميثوكسي او بارا - مثيل بنزالديهايد لتحضير الجالكونات الاحادية $(I)_{a,b}$. كما تفاعل الاسيتوفينون الثنائي مع بارا- ميثوكسي بنزالديهايد لتحضير الجالكونات الثنائية $(I)_{c,d}$ ثم تُحول الجالكونات عبر تفاعل تخليق روبنسون لمشتقات السايكلوهكسينون المقابلة. وبعد ذلك تتفاعل مشتقات السايكلوهكسينون مع الهيدرازين المائي (99%) بوجود حامض الخليك الثلجي للحصول على مشتقات الاندازول-3-اون . اما الثايواوكسوبيرميدينات فُحضرت من تفاعل الجالكونات مع الثايويوريا المذابة في محلول هيدروكسيد الصوديوم الكحولي 80% ، جميع المركبات المحضرة شخصت بمطيافية الأشعة تحت الحمراء وبعض منها بمطيافية الرنين النووي المغناطيسي للبروتون .

Introduction

Chalcones are α, β- unsaturated ketones [1]. Chalcones were synthesized by many workers [2-5]. These flexible molecules appear in various conformations and their properties depend on a suitable ring substitution as well as on the presence of the α-β unsaturated ketone moiety[6] .Chalcones and

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the corresponding heterocyclic analogs are valuable intermediates in organic synthesis [7] .The other importance of these compounds its high photosensitivity[8] and thermal stability [9]

which are used in developing various crystalline electro-optical devices[10]. An important feature of chalcones is their ability to act as an intermediate in the synthesis of biologically active heterocyclic compounds such as, isooxazole, pyrazole and pyrimidine [11-16]. The indazole ring is heterocyclic unit containing two nitrogen atoms and can be functionalized with high selectivity at different positions, indazole nucleus is present in naturally alkaloids[15].The indazole moiety has a great interest in the biological field, including antiviral [17] , anticancer [18] and antihypertensive[19]. Many workers used cyclohexenones as intermediates and starting materials for synthesis of indazoles [20-22]. Al-Bogami[23] reported synthesis and antibacterial activity of new indazole derivatives . Pyrimidine derivatives using in drug design, pyrimidine ring is also found in vitamin B, thiamine, riboflavin and folic acid [11]. Narwal et al. [24] synthesized some pyrimidine derivatives by reaction of chalcones with different reagents to produce different derivatives of pyrimidine.

The aim of the work is synthesis of pyrazolone derivatives fused with cyclohexenone and thioxo pyrimidine mono and twin via chalcones as anintermediates

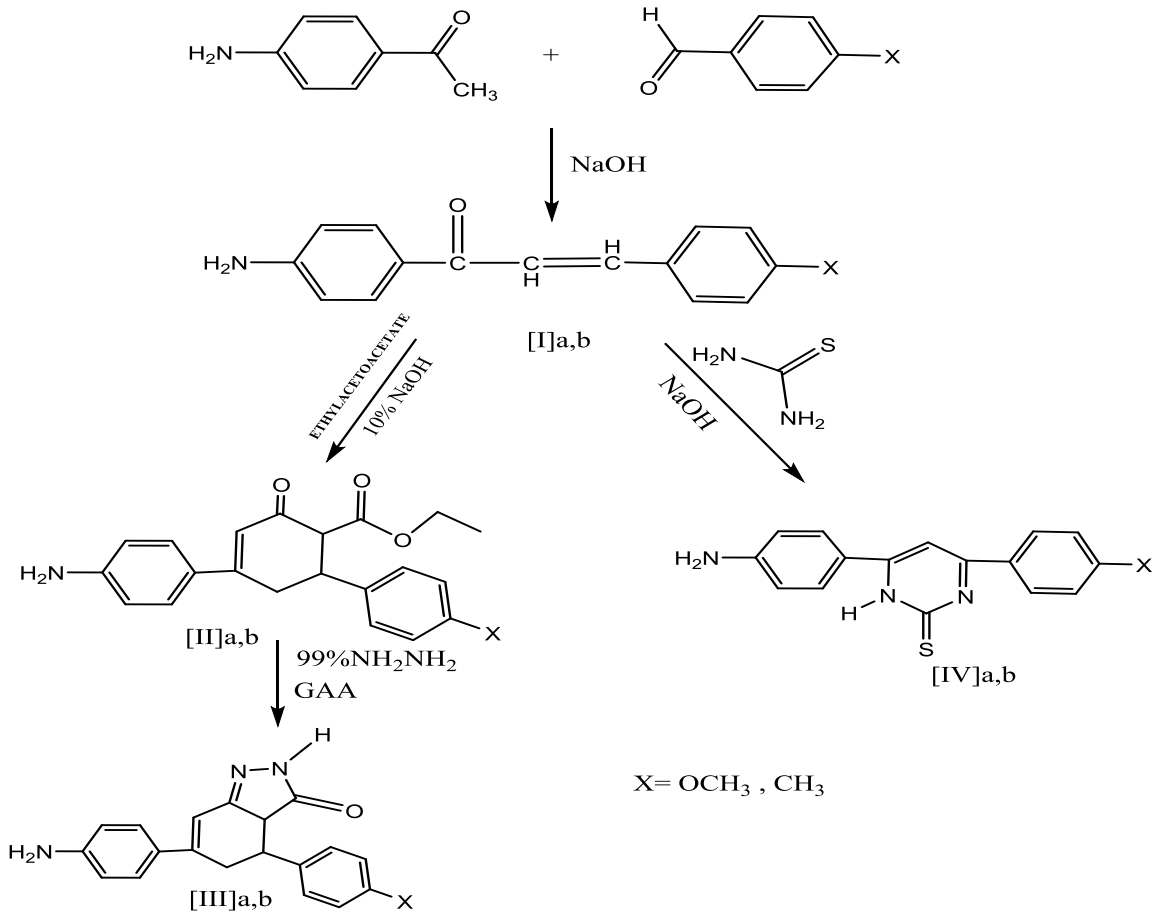
Experimental

Materials

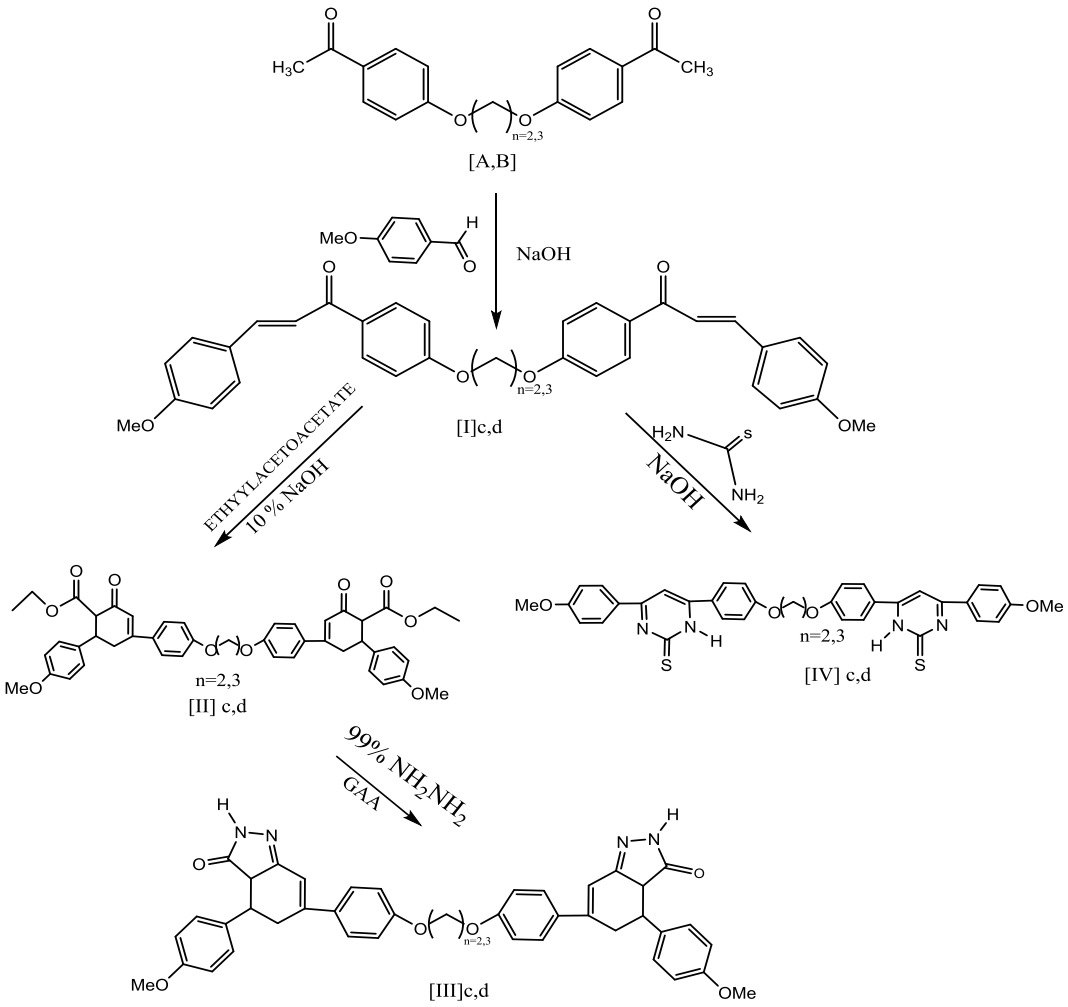
All chemicals were supplied from BDH, Himedia, sigma and Aldrich chemicals co. and used as received.

Instruments: FT-IR spectra were recorded using potassium bromide disc on a Shimadzu (Ir prestige-21) FTIR spectrophotometer. ^{1}H-NMR spectra were obtained with Bruker spectrophotometer model ultra shield at 400 MHz using tetramethylsilane (TMS) as internal standard and DMSO-d_6 as solvent. Uncorrected melting points were determined by using Hot-Stage Gallen Kamp melting point apparatus. Thin layer chromatography (TLC) was carried out on aluminum sheets.

The synthesis routes of new compounds were outlined in schemes 1and 2.



Scheme 1



Scheme 2

Synthesis of 1, 2-bis [4-oxyacetophenone] ethane (A) and 1,3-bis [4- oxyacetophenone] propane(B).

These compounds were prepared according to the procedure hat described by Ayyash et al. [25].

General method for synthesis of Chalcones (I)$_{a-d}$. [26]

Equimolar quantities of 4-amino acetophenone (0.01 mol, 1.35g) and 4-substituted benzaldehyde (0.01 mol) were dissolved in minimum amount of alcohol. Sodium hydroxide solution 40% (0.02 mol, 0.78g in 1.95 mL) was added slowly then cooled the mixture. The mixture was poured slowly onto 200 mL of ice water with constant stirring and kept in refrigerator for 24 h. The precipitate obtained was filtered, washed and recrystallized from ethanol and from synthesis twin chalcones [I]c,d using twice moles from 4-methoxy benzaldehyde(0.02mol) and amount of NaOH. TLC (40:60) (ethyl acetate/n-hexane).

Compounds (I) $_a$ and (I)$_b$ Preparation by workers Suwito et al. [27] and Gan et al. [28] respectively .

Synthesis of 1,1'-((ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(3-(4-methoxy phenyl) prop-2-en-1-one)(I)$_c$. White powder ; yield (93 %) ; mp: 178-180 ºC ; FT-IR(υ cm^{-1}): 3072 **ν** (CH $_{aromatic}$), 2931, 2837 **ν**(CH $_{aliphatic}$) , 1670 **ν**(C=O), 1651 **ν**CH=CH), 1595 **ν**(C=C $_{aromatic}$) , (1249 **ν** (C-O) .

Synthesis of 1,1'-((propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(3-(4-prop-2-en-1-one)(I)$_d$. This compound was prepared according to the procedure described by Insuasty et al. [29]: Yellow powder ; yield (96 %) ; mp: 138-140 ºC ; FT-IR(υ cm^{-1}): 3066 ν(CH $_{aromatic}$), 2964, 2887 **ν**(CH $_{aliphatic}$), 1672 **ν**(C=O), 1654 **ν**(CH=CH), 1597 **ν**(C=C $_{aromatic}$), 1249 **ν**(C-O) ; ^{1}HNMR (DMSO-d$_6$),(δ ppm): 2.28-2.33(quint,2H, CH_2-$\underline{CH_2}$-CH_2), 3.88(s,6H,OCH_3), 4.29-4.35(t,4H,OCH_2),7.06-8.21(m,18H,Ar-H).

General method for synthesis of cyclohexenone derivatives (II)$_{a-d}$. [7]

A mixture of chalcone (3 mmol) and ethyl acetoacetate (0.40 mL, 3 mmol) was refluxed for 2 hrs in 10-15 mL ethanol in presence of 0.5 mL 10% NaOH. The reaction mixture was then poured with good stirring into 200 mL ice-cold water and kept at room temperature until the reaction product separated as a solid, which was filtered off and recrystallized from ethanol. In synthesis twin compounds, twice moles from ethyl acetoacetate and twice amount of 10% NaOH was used. TLC (40:60)(ethyl acetate/n-hexane).

Synthesis of ethyl 4-amino-4''-methoxy-5'-oxo-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate (II)$_a$. Yellow gummy ; yield (60 %) ; FT-IR(υ cm^{-1}): 3473 –3375 (asym, sym, ν NH_2) , 3030 ν(CH $_{aromatic}$) , 2950, 2837 ν(CH $_{aliphatic}$), 1726 ν(C=O$_{ester}$) , 1654 ν(C=O) , 1633 ν(C=C) , 1598 ν(C=C$_{aromatic}$) , 1249 ν(C-O$_{ether}$) , 1220 ν(C-O $_{ester}$). **Synthesis of ethyl 4-amino-4''-methyl-5'-oxo-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate(II)$_b$.** Yellow gummy ; yield (74 %) ; FT-IR(υ cm^{-1}) :3460- 3371(asym, sym νNH_2) , 3024 ν(CH $_{aromatic}$) , 2981, 2893 ν(CH $_{aliphatic}$), 1728 ν(C=O$_{ester}$), 1665 ν(C=O) , 1639 ν(C=C) , 1600 ν(C=C$_{aromatic}$) , 1211 ν(C-O $_{ester}$)

Synthesis of diethyl 4,4'''-(ethane-1,2-diylbis(oxy))bis(4''-methoxy-5'-oxo-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate (II)c. Pale brown ; yield (80 %) ; mp: 76-78 ºC ; FT-IR(υ cm^{-1}): 3041 ν(CH $_{aromatic}$), 2904, 2835 ν(CH $_{aliphatic}$) , 1735 ν(C=O $_{ester}$) , 1654 ν(C=O),1597 ν (C=C),1249 ν (C-O).

Synthesis of diethyl 4,4'''-(propane-1,3-diylbis(oxy))bis(4''-methoxy-5'-oxo-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate(II)$_d$. Pale brown ; yield (94%); mp: 93-95 ºC ; FT-IR(υ cm^{-1}),: 3055 ν(CH aromatic), 2937, 2835 ν(CH $_{aliphatic}$), 1736 ν(C=O$_{ester}$) ,1654 ν(C=O), 1598 ν(C=C) , 1251 ν(C-O) . ^{1}HNMR (DMSO-d_6),(δ ppm): 1.01 (t,3H,CH_2-$\underline{CH_3}$), 2.26(quint,2H,CH_2-$\underline{CH_2}$-CH_2), 3.04-3.06(t,2H,$CO_2C\underline{H_2}$), 3.6-3.61(d,2H,H_c &H_d),3.79(s,6H , OCH_3),3.96-3.98(d,1H,H_a),4.05-4.08(quart,1H,H_b), 4.25- 4.28(t,4H,OCH_2), 6.55(s,1H,C=CH) , 6.94-7.99(m,16 H , Ar-H).

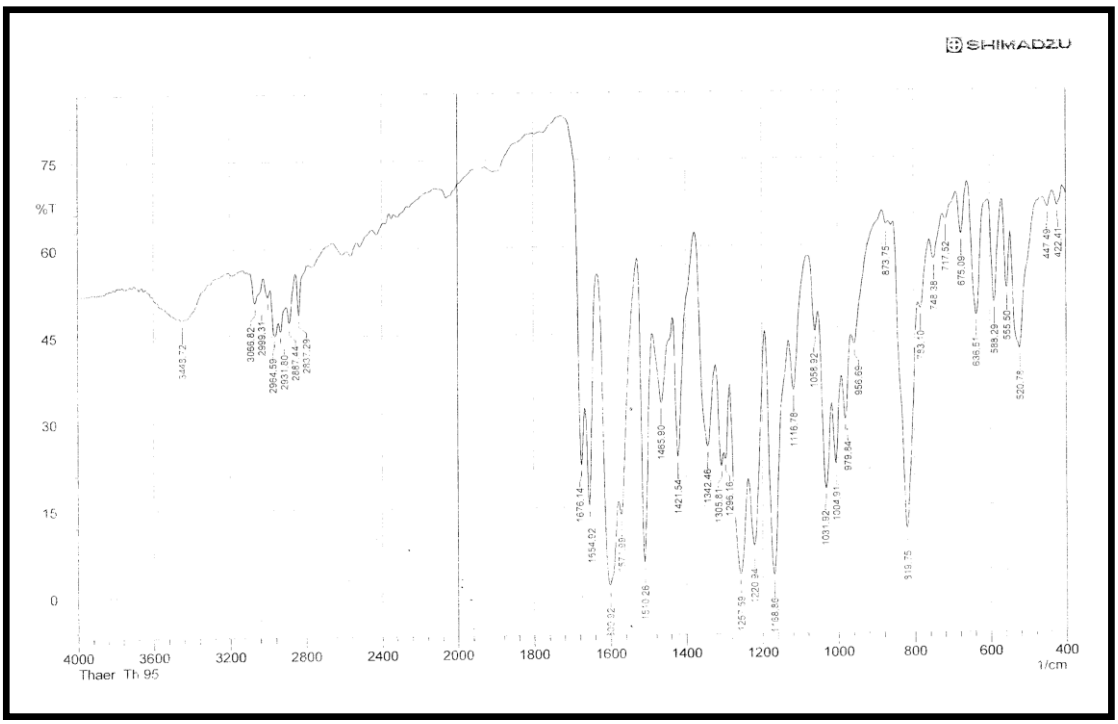


Figure 1- FT-IR spectrum for compound (I)$_d$.

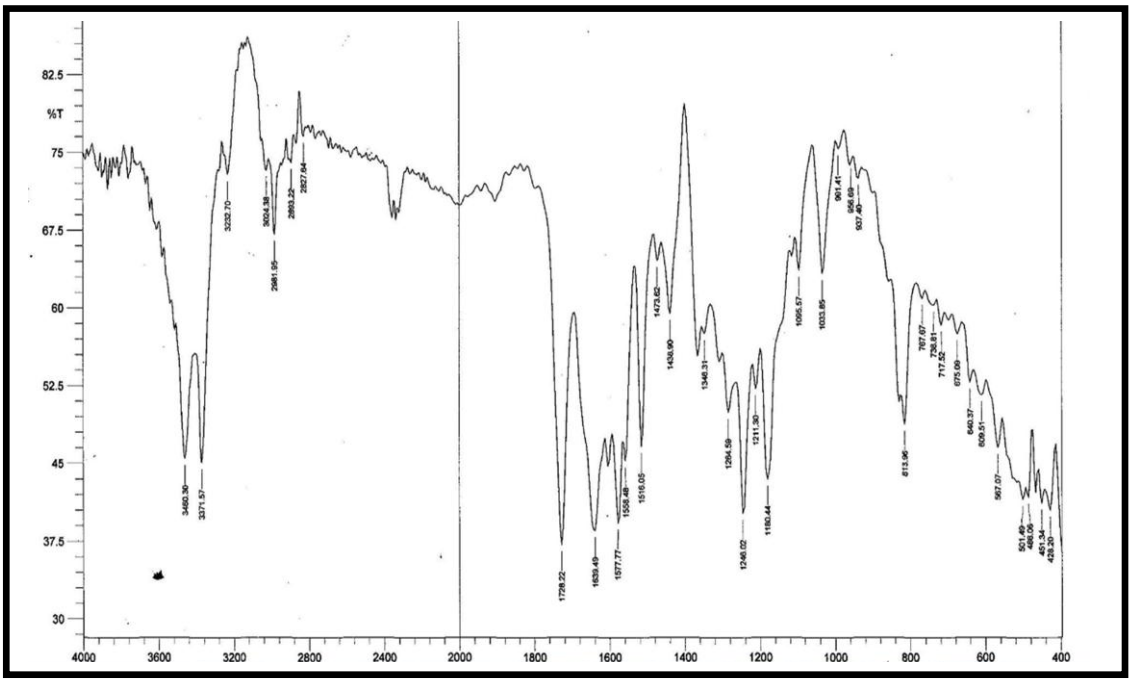


Figure 2- FT-IR spectrum for compound $(II)_b$

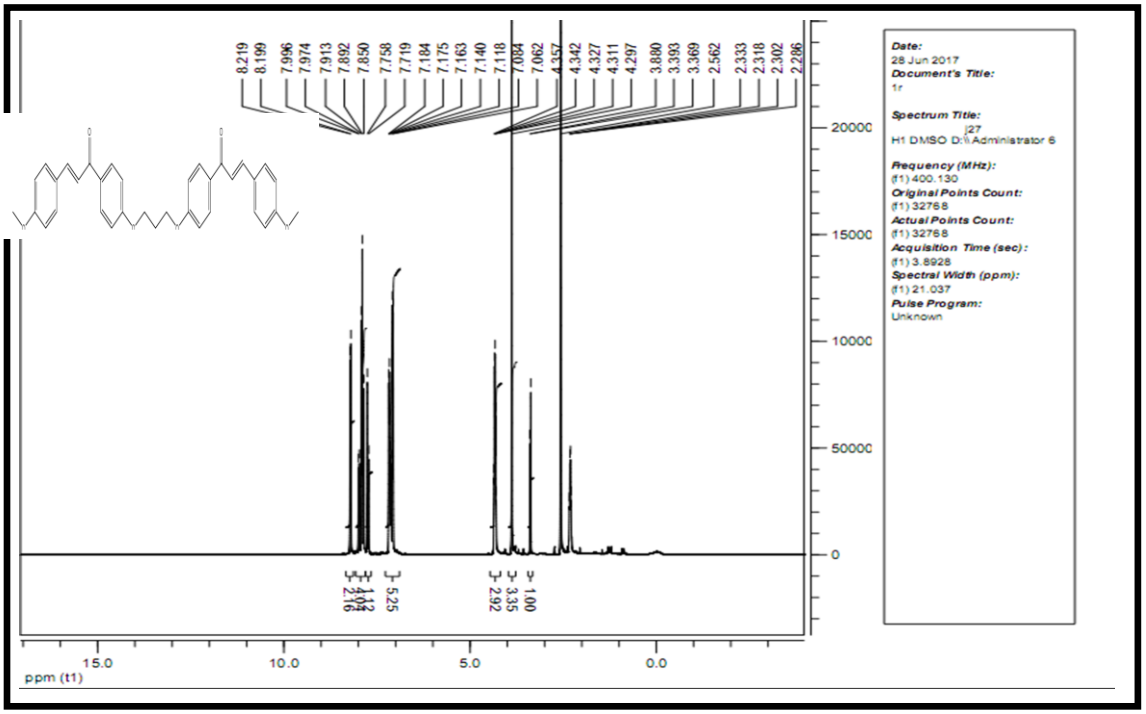


Figure 3- ^{1}HNMR spectrum of compound $(I)_d$.

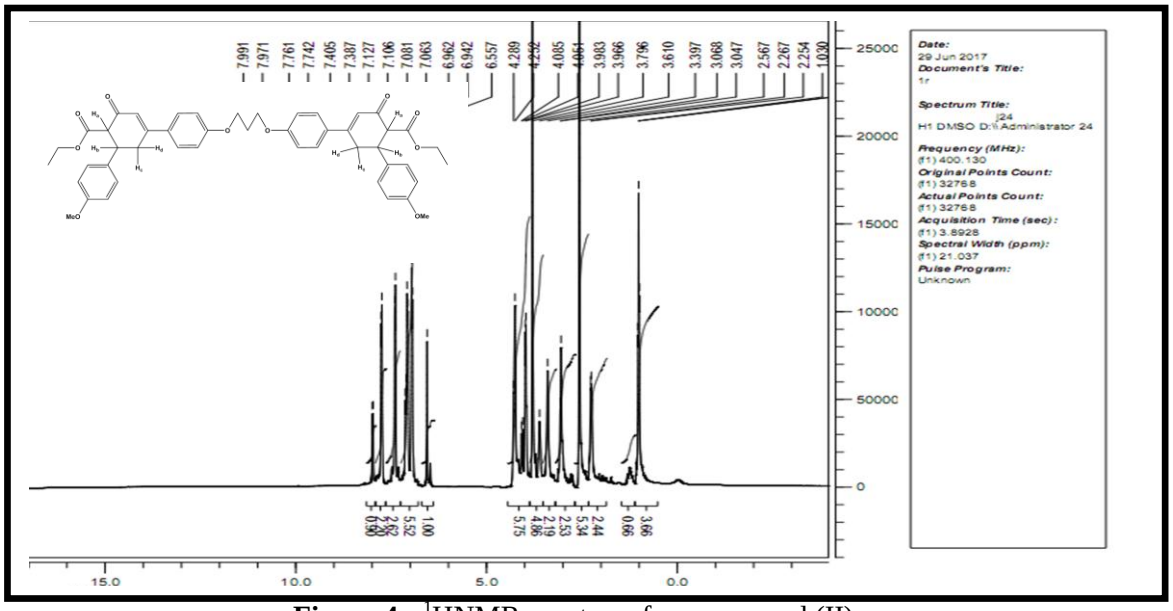


Figure 4 - ^{1}HNMR spectrum for compound $(II)_d$.

General method for synthesis of pyrazolone derivatives $(III)_{a-d}$.[30]

A mixture of the cyclohexenone derivatives $(II)_{a-d}$ (0.1mol) and hydrazine hydrate 99%(5 mL,0.1mol) in absolute ethanol (15 mL) containing glacial acetic acid (0.5 mL) was refluxed for 2hrs . After cooling the solid formed was filtered off , air dried and recrystallized from ethanol. When synthesis twin compounds twice moles from all starting material was used. TLC (40:60)(ethyl acetate/n-hexane).

Synthesis of 6-(4-aminophenyl)-4-(4-methoxyphenyl)-2, 3, 4, 5-tetrahydro-3H-indazol-3-one $(III)_a$. Red powder ; yield (77 %) ; mp:98-100 ºC ; FT-IR(υ cm^{-1}): 3400 - 3226 (asym, sym, νNH_2,NH), 3047 ν(CH $_{aromatic}$), 2922, 2856 ν(CH $_{aliphatic}$), 1695 ν(C=O $_{amide}$) , 1647 ν(C=N), 1595 ν(C=C),1242 ν(C-O).

Synthesis of 6-(4-aminophenyl)-4-(p-tolyl)-2,3,4,5-tetrahydro-3H-indazol-3-one $(III)_b$. Orange powder ; yield (94 %); mp:100-102 ºC ; FT-IR(υ cm^{-1}): 3344 - 3205(asym, sym, νNH_2,NH) , 3022 ν(CH $_{aromatic}$), 2918, 2871 ν(CH $_{aliphatic}$), 1693 ν(C=O $_{amide}$), 1664 ν(C=N), 1593 ν(C=C $_{aromatic}$), ^{1}HNMR (DMSO-d_6),(δ ppm): 2.2 (s,3H, CH_3), 2.85(d,2H,H_c&H_d), 2.86-2.88(d,1H,H_a), 3.64-3.66(d,1H,H_b) ,5.56(s,2H,NH_2), 6.65(s,1H,C=CH),6.75-7.5 (m,8 H , Ar-H),10.70(s,1H, NH).

Synthesis of 6,6'-((ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(4-(4-methoxy phenyl) -2,3,4,5-tetrahydro-3H-indazol-3-one)(III)c . Yellow powder ; yield (50 %) ; mp:92-94 ºC ; FT-IR(υ cm^{-1}): 3188 ν(NH), 3039 ν(CH $_{aromatic}$), 2933, 2833 ν(CH $_{aliphatic}$), 1701 ν(C=O $_{amide}$) , 1640 ν(C=N) , 1604 ν(C=C $_{aromatic}$), 1246 ν(C-O) .

Synthesis of 6,6'-((propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(4-(4-methoxy phenyl) -2,3,4,5-tetrahydro-3H-indazol-3-one)$(III)_d$. Yellow powder ; yield (53 %) ; mp:178-180 ºC ; FT-IR(υ cm^{-1}): 3367 ν(NH), 3099 ν(CH $_{aromatic}$), 2933, 2873 ν(CH $_{aliphatic}$), 1701 ν(C=O $_{amide}$) , 1630 ν(C=N), 1604 ν(C=C), 1246 ν(C-O) ; ^{1}HNMR (DMSO-d_6),(δ ppm): 1.90-2.15(quint,3H,C$\underline{H_2}$-CH_2), 2.82-2.86(d, 4H,2H_c&2H_d), 3.07 (d, 2H,H_a), 3.66(s,6H, OCH_3),3.7(quart, 2H, H_b), 4.11 (t,4H,OCH_2), 6.65(s,2H, C=CH) , 6.67-7.41(m, 16H , Ar-H) ,10.80(s,2H,NH).

General method for synthesis of thioxo pyrimidine derivatives $(IV)_{a-d}$. [31]

A mixture of chalcone (0.001 mol), thiourea(0.001 mol) and sodium hydroxide (0.1 g) in 80% EtOH (25 mL) was refluxed for 6 h. The reaction mixture was concentrated under vacuum. Cooled and the solid was filtered off washed with water, dried and then crystallized from ethanol. In synthesis of twin compounds two moles from thiourea and twice amount of solution NaOH were used . TLC (40:60)(ethyl acetate/n-hexane).

Syntesis of 4-(4-aminophenyl)-6-(4-methoxyphenyl)pyrimidine-2(1H)-thione $(IV)_a$. Yellow powder ; yield (40 %); mp: 280 ºC dec ; FT-IR(υ cm^{-1}): 3468 - 3213(asym, sym, νNH_2,NH) , 3045 ν (CH $_{aromatic}$), 2929, 2852 ν(CH $_{aliphatic}$), 1631 ν(C=N) , 1598 ν(C=C) , 1228 ν(C=S), 1261 ν(C-O).

Synthesis of 4-(4-aminophenyl)-6-(p-tolyl)pyrimidine-2(1H)-thione (IV)$_b$.Yellow powder ; yield (69 %); mp: 270 ºC dec ; FT-IR(υ cm^{-1}): 3456 – 3213(asym, sym, νNH_2,NH), 3047 ν(CH $_{aromatic}$), 2918, 2852 ν(CH $_{aliphatic}$), 1645 ν(C=N) , 1625 ν(C=C), 1600 ν(C=C $_{aromatic}$), 1226 ν(C=S). ^{1}HNMR (DMSO-d_6),(δ ppm): 2.4(s,3H,CH_3), 3.56(s,2H,SH), 6.19(s,2H,NH_2),6.66-7.98(m,9H,Ar-H),7.62(s,2H,$_{pyrimidine}$)[31],7.98(s,H,NH).

Synthesis of 6,6'-((ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(4-(4-methoxyphenyl) pyrimidine -2(1H)-thione) (IV)$_c$. White powder ; yield (46 %) ; mp: 98-100 ºC ; FT-IR(υ cm^{-1}) : 3415 ν(NH), 3040 ν(CH $_{aromatic}$),2960, 2835 ν (H $_{aliphatic}$), 1649 ν C=N) , 1597 ν(C=C $_{aromatic}$), 1220 ν(C=S) , 1257 ν(C-O) ; ^{1}HNMR (DMSO-d_6),(δ ppm): 3.75(s,2H,SH), 3.88 (s,6H,OCH_3), 4.52 (s,4H,OCH_2), 7.06- 8.01 (m,16H ,Ar-H), ,7.76(s,2H, pyrimidine ring). 8.23(s, 2H, H$_{, pyrimidine}$).

Synthesis of 6,6'-((propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(4-(4-methoxyphenyl) pyrimidine-2(1H)-thione)(IV)$_d$. White powder ; yield (48%); mp: 90-92 ºC ; FT-IR(υ cm^{-1}): 3412 ν(NH) , 3064 ν(CH $_{aromatic}$), 2953, 2835 ν(CH $_{aliphatic}$), 1654 ν (C=N) , 1598 ν(C=C $_{aromatic}$), 1220 ν(C=S), 1247 ν(C-O) **.**

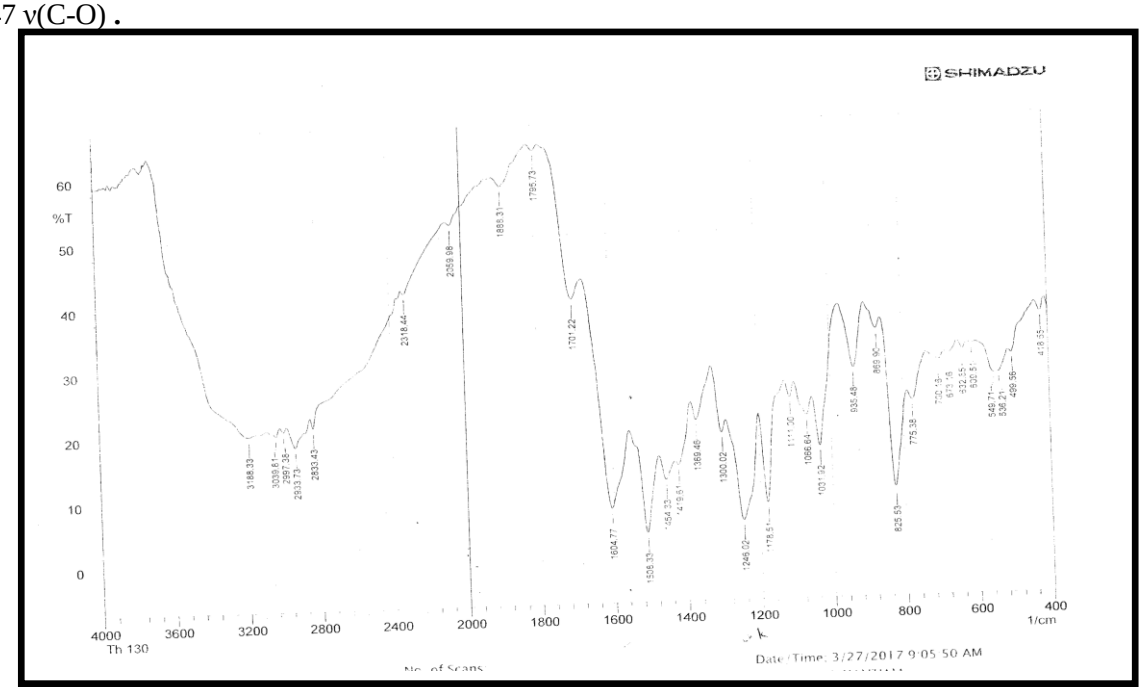


Figure 5- FT-IR spectrum for compound $(III)_C$

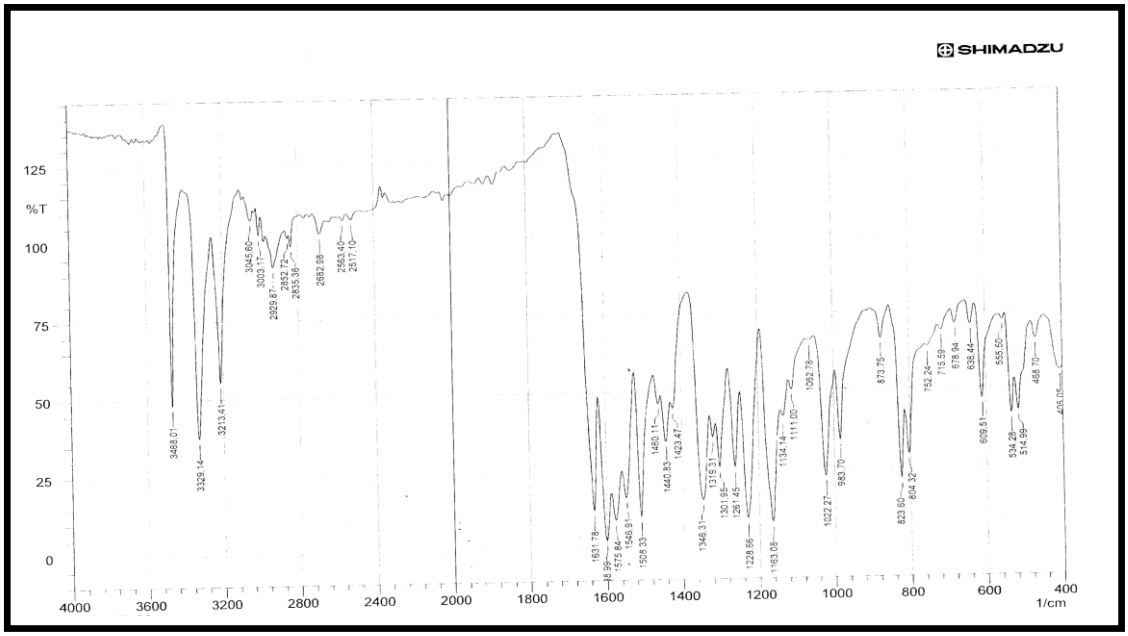


Figure 6- FT-IR spectrum of compound $(IV)_a$.

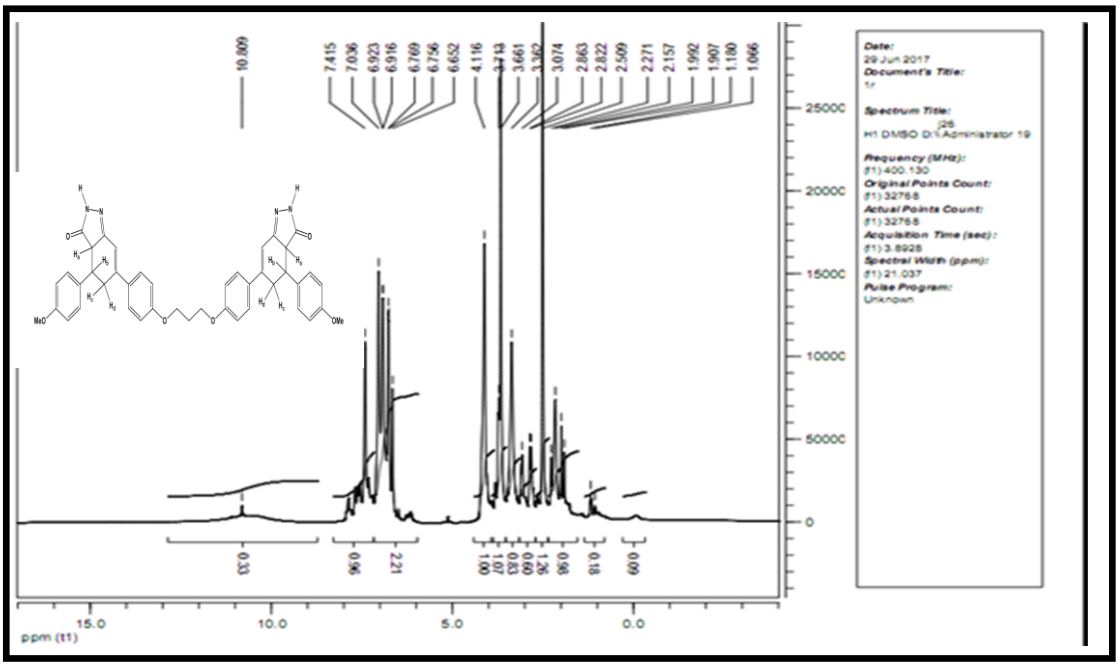


Figure 7- ^{1}HNMR spectrum of compound $(III)_d$

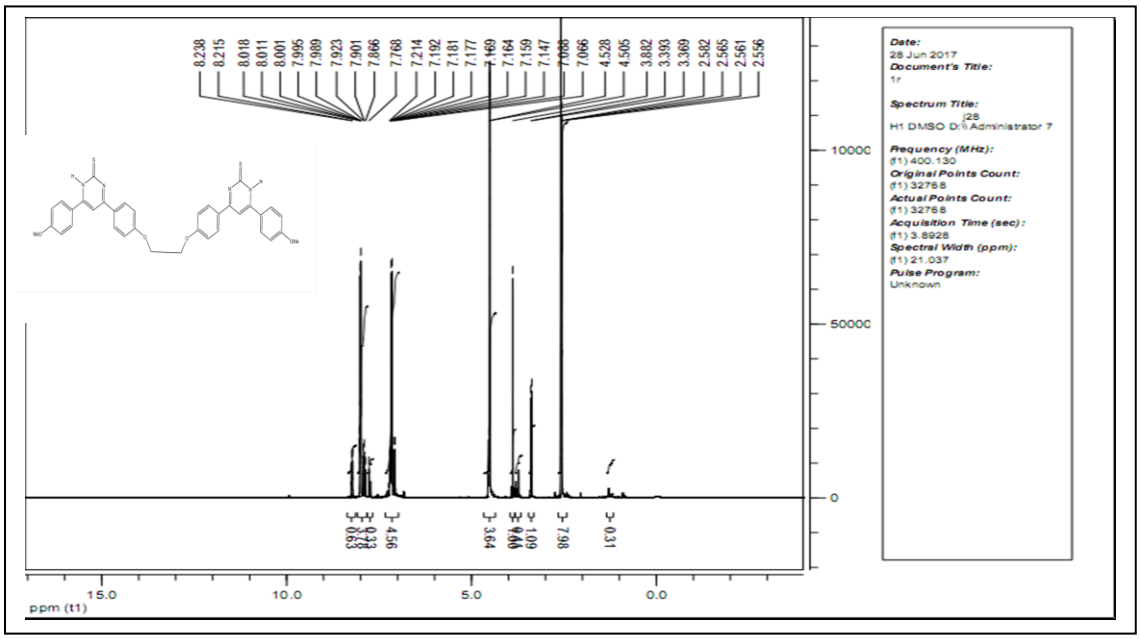
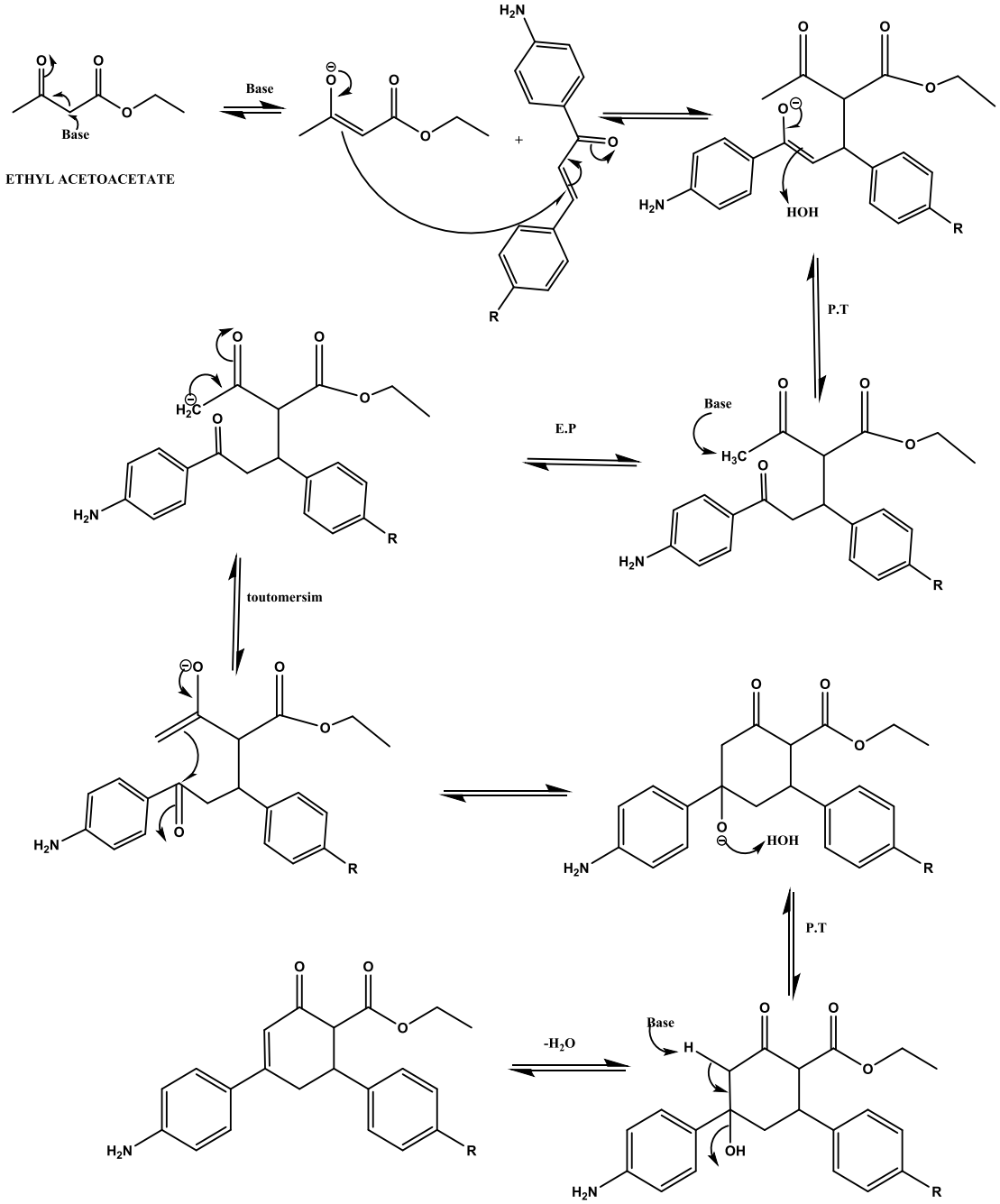


Figure 8- ^{1}HNMR spectrum of compound $(IV)_c$

Results and discussion

All of the synthesized compounds gave satisfactory analysis for the proposed structures, which were confirmed on the basis of their Fourier transform Infrared (FT-IR) spectra and proton nuclear magnetic resonance (^{1}HNMR) spectra. The di-ketone compounds A and B were prepared based on the methods mentioned in the reference[25] , the first step including reaction of different ketones with p-methoxy or p- methyl benzaldehyde according to the aldol condensation reaction to produce α,β-unsaturated ketone(chalcone)$(I)_{a-d}$, The FT-IR spectrum Figure-1 as a sample, showed the stretching vibration band for υC=O of chalcone in the region(1676-1658) $cm^{-1}$and υ C=C in the region of (1654-1625)$cm^{-1}$and the ^{1}H-NMR spectrum for $(I)_d$ Figure-3 showed doublet signal at δ (7.11-7.99) ppm attributed to two protons attached to C=C (alkene) . In the next step reaction of compounds$(I)_{a-b}$ with ethyl acetoacetate this reaction known as (Robinson annulations) lead to formation of cyclohexenone

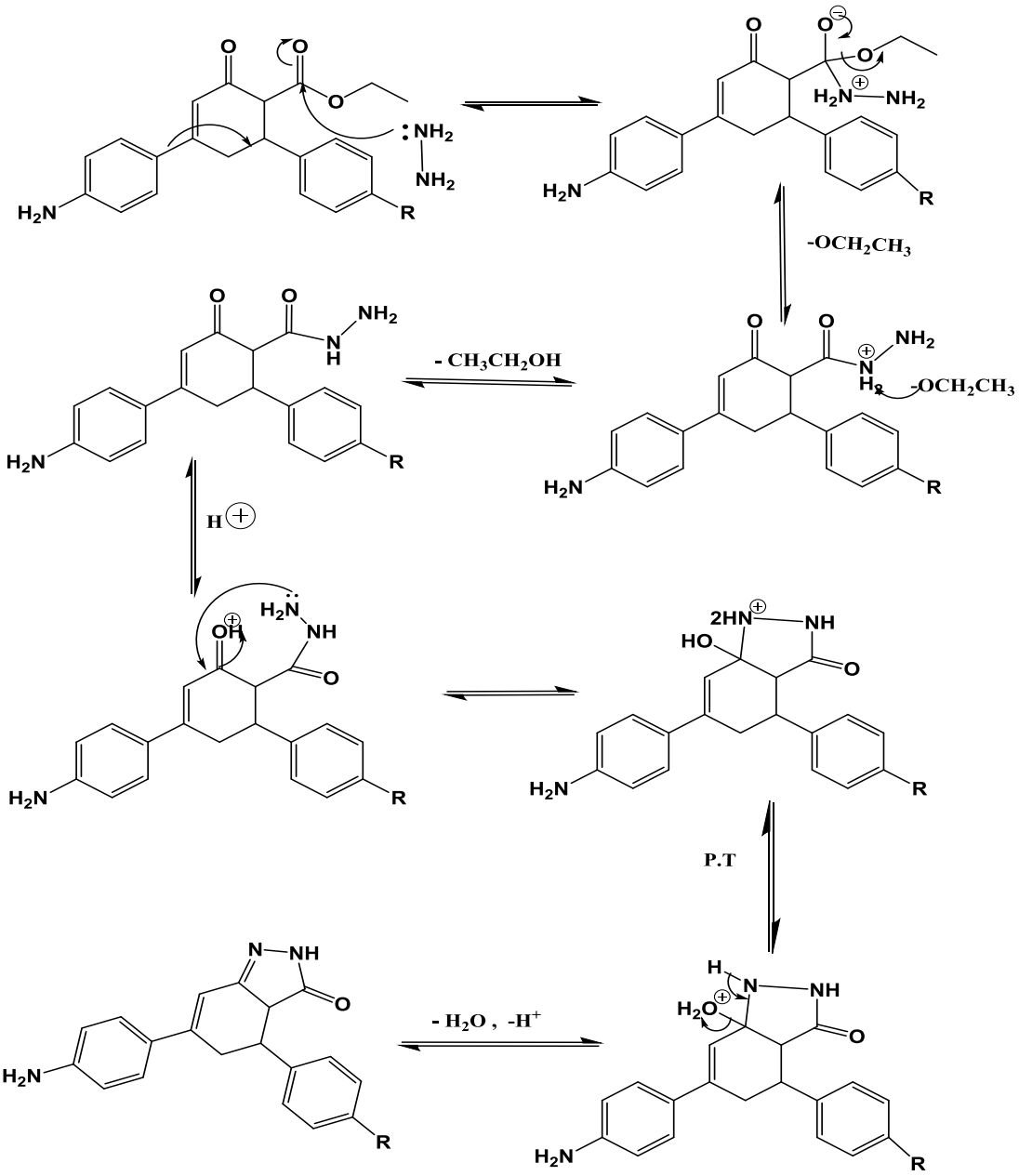
derivatives $(II)_{a-d}$, Scheme-3 explain this mechanism[32]. The FT-IR spectrum, Figure-2 showed strong absorption band for υ C=O ester in the region (1735-1725) cm^{-1} in addition the ^{1}HNMR spectrum for $(II)_d$ Figure-4 showed the appearance of two signals for protons CH_2CH_3 of ester in the region δ (1.01- 2.26) ppm ,On the other hand singlet signal appeared at δ 6.55 ppm can attributed to one proton attached to C=C endo cyclohexenone this good evidence for formation the cyclic derivatives .



Scheme 3- The Robinson annulations mechanism to form cyclohexenone derivatives (II)a,b.

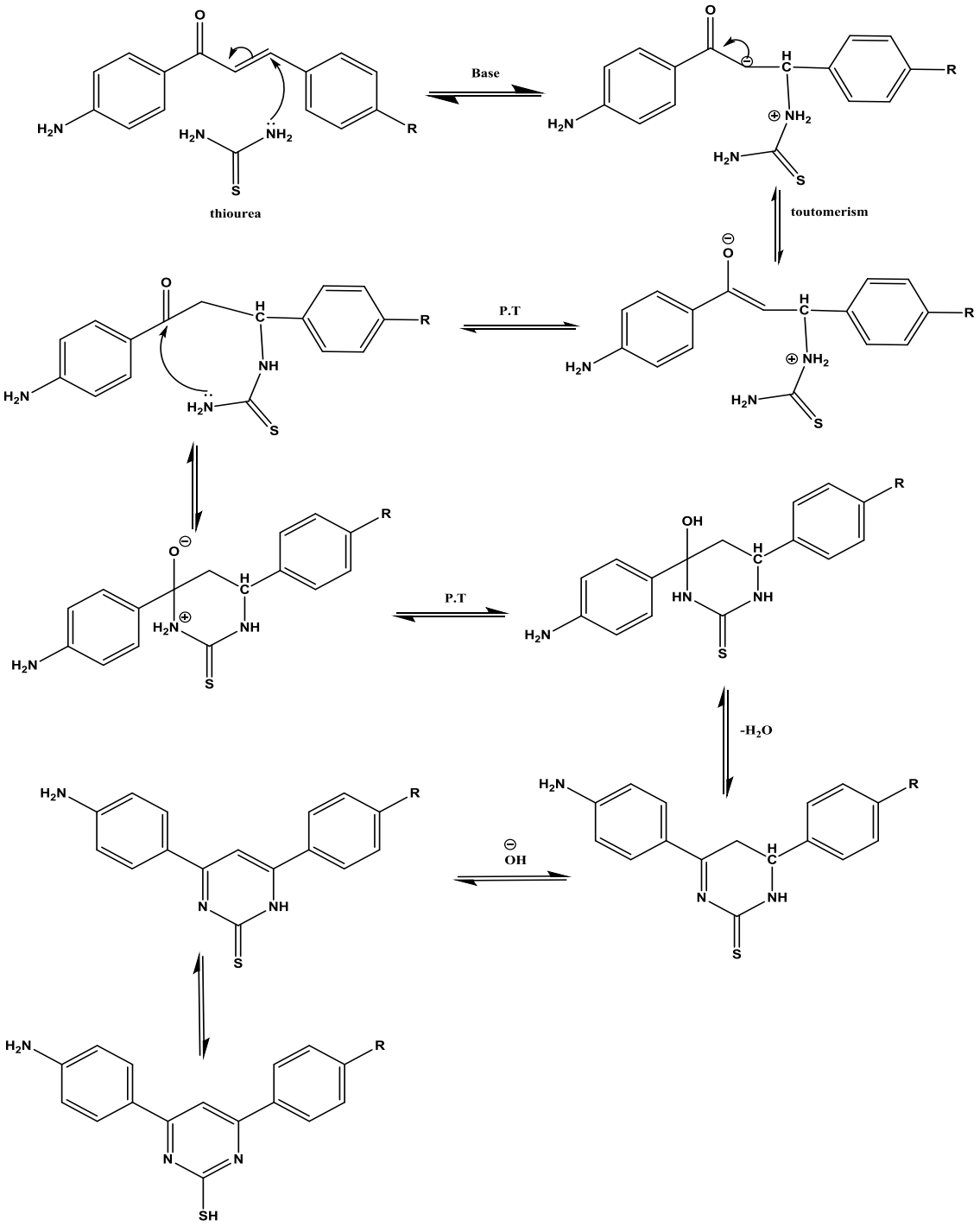
The compounds indazole -3-one(fused pyrazolone with cyclohexene) $(III)_{a-d}$ were synthesized by reaction of cyclohexenones $(II)_{a-d}$ which synthesized in step two with hydrazine 99% in present of glacial acetic acid according to the suggested mechanism Scheme-4 . The FT-IR, Figure-5 as a sample of these compounds showed the υ NH in the region (3226-3200) cm^{-1} and the υ C=O amide appeared in the region (1701-1693)cm^{-1} in addition appearance υ C=N around (1664-1604)$cm^{-1}$and disappearance of the υ C=O ester at 1735cm^{-1} , Moreover the^{1}H NMR spectrum of compound$(III)_d$

Figure-7 showed the appearance of singlet signal at δ 10.80 ppm which can attributed to NH proton and disappearance of the signal of aliphatic protons for ester.



Scheme 4- The suggested mechanism for reaction of synthesis Indazol- 3-one (III) a,b.

Finally, The thioxo pyrimidine derivatives $(IV)_{a-b}$ were synthesized by reaction of $(I)_{a-d}$ with thiourea this reaction was catalytic by NaOH , the reaction mechanism for synthesis of thioxo pyrimidine was explained in Scheme-5 [33] . FT-IR, Figure-6, showed strong absorption band in the region (1654-1625)cm^{-1} for υ C=N of thioxo pyrimidine ring and υNH at 3213 in addition the υC=S band appeared around 1250 cm^{-1} , Moreover the ^{1}HNMR spectrum of $(IV)_c$ Figure-8 showed the appearance of the singlet signal at the δ 3.75 ppm which was attributed to one proton of SH.



Scheme 5- The mechanism reaction for formation of thioxo pyrimidine derivatives (IV) a,b.

Conclusion

The chalcones were synthesized in our work mono and twin in good to excellent yields about 77-95% These compounds are very good intermediates for synthesis of newly thioxo pyrimidines and indazole-3-one . The study showed the low percentage yield of twin compounds in comparison with mono compounds of the same type.

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