Synthesis, Characterization and Theoretical Study of Some Pyrazole Compounds Derived From 1,1,2-Trimethylbenz[e] Indole

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Abstract

Among the important heterocyclic compounds pyrazole is a compound which have 5-membered ring structure with 3 carbon atoms and 2 neighbor nitrogen atoms. Many applications of basic organic molecules based on pyrazole are in different fields including pharmacy, agro-chemical industries. There is an increase in the benefit of synthesizing and analyzing different properties, and searching for possible applications of pyrazole derivatives. In this research the focus was to synthesis of new series of pyrazole derivatives (C_2-C_5) by refluxing hydrazine derivatives with 2-(1,1-Dimethyl1,3-dihydro-benzo[e]indol-2-ylidene)-malonaldehyde, while a last compound was synthesized by reaction compound (1,1,2-Trimethylbenz[e] indole) with phosphoryl chloride in anhydrous dimethylformamide. The synthesized compounds were identified by means of their FT-IR and ^{1}H-NMR spectral data. Density Functional Theory calculations of the synthesized pyrazoles compounds were performed using molecular structures with optimized geometries which indicated that the prepared compounds high values of energy gap, E_{GAP}.

Keywords: Pyrazole derivatives; DFT; 1,1,2-Trimethylbenz[e] indole.

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Synthesis, Characterization and Theoretical Study of Some Pyrazole Compounds Derived From 1,1,2-Trimethylbenz [e] Indole

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تحضير، تشخيص ودراسة نظرية لبعض مركبات البايرزول المشتقة من 1،1،2- تراي مثيل بنزاندول

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الخلاصة

البايرزول من المركبات المهمة غير المتجانسة والذي يمتلك حلقة خماسية متكونة من ثلاث ذرات كربون واثنين من ذرات النتروجين .هناك العديد من التطبيقات للجزيئات العضوية الأساسية المحتوية على البيرازول في مجالات مختلفة بما في ذلك الصيدلة والصناعات الزراعية والكيميائية. سلسلة جديدة من مشتقات البايرزول تم تحضيرها في هذ البحث بواسط تصعيد مشتقات الهيدرازين مع مركب2-(1,1-Dimethyl1,3-dihydro-benzo[e]indol-2-ylidene)-malonaldehyde والذي يحضر من تفاعل1،1،2- تراي مثيل بنزاندول مع $POCl_3$ بوجود مذيب ثنائي مثيل فورماميد. المركبات المحضرة تم تشخيصها بواسطة طيف الاشعة تحت الحمراء FT-IR وطيف الرنين النووي المغناطيسي ^{1}H-NMR. تم اجراء حسابات نظرية لدوال الكثافة لمركبات البايرزول المحضرة باستخدام نظرية DFT وقد اظهرت جميع المركبات قيمة E_{GAP} عالية.

الكلمات المفتاحية: مشتقات البايرزول،نظرية DFT، 1 ،2،1- تراي مثيل بنزاندول

Introduction

Indole derivatives have attracted special attention because their possessing various of pharmacological activities. It's an important class of organic heterocyclic which are commonly found in nature and they have acquired more importance in the recent years due to their wide range of biological and pharmacological activities such as anticancer [1,2], antihypertensive, antiviral, antitumor [2], anti-inflammatory [3], anti-depressant [4], antimicrobial [5] and antifungal [6]. Indole is a nonpolar purine analog that is present in some important biochemical molecules such as tryptophan, serotonin and melatonin. Furthermore there are currently many indole containing drugs in the market [7, 8] and indole ring has attracted the attention of many medicinal chemists as an interesting scaffold in the process of new drug development [9,10].

Pyrazolines are compounds represents a group of heterocycles have very important in industrial, medicine and different methods have been worked out for their synthesis. The literature survey revealed that the derivatives of pyrazole has received great attention in recent years because of its prominent utilization as analgesic, anti-inflammatory, antibacterial, antifungal [11,12], antimalarial [13], antitumor, antioxidant [14].

Experimental Section

1. Materials:

1,1,2-Trimethyl-1H-benzo[e]indole, anhydrous dimethylformamide (DMF) , phosphoryl chloride ($POCl_3$), 2,4-Dinitrophenyl hydrazine, 4-Nitrophenyl hydrazine benzene, 4-Chlorophenyl hydrazine , 4-Bromophenyl hydrazine, Hydrazine hydrate, absolute ethanol, sodium hydroxide and glacial acetic acid were of reagent grade obtained from Sigma-Aldrich, chemicals and used as received.

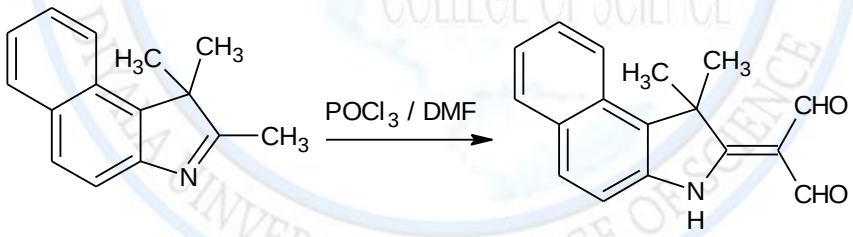
2. Instrumentations:

The Melting points of compounds were determined using GallenKamp (MFB-600) melting point apparatus. Purity of prepared compounds were checked by pre-coated thin layer chromatography (TLC) plates MERCK, 60F254 with a mixture of hexane : ethyl acetate (8:2) as an eluent. FT-IR of prepared compounds were obtained by PERKIN ELMER SPEACTUM-65 within the range of [4000- 400] using KBr Disc in the Chemistry Department / Diyala University while the ^{1}H-NMR spectra (solvent DMSO-d_6) of compound $C_1$was obtained on Bruker 400 MHz spectrophotometer using TMS as internal standard in faculty of science university of Malaya(kualalumpur) and the ^{1}H-NMR spectra (solvent DMSO-d6) of compounds (C_2-C_6) was obtained on (NMReady 60 Pro 60 MHz High resolution) spectrophotometer using TMS as internal standard in the college of Education for Pure Science (Ibn AL-Haitham). University of Baghdad

3. Synthetic methods

3. 1. Synthesis of 2-(1,1-Dimethyl-1,3—dihydrobenzo [e] indol-2-ylidene)-malonaldehyde.

The 1,1,2-Trimethyl-1H-benzo [e] indole (10 g, 47.8mmol) dissolved in 20 ml anhydrous dimethylformamide and cooled into ice bath. The solution of (17.56 ml, 191 mmol) of phosphoryl chloride in 10 ml of anhydrous dimethylformamide(DMF) was cooled in an ice bath also and then was added drop wise to first solution with stirring over a period of 1 h at below 5 °C. After that the reaction mixture was stirred at 85 °C for 3 h. The mixture of reaction was poured on to ice water, the pH was mend to 8.0 by added aqueous (NaOH 35%) , the solid product was precipitated and the product was filtered, washed with hot water and then dried in oven to afford solid product of pale yellow crystals to 2-(1,1-Dimethyl1,3-dihydro-benzo [e] indol-2-ylidene)-malonaldehyde. The solid product thus obtained recrystallized from ethanol. The physical properties of compounds C_1 are listed in table 1 and the scheme of synthesis is given below (Scheme I) (15).

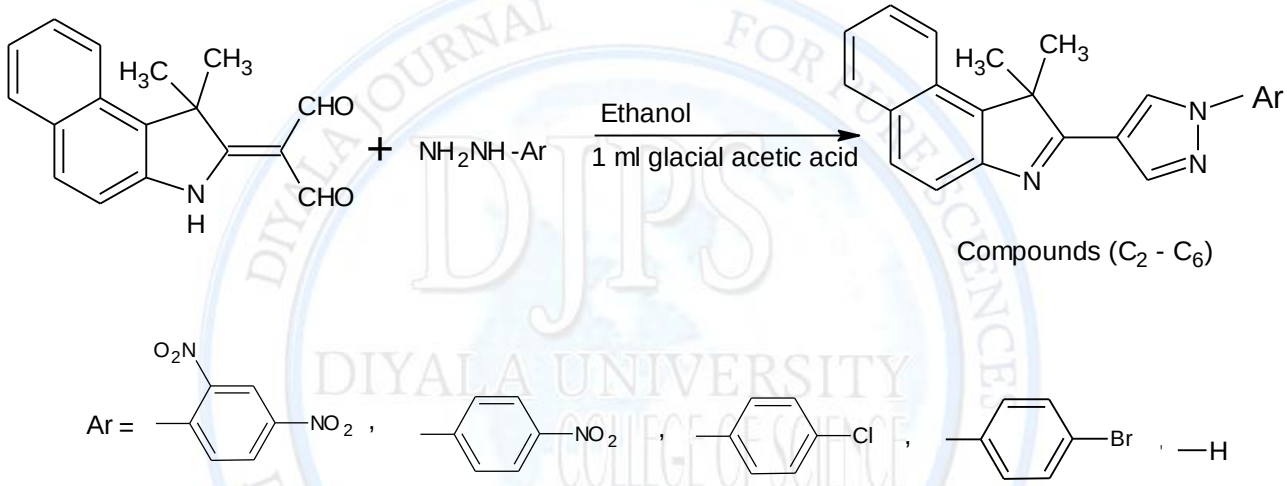


Scheme I: Synthetic route for compoundC_1

3. 2. Synthesis of compounds (C_2-C_6) (2-[1-(substituted)-1*H*-pyrazol-4-yl]-1,1-dimethyl-1*H*-benzo[*e*]indole)

Hydrazine derivatives (2,4-dinitrophenylhydrazine,4-nitrophenylhydrazine ,4-Chlorophenyl hydrazine, 4-Bromophenyl hydrazine, Hydrazine hydrate) (0.01mol) was dissolved in 25 ml absolute ethanol and added to (0.01mol) of 2- (1,1-Dimethyl1,3-dihydro-benzo[e] indol-2-ylidene) - malonaldehyde dissolved in 25 ml absolute ethanol. Then, 1 ml of glacial acetic acid

was added into the above mixture and resulted one was refluxed in a water bath at 80°C. The progress of reaction was monitored by thin layer chromatography (TLC). After 6 hours, the reaction was completed as indicated by TLC. After cooling of mixture the precipitated solid was filtered off and dried, finally recrystallized from appropriate solvent. The physical properties of compounds (C_2-C_6) are listed in table 1 and the scheme of synthesis is given below (Scheme II).



Scheme II: Synthetic route for compounds(C_2-C_6)

Table 1: The physical properties of compound [C_1-C_6]

Comp. No	M.P ° C	Yield %	Rec. solvent	Molecular formula
C_1	199-200	91	Ethanol	$C_{17}H_{15}NO_2$
C_2	240-242	80	Ethanol	$C_{23}H_{17}N_5O_4$
C_3	235-237	82	Ethanol	$C_{23}H_{18}N_4O_2$
C_4	213-215	88	Ethanol	$C_{23}H_{18}N_3Cl$
C_5	198-200	85	Ethanol	$C_{23}H_{18}N_3Br$
C_6	108-110	79	Ethanol: Water 1 : 1	$C_{17}H_{15}N_3$

Results and Discussion

1. FT-IR and ^{1}H-NMR Study

The first part involve the synthesis of 2-(1,1-Dimethyl1,3-dihydro-benzo [e] indol-2-ylidene)-malonaldehyde and this compound was used as starting material for the synthesis of other compounds and was identified by FT-IR which exhibits characteristic bands in the following range. The bands at 3100 cm^{-1} assigned for the stretching vibration of (N-H), 3000 cm^{-1} to the (C-H aromatic), 2924 cm^{-1} to (C-H aliphatic) 1679 cm^{-1} to (C= O), 1617-1508 cm^{-1} to (C= C) and (C-N) band appears at 1220 cm^{-1}. The spectrum of ^{1}H-NMR to compound (C_1) appears the following data: 13.77 (s, 1H, NH), 9.70 (s, 2H, CHO), 7.33-8.01 (6H, Ar-H) and 1.95 (s, 6H, 2 CH_3).

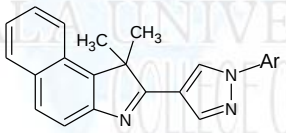
Compound (C_1) was reacted with hydrazine derivatives in absolute ethanol with addition of 1 ml glacial acetic acid to get compounds (C_2-C_6). The structure of thus prepared compounds has been characterized by both FT-IR and ^{1}H-NMR spectra. Compound C_2 was prepared from reaction of compound C_1 with 2,4-dinitrophenylhydrazine. The FT-IR of compound C_2 demonstrate the following stretching bands: (1647 cm^{-1}) for stretching vibration of C=N, while (1616-1577 cm^{-1}) for (C= C) stretching vibration of double bonds. The bands of stretching vibration of NO_2 group at (1328,1541 cm^{-1}), The success of reaction was confirmed by the disappearance of the (C=O) stretching vibration band at (1679 cm^{-1}) shown in Table 2, the ^{1}H-NMR spectrum of compound (C_2) was extracted the following data :7.3-8.3 (9H,Aromatic H), 10.15 (S, 1H, pyrazolyl -H) , 8.5 (S, 1H, pyrazolyl -H), and 1.7 (S, 6H, 2CH_3). Compound C_3 was prepared from the reaction of compound C_1 with 4-nitrophenylhydrazine. The FT-IR spectrum of compound C_3 indicated the following stretching bands: (1650 cm^{-1}) for stretching vibration of C=N, while (1566-1599 cm^{-1}) for (C= C) stretching vibration of double bonds. The bands at (1339,1526 cm^{-1}) was assigned to the stretching vibration of NO_2 group. The spectrum of ^{1}H-NMR of compound (C_3) appears to show the following data :7.4-8.5 (10H,Aromatic H), 9.48 (S, 1H, pyrazolyl -H, 8.5 (S, 1H, pyrazolyl -H), and 1.7 (S, 6H, 2CH_3).

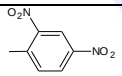
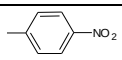
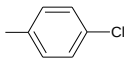
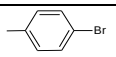
Compound C_4 and C_5 was prepared from reaction of compound C_1 with 4-chlorophenyl hydrazine hydrochloride and 4-Bromophenyl hydrazine hydrochloride respectively. The FT-IR

spectrum of compound C_4 appearance is a stretching bands: (1610 cm^{-1}) for stretching vibration of C=N, the bands (1519-1573 cm^{-1}) for stretching vibration of (C= C) double bonds. The bands at (3056 cm^{-1}) assigned to the stretching vibration (aromatic C-H). The spectrum of ^{1}H-NMR of compound (4) appears with the following data :7.4-8.3 (10H, Aromatic H), 9.46 (S, 1H, pyrazolyl -H, 8.5 (S, 1H, pyrazolyl -H), and 1.7 (S, 6H, $2CH_3$).

The spectrum of ^{1}H-NMR to compound (C_5) appears to show the following data :7.5-8.3 (10H, Aromatic H), 9.57 (S, 1H, pyrazolyl-H, 8.7 (S, 1H, pyrazolyl-H), and 1.8 (S, 6H, 2CH3). Finally compound C_6 was prepared from the reaction compound C_1 with hydrazine hydrate. The spectrum of FT-IR to compound C_6 appearance with the prominent following stretching bands: (1640 cm^{-1}) for stretching vibration of C=N, while (1491-1531 cm^{-1}) for (C= C) stretching vibration of double bonds and finally the bands at (3272 cm^{-1}) was assigned to the N-H group stretching vibration.

Table 2: Spectral data of compounds [C_2- C_6]



Comp. No.	Ar.	Characteristic bands of FT-IR spectra (cm^{-1}, KBr)				
		υC=C ar.	υC-H ar.	υC-H alph.	υC=N	Others
C_2		1616-1577	3093	2976	1647	ν NO_2 1328-1541
C_3		1566-1599	3100	2939	1650	ν NO_2 1339-1526
C_4		1519-1573	3056	2976	1610	ν C-Cl 747
C_5		1493-1570	3071	2983	1628	ν C-Br 783
C_6	-H	1491-1531	3007	2960	1640	ν N-H 3272

2. Computational Study

According to DFT- B3LYP / 3-21G calculations, it can be concluded that the real geometry of the sixth prepared compounds depend on the rule that: the large HOMO-LUMO energy gap, the most stable compound. So as shown in table 3, that all these prepared compounds showed a high value of E_{GAP} which can be arranged according to the values of E_{gap}.. C_1 have a highest value, C_6, C_4, C_5, C_2, and C_3 have the lowest value of E_{gap}.. The geometry of these compounds are shown in Figureureures (1- 6).

Table 3: The energy gap of the prepared componds

Compound no.	HUMO (ev)	LUMO (ev)	Egap(ev)
C_1	-11.199	-4.036	7.163
C_2	-10.752	-4.664	6.088
C_3	-10.805	-4.755	6.050
C_4	-10.782	-4.074	6.708
C_5	-10.615	-4.065	6.550
C_6	-10.813	-4.050	6.753

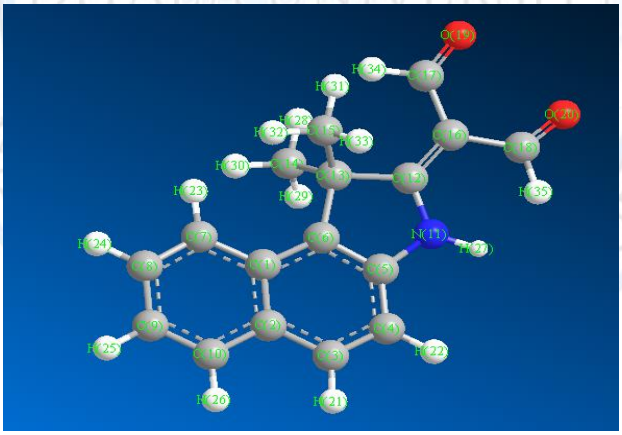


Figure1: Geometry of C_1 compound by compound by DFT-B3LYP/3-21G method

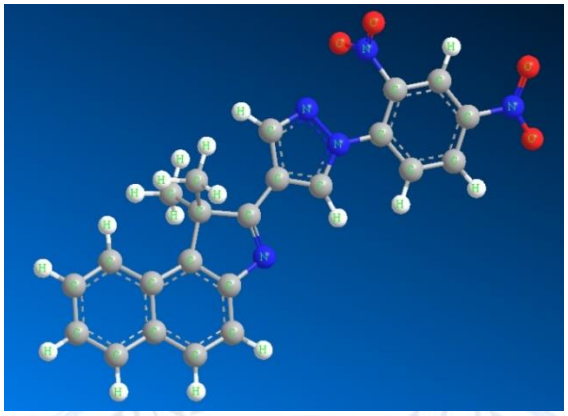


Figure 2: Geometry of C_2 DFT-B3LYP/3-21G method

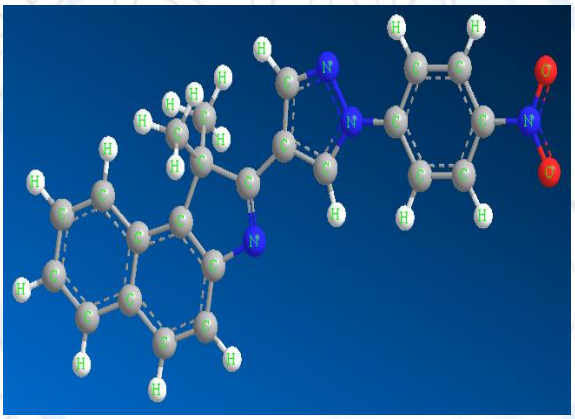


Figure 3: Geometry of C_3 compound by compound by DFT-B3LYP/3-21G method

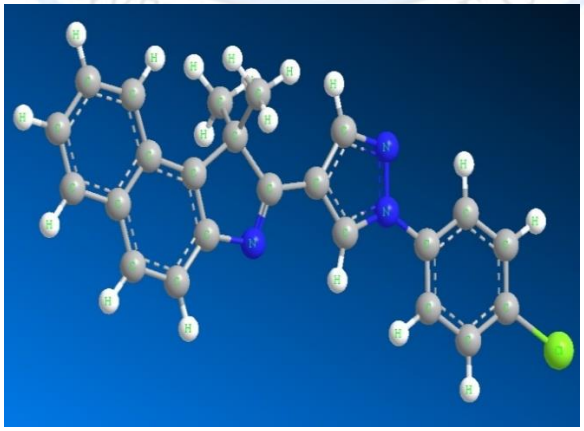


Figure 4: Geometry of C_4 DFT-B3LYP/3-21G method

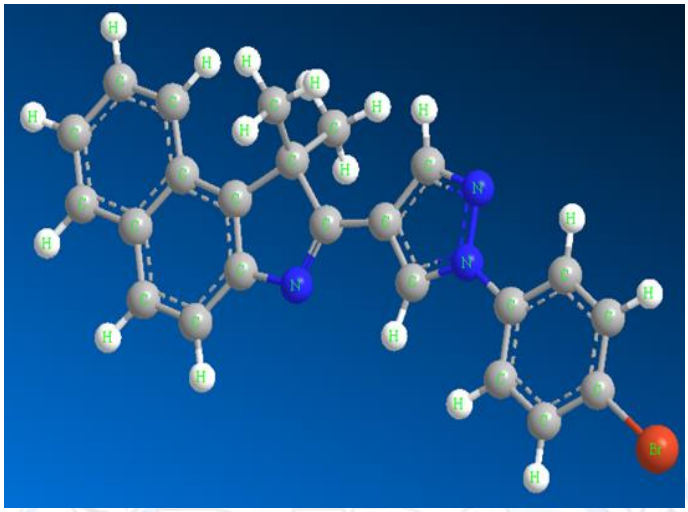


Figure 5: Geometry of C_5 compound by compound by DFT-B3LYP/3-21G method

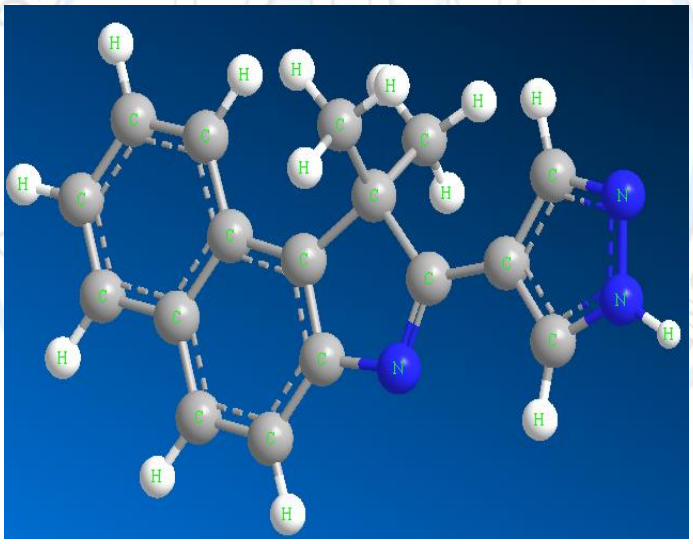


Figure 6: Geometry of C_6 DFT-B3LYP/3-21G method

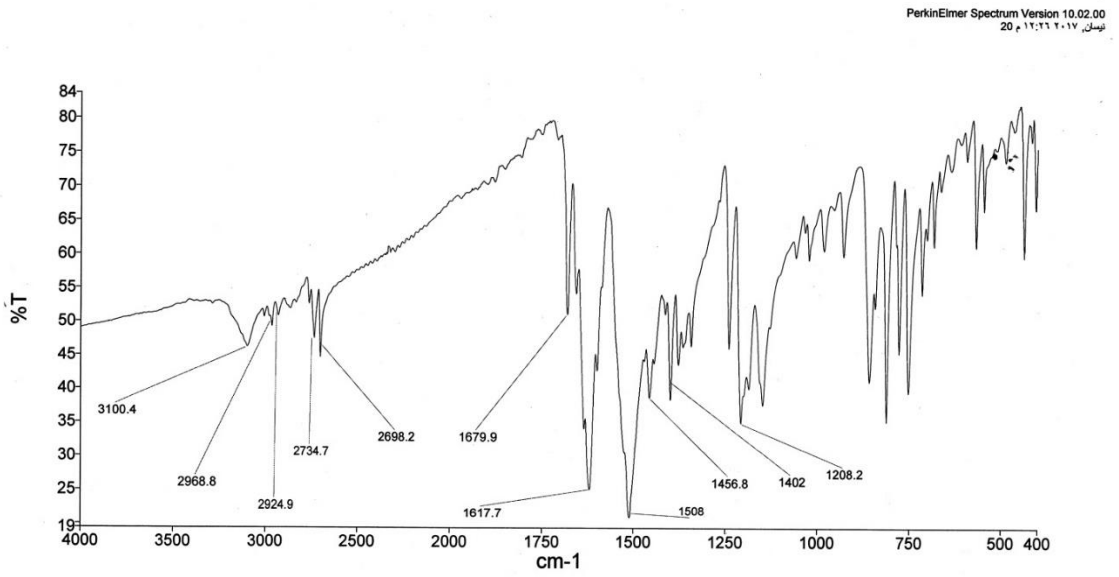


Figure 7: The spectrum FT-IR of compound C_1

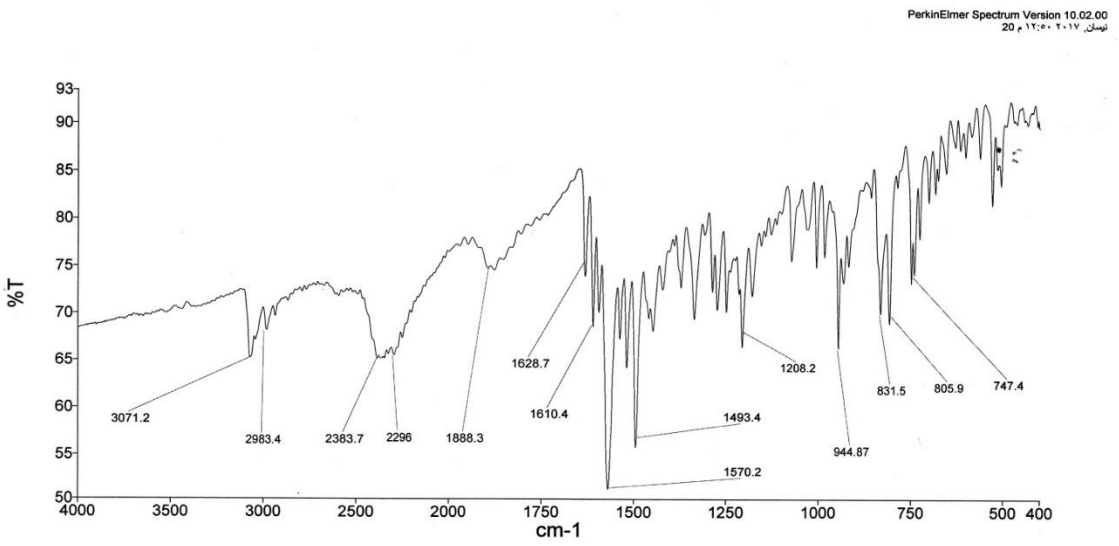


Figure 8: The spectrum FT-IR of compound C_5

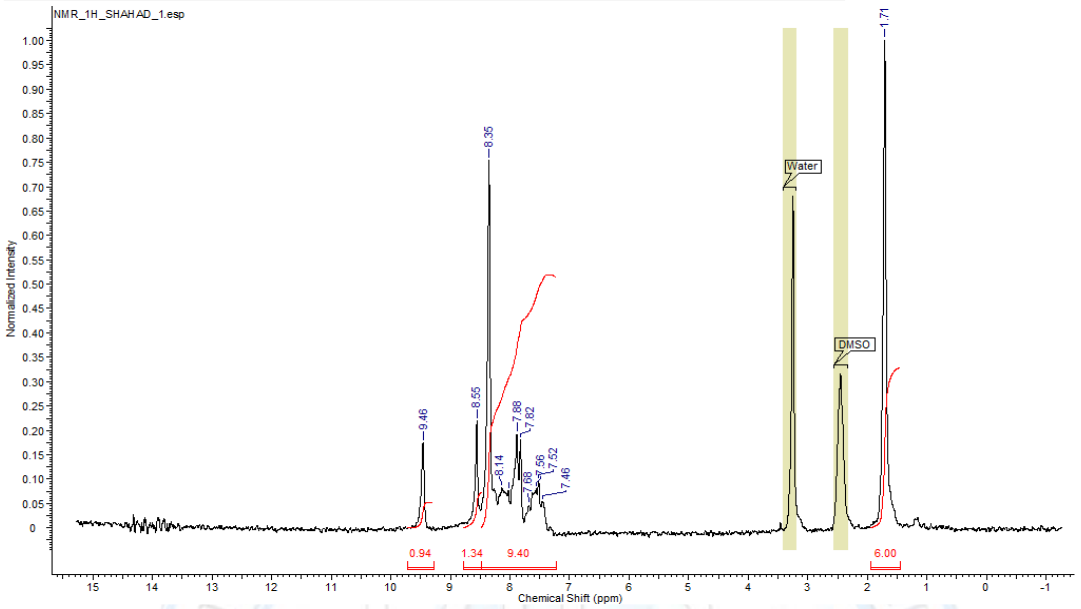


Figure 9: The ^{1}H-NMR spectrum of compound C_4

Conclusion

In the present work, new derivatives of pyrazole compounds derived from 1, 1, 2-Trimethylbenz[e] indole were synthesized and identified by melting point and spectral methods "(FT-IR, ^{1}H-NMR)". The geometry of the synthesized compounds were optimized with DFT-B3LYP/3-21G method.

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