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Efficient Synthesis of highly new substituted Imidazoles starting from Benzil using $KMnO_4$ as an efficient catalyst

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Abstract

Reaction of Benzil with an aldehyde, 4-trityl aniline and NH_4OAc under reflux gave highly substituted imidazoles in good yields using accessible and nontoxic $KMnO_4$ as catalyst under mild reaction conditions. This method is simple, efficient and eco-friendly. All imidazoles were characterized using FT-IR, Mass spectrometry, ^{1}H-NMR and ^{13}C-NMR Nuclear magnetic resonance spectral techniques.

KEYWORDS: Highly substituted imidazoles, Benzil, aromatic aldehyde, tritylaniline, (MCR) multi-component reaction.

1. Introduction:

Heterocyclic compounds containing imidazole ring systems have many pharmaceutical activities and play fundamental roles in biochemical processes[1]. Imidazole is a five-membered ring heteroaromatic compound with two nitrogenatoms at 1 and 3[2].In 1882, Redziszewski and Japp proposed the first synthesis of the imidazole core, starting from

1,2-dicarbonyl compounds, aldehydes and ammonia, to obtain 2,4,5-triarylimidazoles[3-5]. Highlysubstituted imidazoles are also the key intermediates in the synthesis ofmany important drugs. Omeprazole[6], Pimobendan[7], Losarton[8], Olmesartan[9], Eprosartan[10] and Triphenagrel[11] are some of the leading drugs in the market withdiverse functionality.Imidazoles possess various important biological properties includingfungicidal, herbicidal, and plant-growth regulator activities[12, 13]. Some of theimidazolesshow antiviral and anticancer properties[14]. Substituted imidazoles arein the core portion in many bioactive molecules such as losartan and olmesartan[15].Thus, the synthesis of imidazoles is an important task in medicinal chemistry. Themethods for the synthesis of other substituted imidazoles starting from benzil are limited[16]. The aim of this study was to synthesize new imidazoles derivatives with high biological activity.

2. Experimental and method:

2.1 Instrumental analysis:

Melting point apparatus, a status thermal point apparatus (England), was used for measuring melting points. IR spectra were recorded by using SHIMADUS FT.IR-8400 Affinity (JAPAN). ^{1}H-NMR and ^{13}C NMR spectra were recorded in chloroform solvent using JEOL-JNM-EX 500MHz, type advance Ultrasheild instrument (Japan), and BRUKER 120 MHz type AVANCE III DRX 500 (GERMANY). All chemicals and solvents were purchased from Sigma-Aldrich, Merck and Fluka, and were used as received.

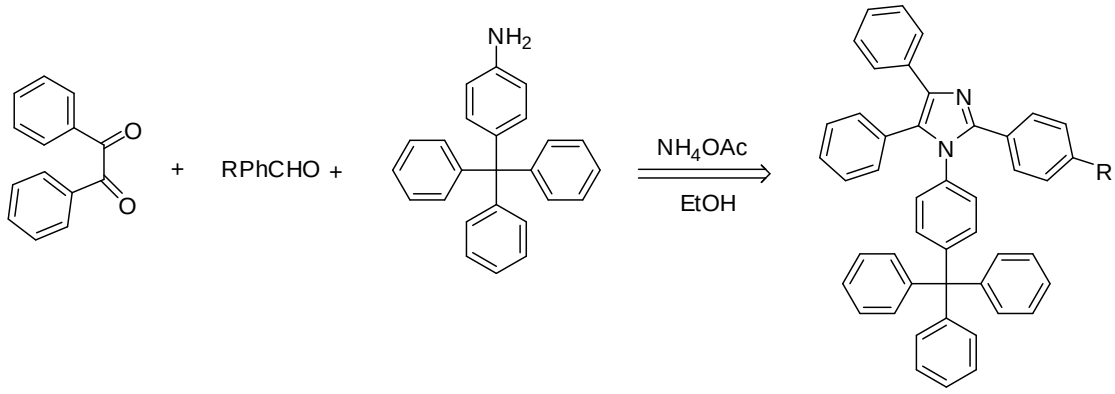
2.2 General Procedure for the Synthesis of highly Substituted Imidazoles:

Benzil (0.210g, 1 mmol), 4-tritylaniline (0.335g, 1 mmol), $KMnO_4$ (0.047g, 0.03 mmol) and 10 mL ethanol were placed in a 50 mL flask and were stirred for one hour to make homogeneous solution (1). Ethanol (10 mL), aromatic aldehydes (1 mmol), $KMnO_4$(0.03 mmol) and excess of ammonium acetate (0.115g, 1.5 mmol) were mixed thoroughly in a 50 mL beaker flask to make solution (2). After that, the solution (2) was added dropwise to the solution (1), and the mixture was refluxed for a specific time[20]. The reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room

temperature and then poured in ice water (50 mL). The precipitated solid was filtered, washed several times with water, dried and purified by column chromatography using (n-hexane ethyl acetate) (9:1) to get the corresponding 1,2,4,5-tetra aryl-imidazoles. The products were obtained in 50-56 % yield.

3. Results and Discussion:

The multi-component reaction (MCR) strategy was used to the synthesis of highly substituted imidazole by reacting benzil, various substituted aldehydes, 4-trityl aniline and ammonium acetate in presence of $KMnO_4$ as catalyst in ethanol at reflux condition[17]. The synthetic routes to the target imidazoles are outlined in Scheme 1.



Scheme (1): Synthesis of highly substituted Imidazoles; R=H (**T1**), CH_3 (**T2**), OCH_3 (**T3**) and Br (**T4**)

The structure of all the synthesized compounds (T1-T4) were confirmed using melting point (m.p.), Fourier transform-infrared spectra (FT-IR), Mass spectrometry (MS), ^{1}H-NMR and ^{13}C-NMR Nuclear magnetic resonance (NMR) spectral techniques. All Spectral results are depicted in Figures (1 – 16). The results were in good agreement with the previous literature reports. FT-IR spectra of all the derivatives showed five important characteristic stretchingvibration bands. The band near 3100 cm^{-1} due to aromatic C-H. stretching, the band near2900cm^{-1}due to aliphatic C-H,

the band near 1600 cm^{-1} to aromatic C=C stretching and the band near 1500 cm^{-1} to C=N stretching vibrations, the band near to 1300 due to C-N stretching. In order to determine the structure of all synthesized products,^{1}H and ^{13}C-NMR spectral analysis were also carried out. The peaks in the range of δ 6.6-8.0 ppm were due to the phenyl rings protons[18]. The splitting pattern was notclear for these derivatives. In ^{13}C-NMR spectra, the Peaks at around 120-140 ppm were for the aromatic carbons of the derivatives. The peak around 65 ppm for the quaternary carbon, the peak around 160 due to *para* carbon of substituted benzaldehyde andthe peak above 140 ppm for C-2 carbon of imidazole ring[19]. M^{+} peak of MS spectra also added evidence to the product formation, all synthesized compounds were confirmed by characterization the peaks at (615, 628.1, 644.4 and 692 m/z) which belong to T1, T2, T3 and T4 respectively. The advantages of this procedure are the use of ethanol as a green solvent, a cheap, readily available oxidizing agent and high product yields when starting from benzil.

4. Anti-bacterial and Anti-fungal activity:

All synthesized imidazoles, except T1, showed activity either as antibacterial or antifungal; or against both. The results of antibacterialand anti-fungal screening of all the newly synthesized compounds, T2, T3 and T4, arepresented in table 2. The results, as shown in table 2, indicate thatT2, T3 and T4 imidazoleshavea moderate anti-bacterial activity with value in therange of (6-9) mg/ml in DMSO against *S. Aureus*. Some of these imidazolesshowed a moderate to good antifungal activity with value in the range of 8-12 mg/ml in DMSO.Compounds T2, exhibited a moderate activity against fungal strains. Compounds T2and T4 showed good activity against *Tricophyton*, compound T3 showed a moderate activity against *A.niger*.

5. Conclusion:

A new series of imidazoles were synthesized and their structures were confirmed using IR, ^{1}H-NMR, ^{13}C-NMRand Mass spectral data spectroscopy. Three compounds exhibited antibacterialactivity but they showed moderate antifungal activity. Further bioassay, optimizationand quantitative structure-activity relationship of the highly substituted imidazoles compounds are underway.

Table (1): some physical data of new tetra-substituted imidazoles

Symbol of new tetra substituted imidazole		Name of tetra substituted imidazole	Time in mint	Colour	Melting Point (0C)	Yield (%)	R_f*
T1	H	2,4,5-triphenyl-1-(4-tritylphenyl)-1H-imidazole	70	white	291-294	56	0.28
T2	4-CH_3	4,5-diphenyl-2-(p-tolyl) -1-(4-tritylphenyl)-1H-imidazole	85	white	201-204	54	0.17
T3	4-OCH_3	2-(-4-methoxy)-4,5-diphenyl-1--(4-tritylphenyl)-1H-imidazole	110	white	212-214	55	0.22
T4	4-Br	2-(-4-bromophenyl)-4,5-diphnyl-1-(4-tritylphenyl)-1H-imidazol	80	Pale yellow	≥300	50	0.25

***in eluent n-hexane:ethylacetate (ratio, 9:1)**

Table (2) antimicrobial screening data (zone of inhibition in nm) of synthesized compounds

Compd.	Inhibition diameter (mm)		Inhibition diameter (mm)		
	***S. Aureus**	***E. coli**	***C.albicans**	***A.niger**	***Tricophyton***
T2	9	-	8	-	10
T3	8	-	-	8	-
T4	6	-	-	-	12

(-)= zero activity, S=staphylococcus=Escherichia, C=Candida, A=Aspergillus.

6. Spectroscopic analysis of synthesized compounds:

2,4,5-triphenyl-1-(4-tritylphenyl)-1H-imidazole (T1): IR (KBr, cm^{-1}), υ_{max}: 3066, 1608, 1508 and 1298. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.95-6.61(m, 34H).^{13}C-NMR (126 MHz, $CDCl_3$) δ 162.14, 154.90, 146.24, 143.06, 135.98, 133.86, 131.06, 130.14, 128.91, 128.02, 126.84, 126.44, 126.33, 124.87, 124.72, 113.18, 76.27, 76.02, 75.76, 63.28 and 25.1. MS (M^+) 615.

4,5-diphenyl-2-(p-tolyl)-1-(4-tritylphenyl)-1H-imidazole(T2): IR (KBr, cm^{-1}) υ_{max}: 3055, 2862, 1666, 1589 and 1323. ^{1}H-NMR (500 MHz, $CDCl_3$) δ7.95-6.6(m, 33H) and 1.29(s, 3H).^{13}C-NMR (126 MHz, $CDCl_3$) δ 168.91,151.99, 147.38, 144.52, 133.77, 133.17, 132.23, 131.29, 129.07, 128.77, 127.98, 127.65, 127.48, 125.86, 125.41, 114.32, 68.03 and 29.86. MS (M^+) 628.1.

2-(-4-methoxy)-4,5-diphenyl-1-(4-tritylphenyl)-1H-imidazole(T3): IR (KBr, cm^{-1}) υ_{max}: 3028, 2858, 1616, 1566 and 1357. ^{1}H-NMR (500 MHz $CDCl_3$) δ 7.85-7.0(m, 33H) and 3.98(s,3H).^{13}C NMR (126 MHz, $CDCl_3$) δ160.48, 151.95, 147.83, 146.20, 132.72, 132.13, 132.13, 131.09, 127.93, 127.80, 126.30, 122.03, 121.52, 114.45, 64.85 and 55.15. MS (M^+) 644.4.

2-(-4-bromophenyl)-4,5-diphenyl-1-(4-tritylphenyl)-1H-imidazole (T4): IR (KBr, cm^{-1}) υ_{max}: 3055, 1604, 1492, 1319 and 1022. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.95-6.6(m, 33H).^{13}C-NMR (126 MHz, $CDCl_3$) δ 162.12, 153.70, 146.23, 144.59, 141.09, 131.06, 130.13, 128.90, 128.57, 128.01, 127.56, 126.84, 126.48, 126.40, 126.32, 124.92, 124.71, 124.27, 113.19, 75.75 and 65.24. MS (M^+) 692.

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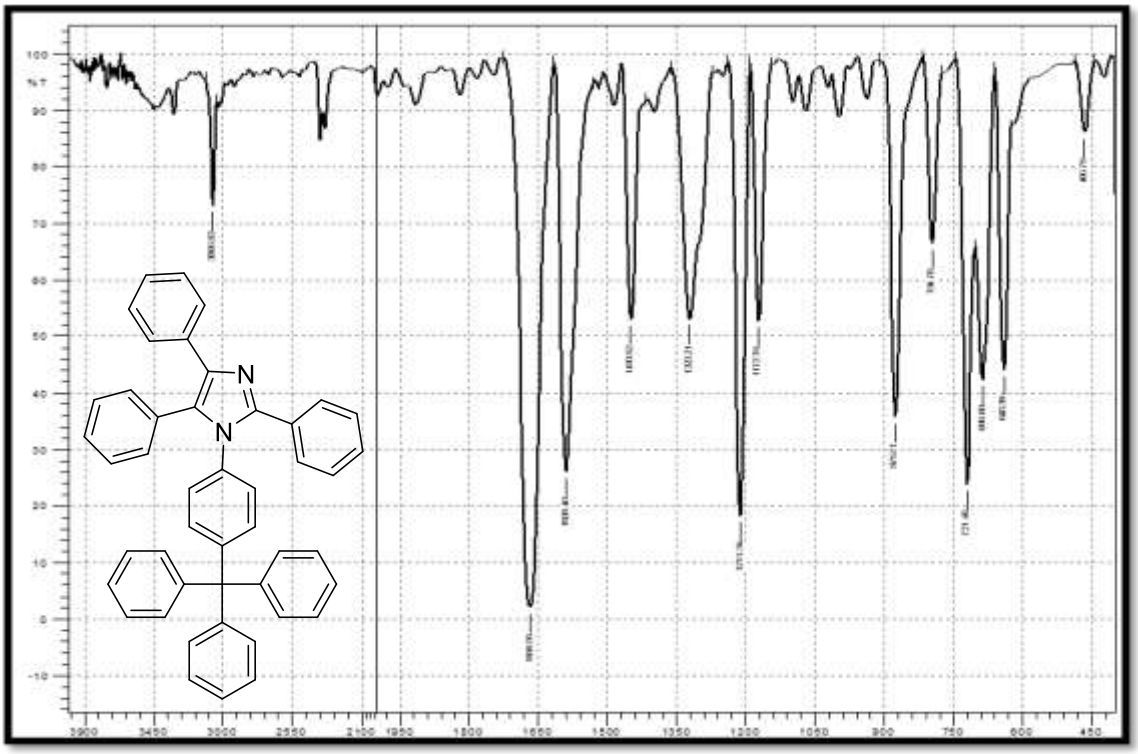

Fig (1) FT-IR of compound [T1]

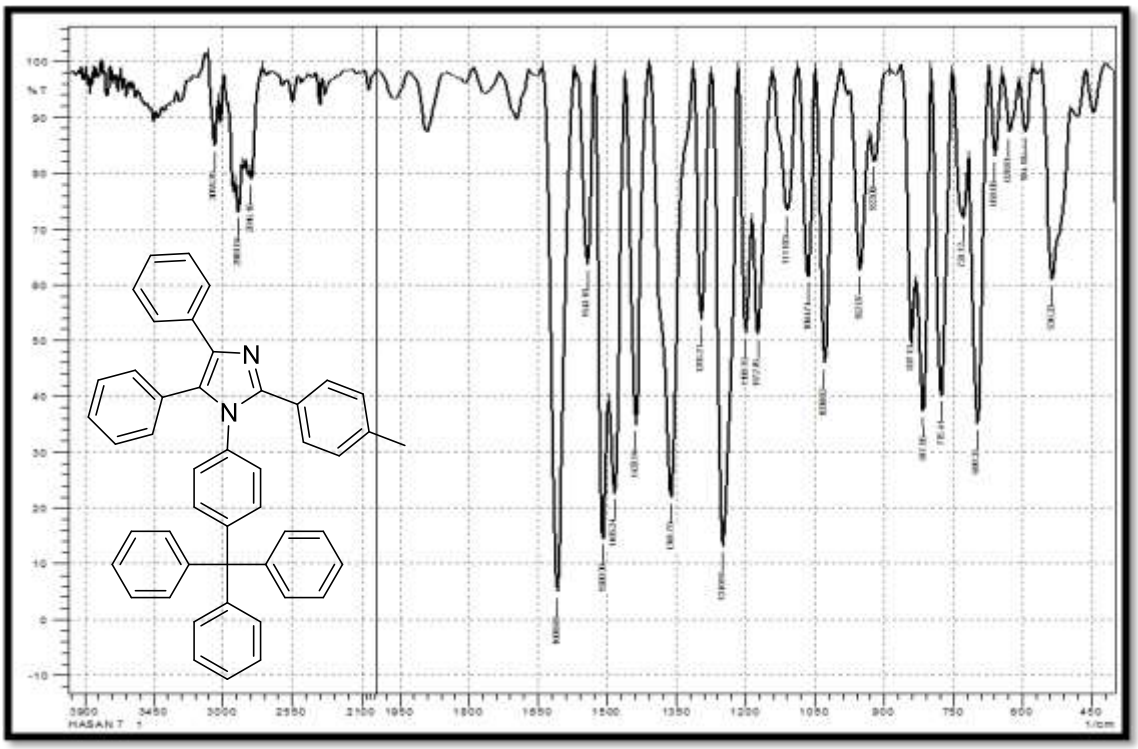

Fig (2) FT-IR of compound [T2]

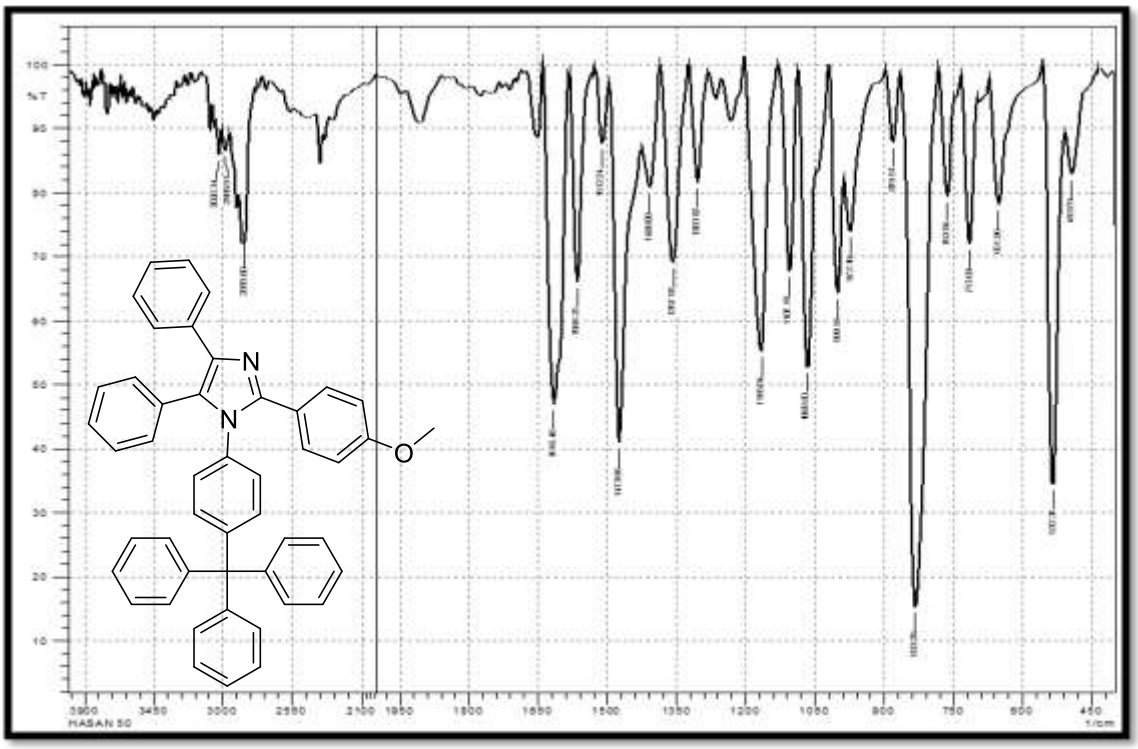

Fig (3) FT-IR of compound [T3]

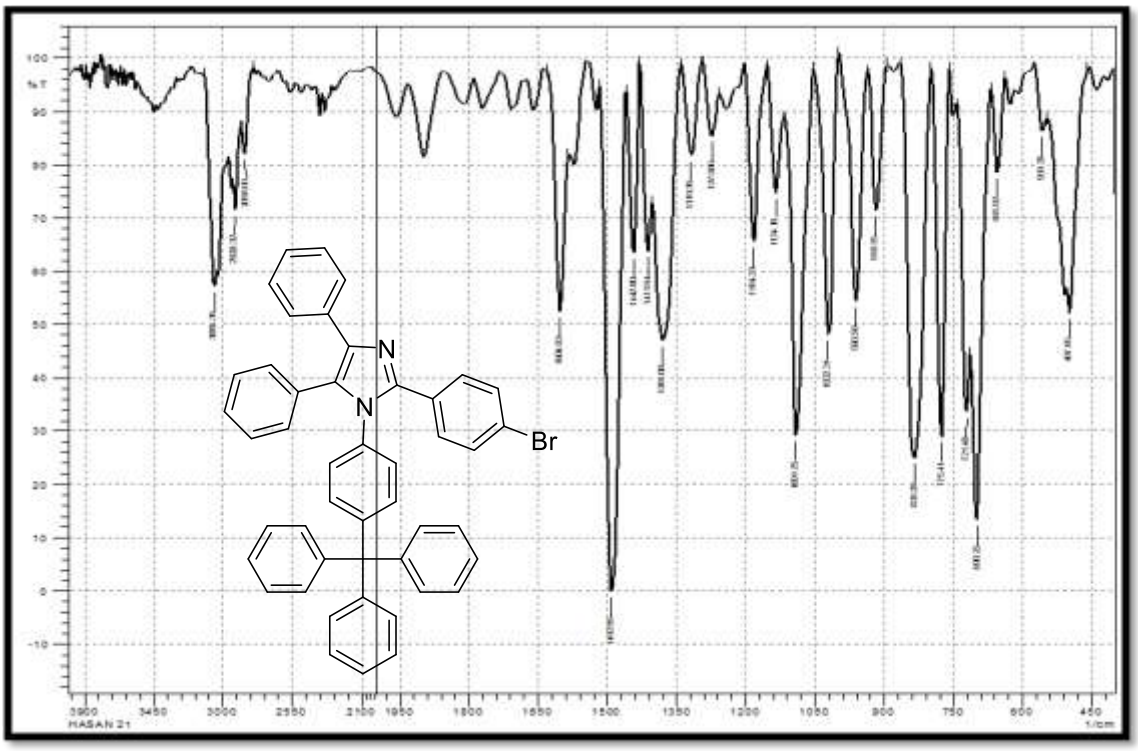

Fig (4) FT-IR of compound [T4]

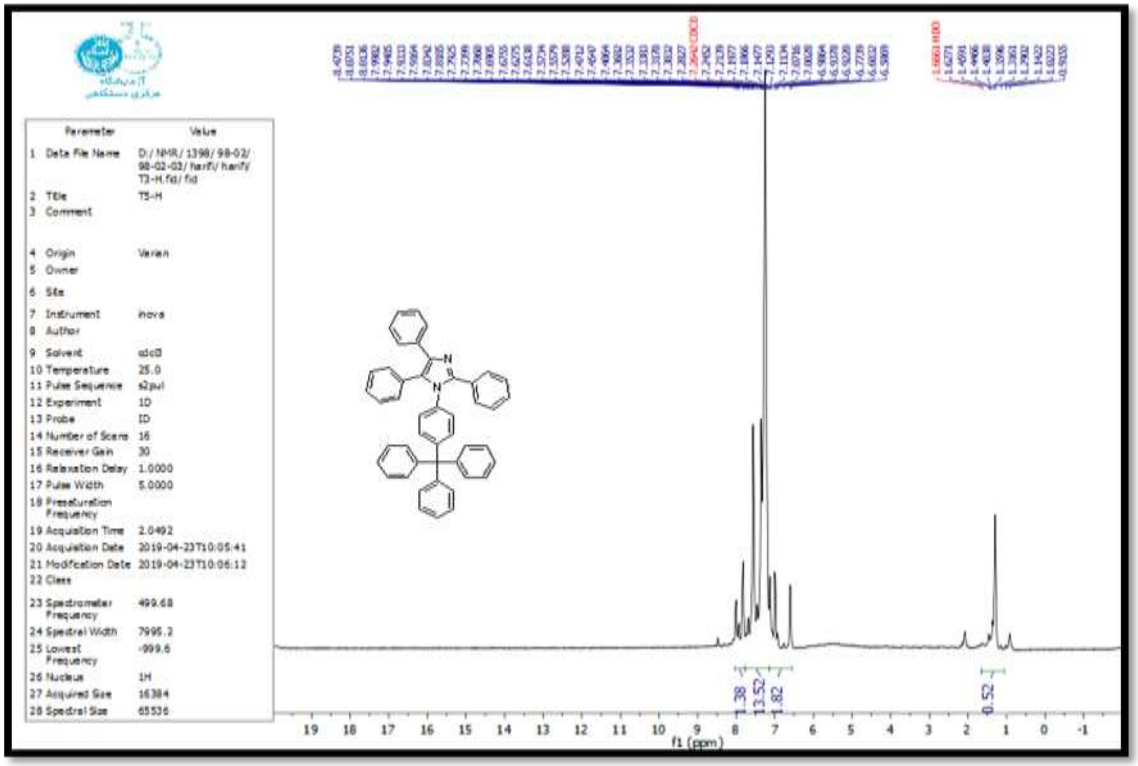

Fig (5) H-NMR of compound [T1]

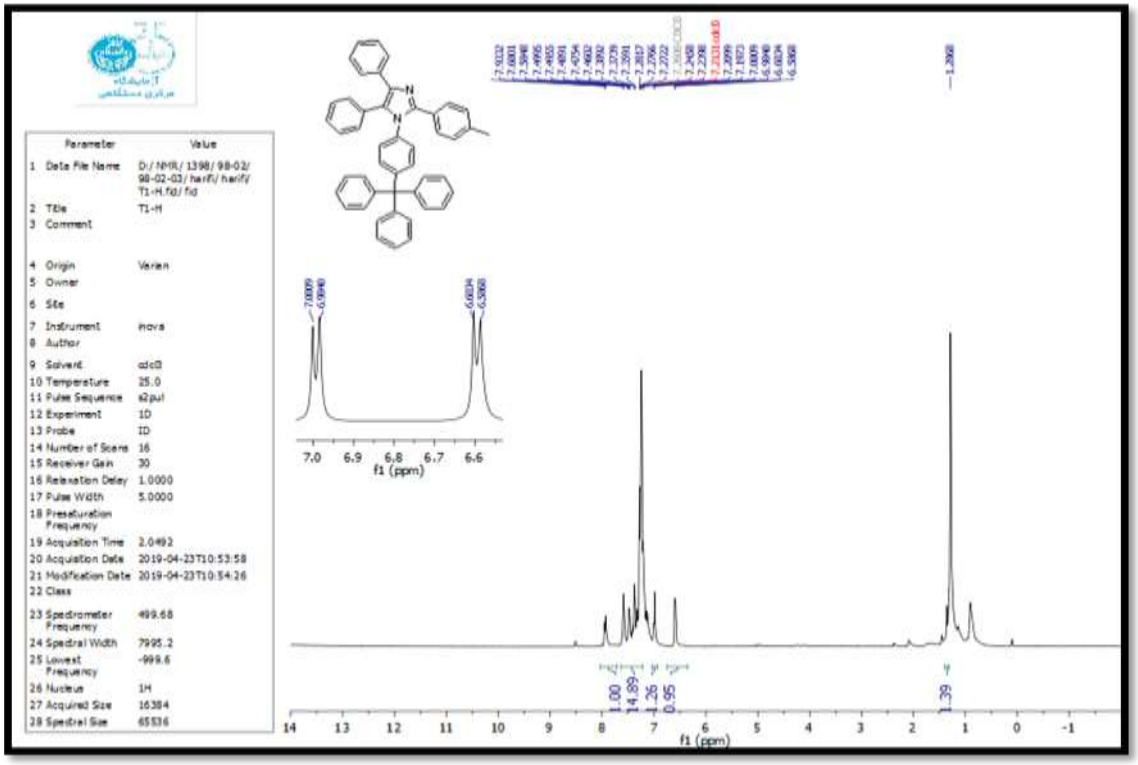

Fig (6) H-NMR of compound [T2]

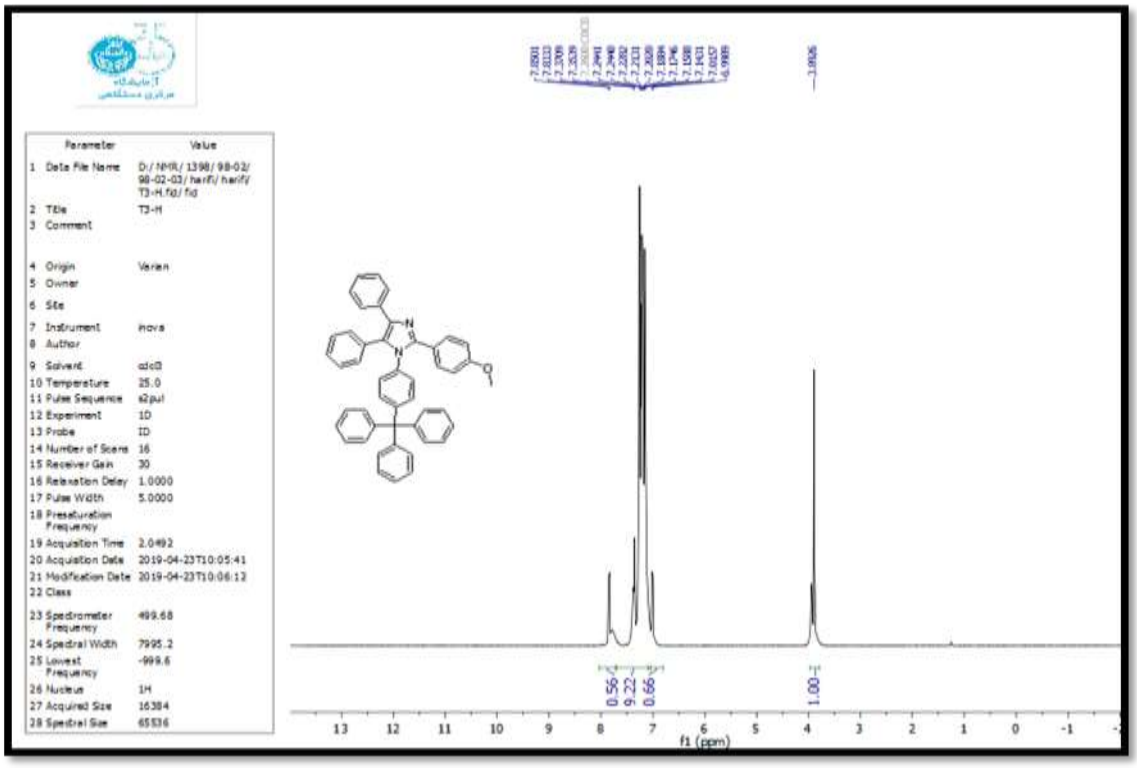

Fig (7) H-NMR of compound [T3]

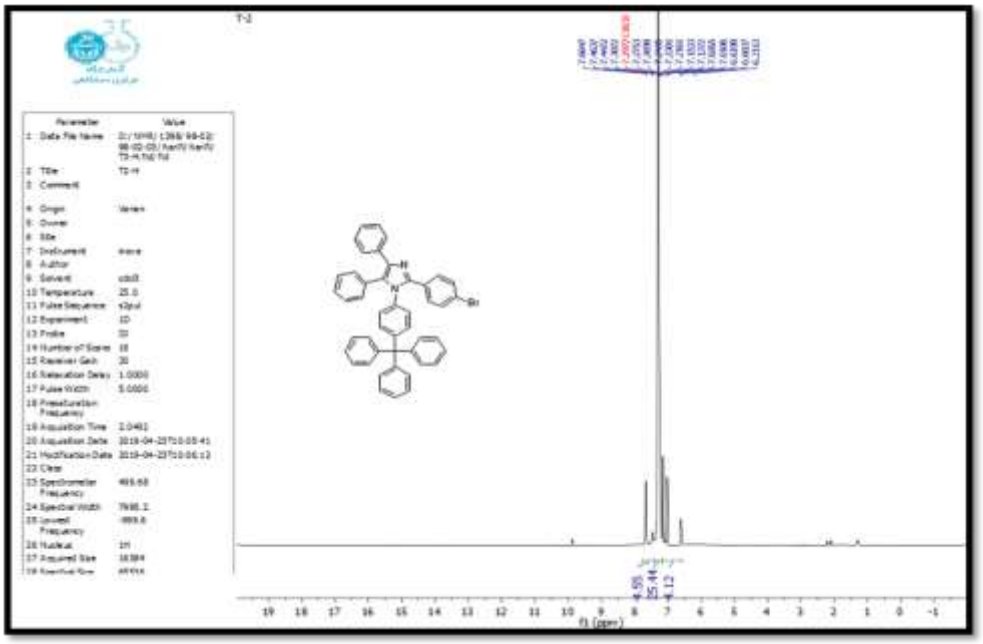

Fig (8) H-NMR of compound [T4

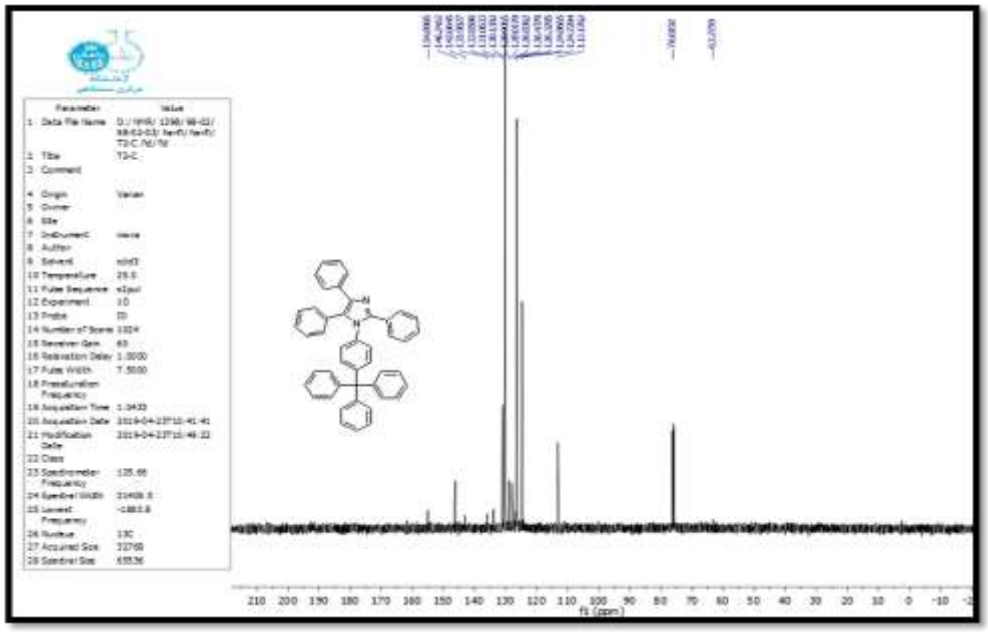

Fig (9) ^{13}C-NMR of compound [T1]

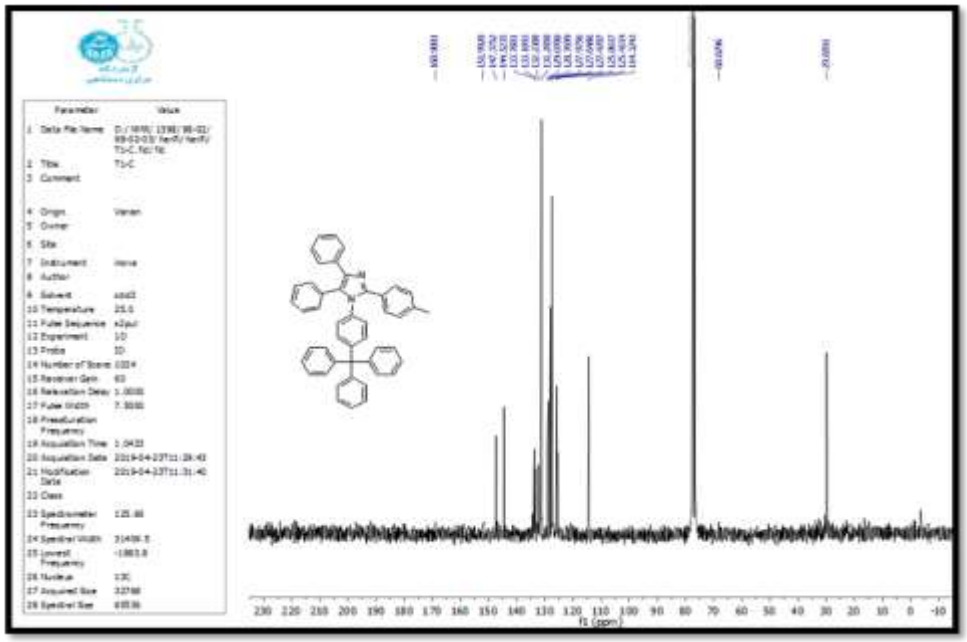

Fig (10) ^{13}C-NMR of compound [T2]

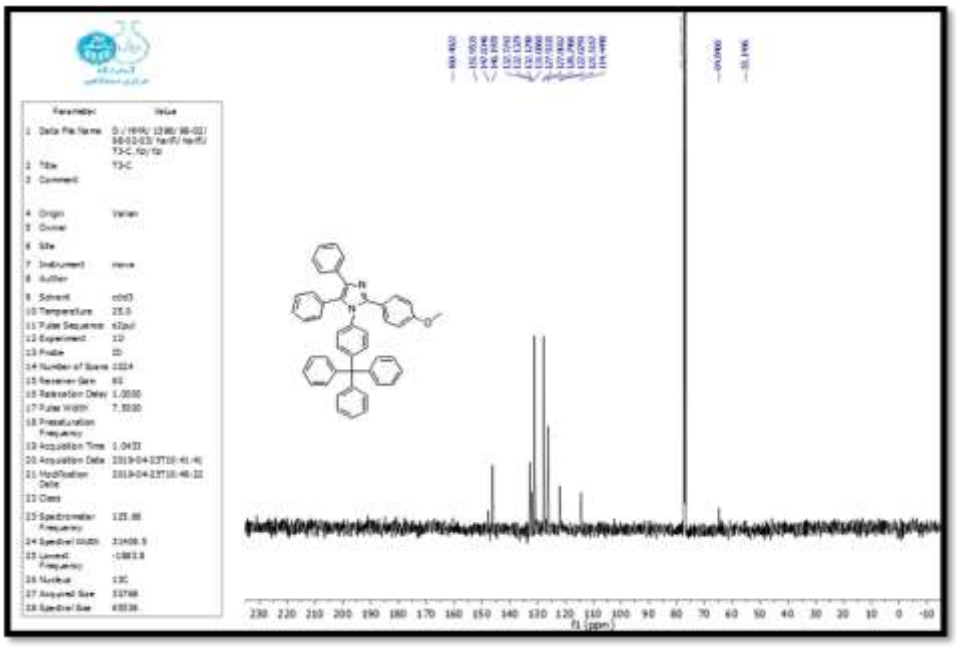

Fig (11) ^{13}C-NMR of compound [T3]

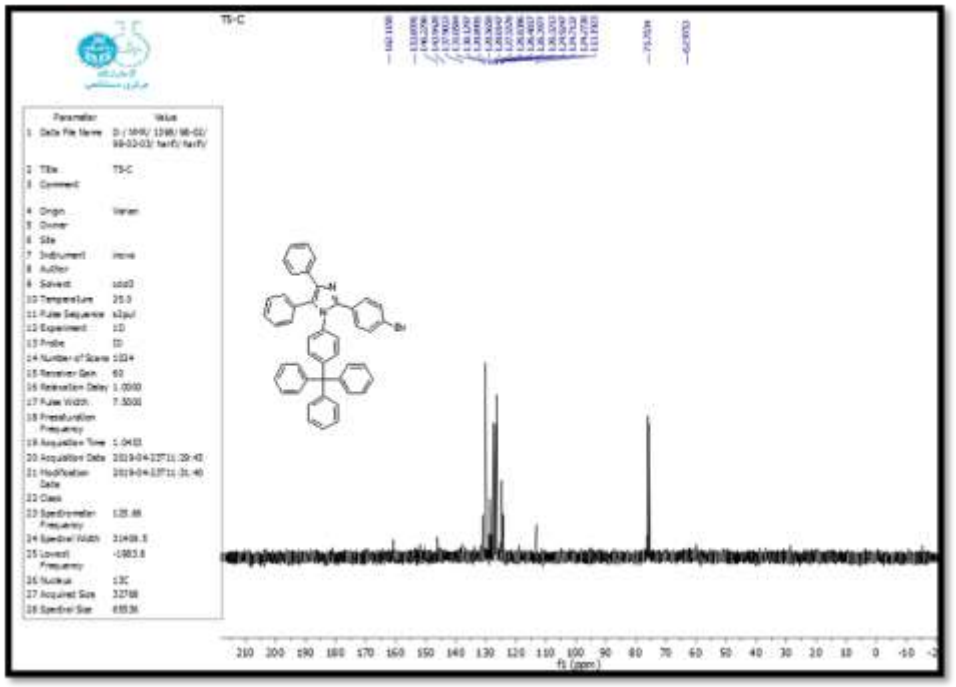

Fig (12) ^{13}C-NMR of compound [T4]

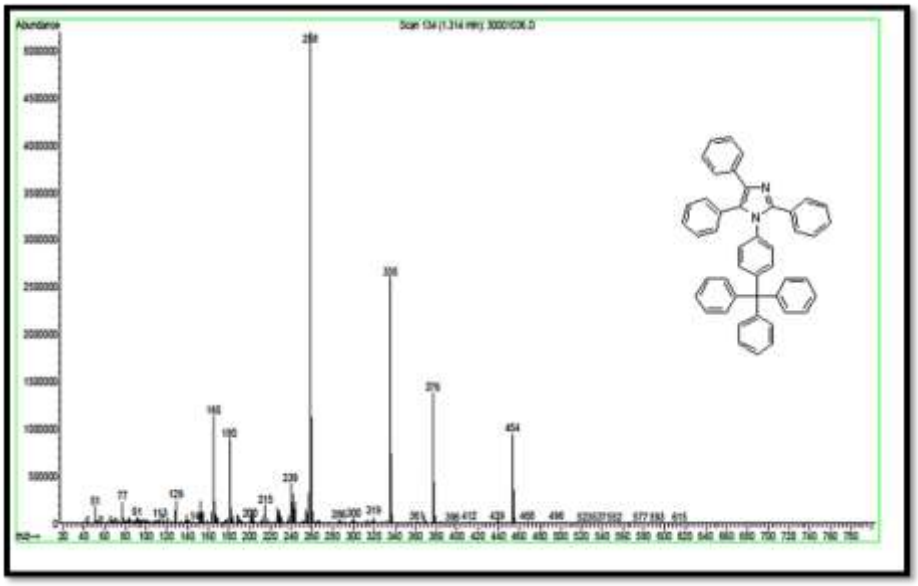

Fig (13) mass of compound [T1]

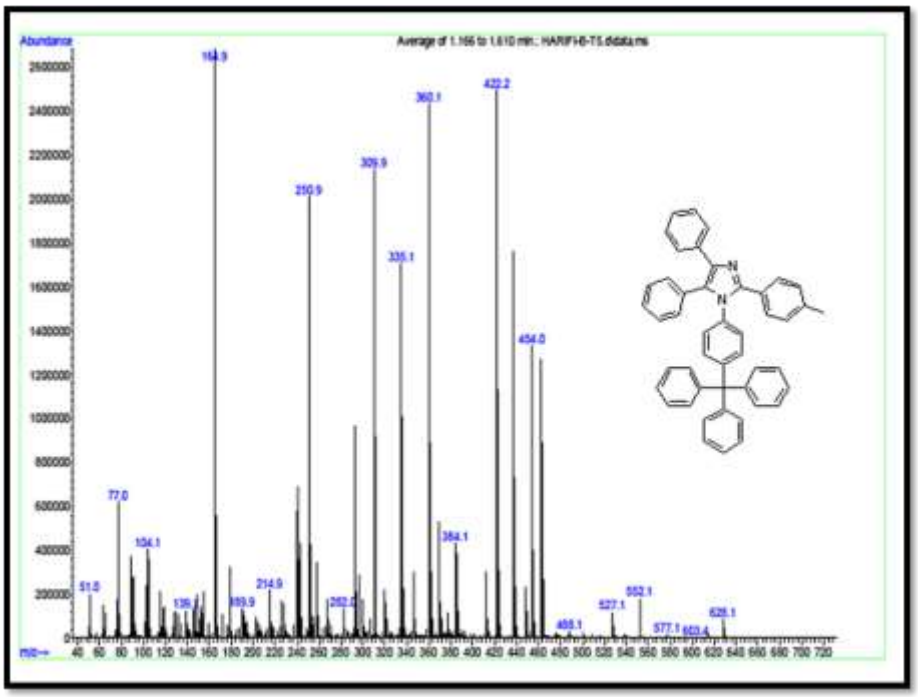

Fig (14) mass of compound [T2]

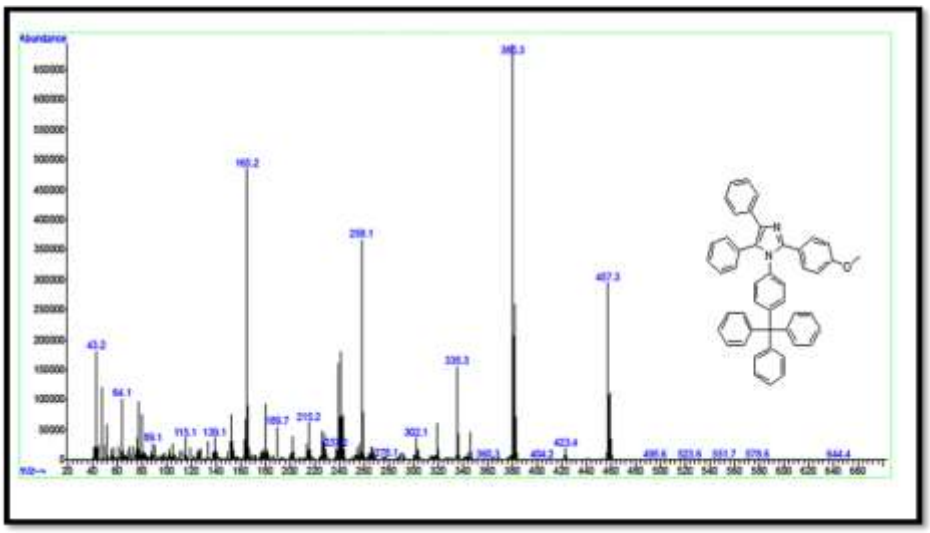

Fig (15) mass of compound [T3]

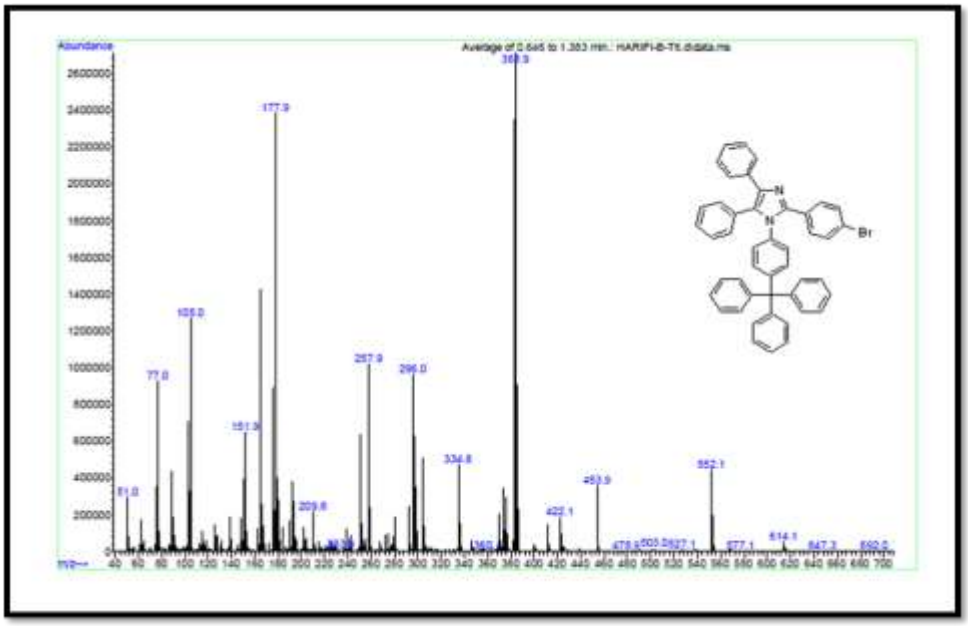

Fig (16) mass of compound [T4]

تحضير وتشخيص بعض مركبات الايميدازول الجديدة باستخدام برمنكنات البوتاسيوم $KMnO_4$ كعامل مساعد

حسن عريمش جرف، باسل عبد المهدي صالح، علي هاشم عيسى

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الخلاصة:

حضرت اربعة ايميدازولات معوضة جديدة من تفاعل البنزل والبنزالديهايد المعوض وترايتايل بطريقة التصعيد الارجاعي وباستخدام العامل المساعد غير السام وبظروف تفاعل معتدلة، واعطى هذا التفاعل حصيلة جيدة. اذ تعتبر هذة الطريقة بسيطة وفعالة وصديقة للبيئة. شخصت المركبات المحضرة بهذه الدراسة بمطيافية الاشعة تحت الحمراء FT-IR و مطيافية الرنين النووي المغناطيسي NMR بالاضافة الى استخدام مطيافية الكتلة MS.

الكلمات المفتاحية: ايميدازول رباعي التعويض، بنزل، بنزالديهايد معوض، تفاعل متعدد المكونات، ترايتايل انيلين