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Synthesis and identification Of Four Membered Rings Heterocyclic Compounds Derived From Trimethoprim

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ABSTRACT

This study includs the preparation and identification of four membered rings Hetrocyclic Compounds derived from Trimethoprim by reaction Schiffs' bases(1a-h)(prepared by reaction some aromatic aldehyde with Trimethoprim using Microwave technique) with chloro acetyl chlorid in the presence of triethylamine , the prepared compounds were identified by I.R spectroscopy and some of them by NMR spectroscopy and C.H.N.S micro analysis.

Keywords: *Synthesis Four Membered Rings, Heterocyclic, Trimethoprim .*

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تحضير وتشخيص مركبات حلقية رباعية غير متجانسة مشتقة من البرايميثوبريم

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الملخص

هذا البحث يتضمن تحضير وتشخيص مركبات حلقية غير متجانسة رباعية مشتقة من البرايميثوبريم من خلال تفاعل قواعد شف *(1a-h)* (والتي حضرت من خلال تفاعل بعض الألديهايدات الاروماتية مع البرايميثوبريم باستخدام تقنية المايكروويف) مع الكلورو اسيتايل كلورايد بوجود التراي أثيل أمين، تم تشخيص المركبات المحضرة باستخدام التحليل الدقيق للعناصر بالاضافة لمطيافيتي الاشعة تحت الحمراء والرنين النووي المغناطيسي.

الكلمات الدالة: تحضير حلقات رباعية، حلقات غير متجانسة، ترايميثوبريم .

1. INTRODUCTION

Azetidine- 2- one compounds are classes of four membered rings containing three carbon atoms ,one nitrogen atom and carbonyl group commonly known as β-lactams, The first ring has been prepared by Staudinger [1] year in 1907, and it one of the biologically active compounds, Many Studies have proven to be effective against bacteria and anti-inflammatory [2], anti-Cancer[3],and the most widely used antibiotics such as Penicillins contains the β-lactum ring, You may get these rings through the electrophlic addition on (C=N) in Schiffs'

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bases derivatives[4], the Staudinger reaction ([2+2] ketene-imine cycloaddition reaction) is regarded as one of the most fundamental and versatile methods for the synthesis of (β-lactam) derivatives[5]. A series of novel azetedinones have been synthesized by cyclocondensation of various Schiff bases (1a-h) with chloroacetyl chloride in presence of triethylamine to give a four-membered heterocyclic ring derivatives[6] (2a-h).

2. EXPERIMENTAL

Melting points were determined in open glass capillaries and were found uncorrected. The purity of the compounds was checked by TLC. IR spectra were recorded in KBr on Shimadzu infrared Spectrophotometer Fourier Transform FT- IR 8400S. ^{1}H NMR spectra were recorded on a Bruker Ultrashield 400MHZ instrument in DMSO as solvent and TMS as an internal standard. Elemental analysis was carried out on a Eurovectro, EA 3000A, Italy. All reagents were purchased from (Aldrich,Scharlau,AlfaAesar,Solarbio) and used without further purification.

2.1.Synthesis of Schiffs' bases(N,N'-(5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diyl)bis(Schiffs' bases)) (1a-h)

A series of Schiff bases were prepared from the reaction of trimethoprim(TMP) (1 mole), with different aldehydes (2 moles), in presence of afew drops of (ethanol absolute and glacial acetic acid). A mixture was transfered to a round bottom flask, and was irradiated in microwave system for (2.5-5) min then the mixture was left to dry for (10-15) day and the formed crystals were filtered and washed with little cold ethanol and dried, the physical and analytical data for the prepared derivatives are shown in Table (1) .

2.2.Synthesis of 1,1'-(5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diyl)bis(3-chloro-4-(substituted)azetidin-2-one) (2a-h)

A mixture of Schiff base (1a-h) (0.005 mol) and triethyl amine [TEA] (0.01 mol) was dissolved in 1,4-dioxane (40 ml), cooled and stirred. To this well-stirred cooled solution chloro acetyl chloride (0.01 mmol) was added drop wise with in a period of 20 min, the reaction mixture was then stirred for an additional 3 hrs and left at room temperature for 48 hrs. The resultant mixture was concentrated, cooled, poured in to ice cold water, filter and

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then dired and recrystallization from absolute ethanol**[7]**. The physical properties data for the prepared derivatives are shown in Table (2) .

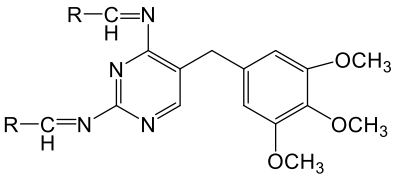
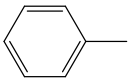
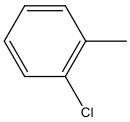
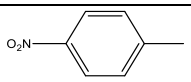
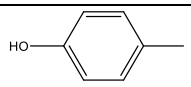
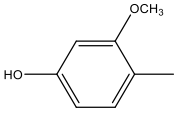
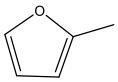
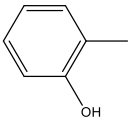
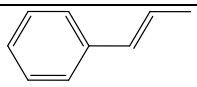


Table (1): physical properties of (N,N'-(5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diyl)bis(Schiffs' bases)) (1a-h)

Comp. No	R	Colour	Reaction Time min.	M.P C°	Yield %
1a		Milky	5.	75-78	82
1b		Yellow Greenish	4	66-69	90
1c		Orange	3	65-67	91
1d		Yellow	4.5	101-103	85
1e		White Green	4	70-73	78
1f		Dark Brown	3	107-109	86
1g		Orange	3.5	142-145	75
1h		Dark Yellow	2.5	78-80	88

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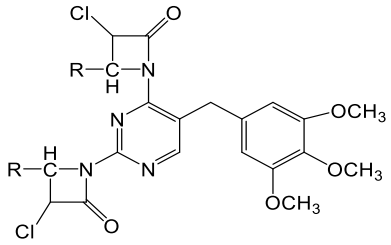
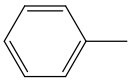
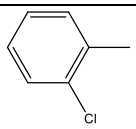
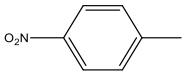
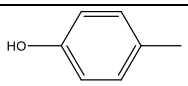
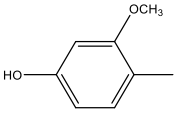
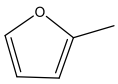
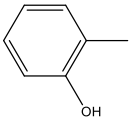
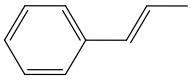


Table (2): Analytical data of1,1'-(5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diyl)bis(3-chloro-4- (substituted)azetidin-2-one) (2a-h)

Comp.No	R	Colour	M.P C°	Yield %
2a		White .	250-253	68
2b		Yellow	140-143	65
2c		Orange Yellowish	178-180	75
2d		Orange	165-168	60
2e		White	160-163	58
2f		Milky	260 dec	77
2g		White Yellowish	225-228	71
2h		Yellow	90-93	81

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3. RESULTS AND DISCUSSION

Schiff bases (1a-h) were prepared by mixing of trimethoprim(1) with substituted aromatic aldehydes , the reactions were performed under microwave irradiation. The compounds (1a-h) when reacted with chloroacetyl chloride in 1,4-dioxane in the presence of triethylamine gave 1,1'-(5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diyl)bis(3-chloro-4-(substituted)azetidin-2-one) azetidine- 2- one derivatives (2a-h). The reactions pathway is shown in **Scheme (1)**. The Schiff bases (1a-h) were then characterized by the elemental analysis, IR spectral studies and ^{1}H-NMR spectral studies. The IR spectra of the Schiff bases are recorded using the KBr disc and showed the prominent band at (1560-1670) cm-1 for the azomethine group and the disappearance of band to a group (NH_2) which was shown at (3300-3500) cm-1. The ^{1}H-NMR spectral data of Schiff base (1c) are shwon in Table (3) . These Schiff bases on cyclo-condensation reaction with chloro acetyl chloride afforded 2- azetidinone (2a-h) and the structures of compounds (2a-h) have been confirmed by IR spectral studies, some by elemental and ^{1}H-NMR spectral studies, the IR spectrum showed a band at (1622-1670) cm-1 for cyclic >C=O group and (621-802) cm-1 for the(C-Cl),and the ^{1}H-NMR spectral data of azetidine- 2- one Compound (2g) are shown in Table (3) [8,9] .

Table (3): FT-IR, ^{1}H-NMR spectral data for some synthesized compounds

	Spectra data		% Analysis		
	IR-Spectra(cm-1 KBr-pellets)	**^{1}HNMR – Spectra (DMSO) (ppm)**	**C (found)**	**H (found)**	**N (found)**
1a	2835cm^{-1} (C-HAlph.) 3045 (νC-HAr.) 1461cm^{-1} (ν C=CAr.),1610 (νC=N)cm^{-1}				
1b	2937cm^{-1} (C-HAlph.) 3065 (νC-HAr.) 1472cm^{-1} (ν C=CAr.), 1611 (νC=N)cm^{-1}, 724(νC-Cl)				
1c	2915cm^{-1} (C-HAlph.) 3065 (νC-HAr.) 1473cm^{-1} (ν C=CAr.), 1590 (νC=N)cm^{-1}, 1521(NO_2) cm^{-1}	2.5 DMSO 3.33(d,2H,CH_2) 3.52(s,3H,OCH_3) 3.63(s,6H,2OCH_3)	(60.43) 60.22	(4.35) 4.48	(15.10) 15.23

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		6.27(s,2H,aro.) (7,52-7.63) (m,8H,Ar.) 8.63(s,2H,imine.) 9.08(s,1H,in pyri. cyclic)			
1d	2855cm^{-1} (C-HAlph.) 3025 (νC-HAr.) 1462cm^{-1} (ν C=CAr.), 1560 (νC=N)cm^{-1}, 3496 (OH) cm^{-1}				
1e	2870cm^{-1} (C-HAlph.) 3019 (νC-HAr.) 1471cm^{-1} (ν C=CAr.),1590 (νC=N)cm^{-1} , 3310 (OH) cm^{-1} , 1269 (O-C-O) cm^{-1}				
1f	2835cm^{-1} (C-HAlph.) 3007 (νC-HAr.) 1458cm^{-1} (ν C=CAr.),1640 (νC=N)cm^{-1} ,1236 (O-C-O) cm^{-1}				
1g	2870cm^{-1} (C-HAlph.) 3093 (νC-HAr.) 1490cm^{-1} (ν C=CAr), 1615 (νC=N)cm^{-1} ,3331 (OH) cm^{-1}				
1h	2833cm^{-1} (C-HAlph.) 3040 (νC- HAr.) 1450cm^{-1} (ν C=CAr), 1672 (νC=N)cm^{-1}1577 (C=C Alph.) cm^{-1}				
2a	2807cm^{-1} (C-HAlph.) 3020 (νC-HAr.) 1455cm^{-1} (ν C=CAr.),1646 (νC=O)cm^{-1} , 725				

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	(C-Cl)cm^{-1}1263(νC-N)cm^{-1}				
2b	2907cm^{-1} (C-HAlph.) 3082 (νC-HAr.) 1417cm^{-1} (ν C=CAr.), 1654 (νC=O)cm^{-1}, 756 (C-Cl)cm^{-1}1267(νC-N)cm^{-1}		(55.83) 55.99	(3.81) 3.65	(8.14) 8.25
2c	2837cm^{-1} (C-HAlph.) 3107 (νC-HAr.) 1421cm^{-1} (ν C=CAr.), 1705 (νC=O)cm^{-1}, 738 (C-Cl)cm^{-1}1236(νC-N)cm^{-1} ,1456(NO_2)cm^{-1}				
2d	2837cm^{-1} (C-HAlph.) 3107 (νC-HAr.) 1420cm^{-1} (ν C=CAr.),1660 (νC=O)cm^{-1} , 745 (C-Cl)cm^{-1}1250 (νC-N)cm^{-1} ,3490(OH)cm^{-1}				
2e	2877cm^{-1} (C-HAlph.) 3024 (νC-HAr.) 1420cm^{-1} (ν C=CAr.),1672 (νC=O)cm^{-1} , 752 (C-Cl)cm^{-1}1244 (νC-N)cm^{-1} ,3230(OH)cm^{-1}	2.50 DMSO 3.10(s, 2H,CH_2) 3.30(s,3H,OCH_3) 3.41(s,6H,2OCH_3) 3.71(s,6H, 2OCH_3) 5.55(d,2H,CH-N.) 5.86(d,2H,CH- Cl) 6.61(s,2H,OH) 6.91(s,2H,Ar.) (7.21-7.54) (m,6H,Ar.)			
2f	2881cm^{-1} (C-HAlph.) 3015 (νC-HAr.) 1420cm^{-1} (ν				

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	C=CAr.),1669 (νC=O)cm^{-1} , 760 (C-Cl)cm^{-1}1248 (νC-N)cm^{-1} ,1240(C-O-C)cm^{-1}				
2g	2833cm^{-1} (C-HAlph.) 3019 (νC-HAr.) 1421cm^{-1} (ν C=CAr.),1689 (νC=O)cm^{-1} , 769 (C-Cl)cm^{-1}1263 (νC-N)cm^{-1} ,3132(OH)cm^{-1}	2.50 DMSO 3.60(s,2H,CH_2) 3.74 (s,3H, OCH_3) 3.83(s,6H,2OCH_3) 5.74(d,2H,CH-N) 6.07(d,2H,CH-Cl) 6.61(s,2H,Ar.) (7,20-7.42) (m,8H,Ar.) 7.54(s,1H,in pyri. cyclic) 9.76(s,2H,OH)			
2h	2860cm^{-1} (C-HAlph.) 3020 (νC-HAr.) 1426cm^{-1} (ν C=CAr.),1673 (νC=O)cm^{-1} , 771 (C-Cl)cm^{-1}1252 (νC-N)cm^{-1} ,1572(C=CAlph.)cm^{-1}				

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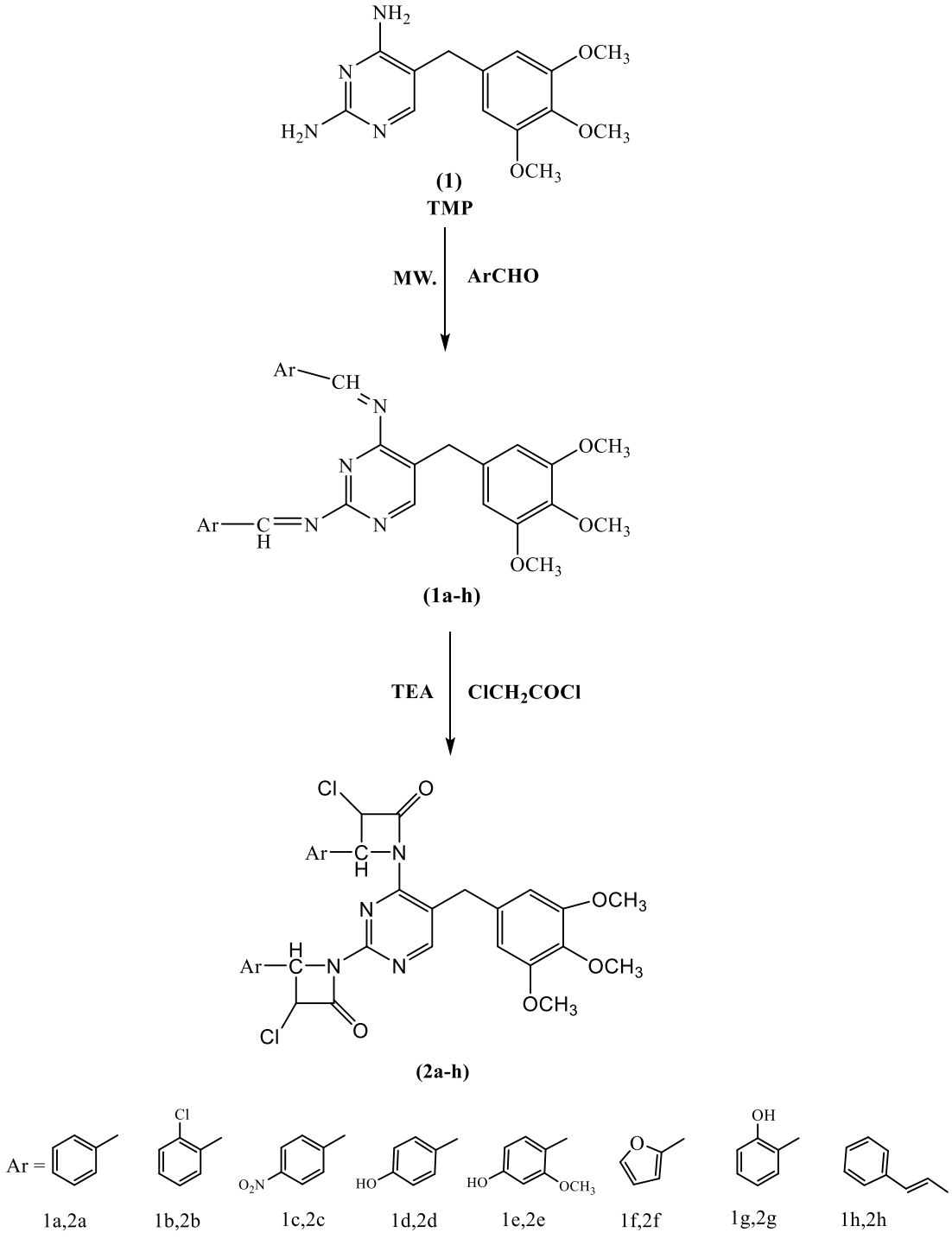

Scheme (1): Show the prepared compounds

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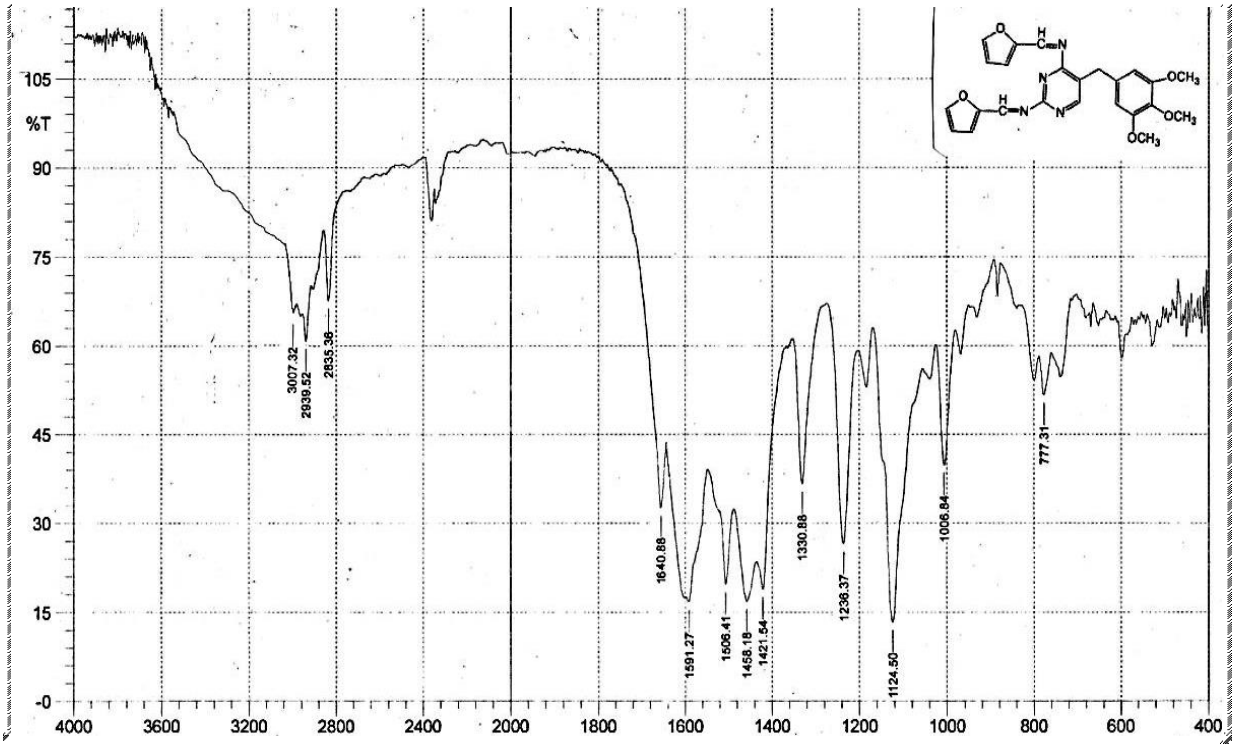

Fig. (1): FT-IR spectrum of Compound(1f)

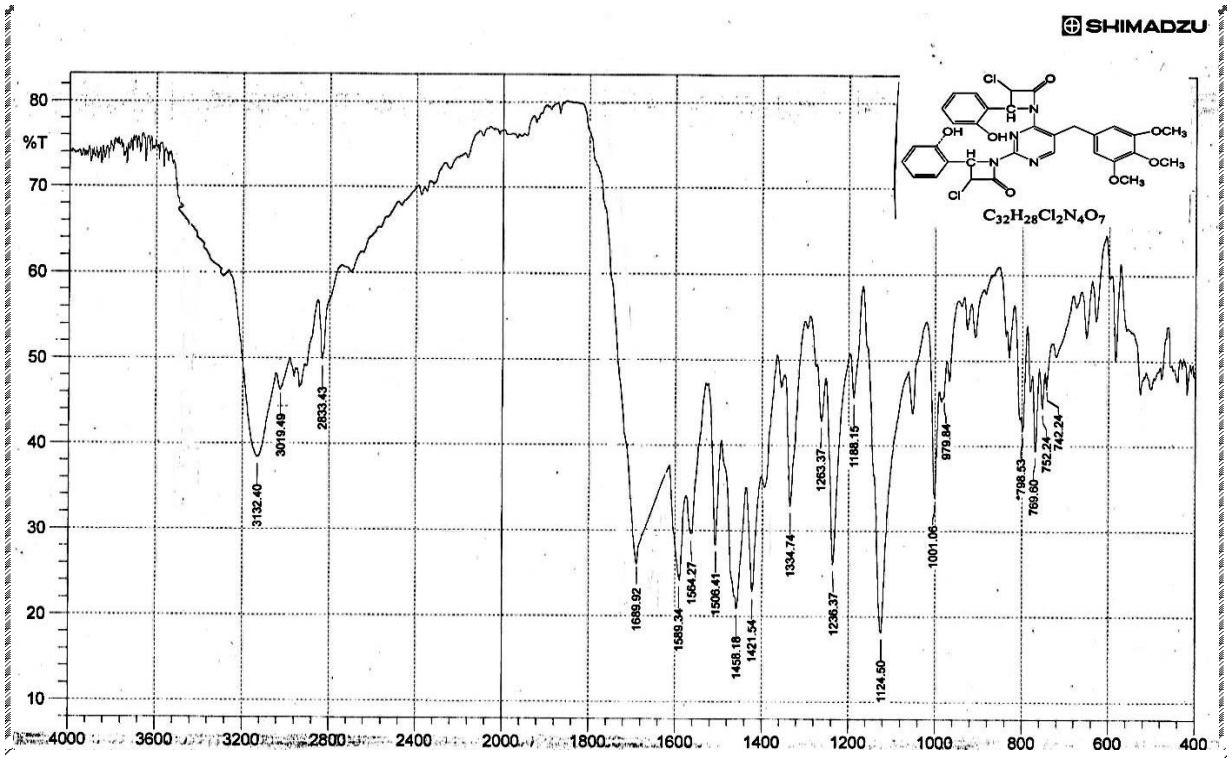

Fig. (2): FT-IR spectrum of Compound(2g)

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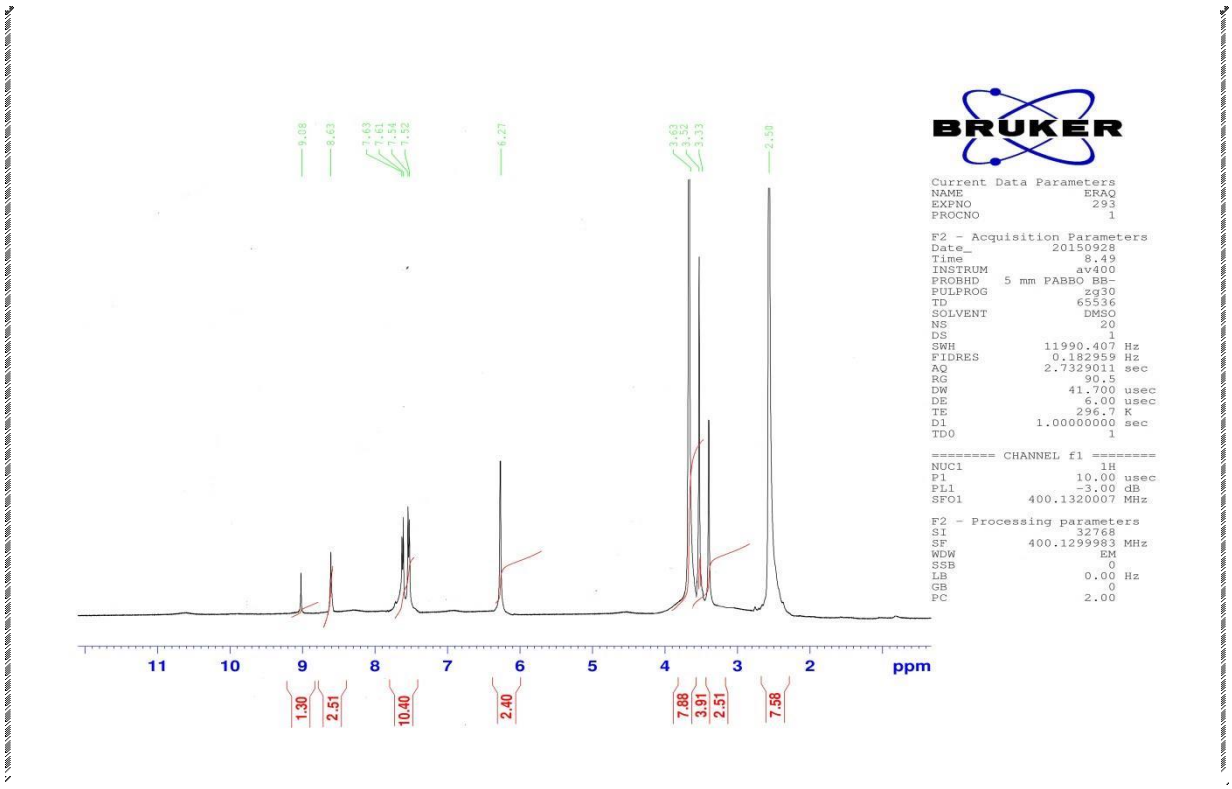

Fig. (3): ^{1}H-NMR spectrum for compound (1c)

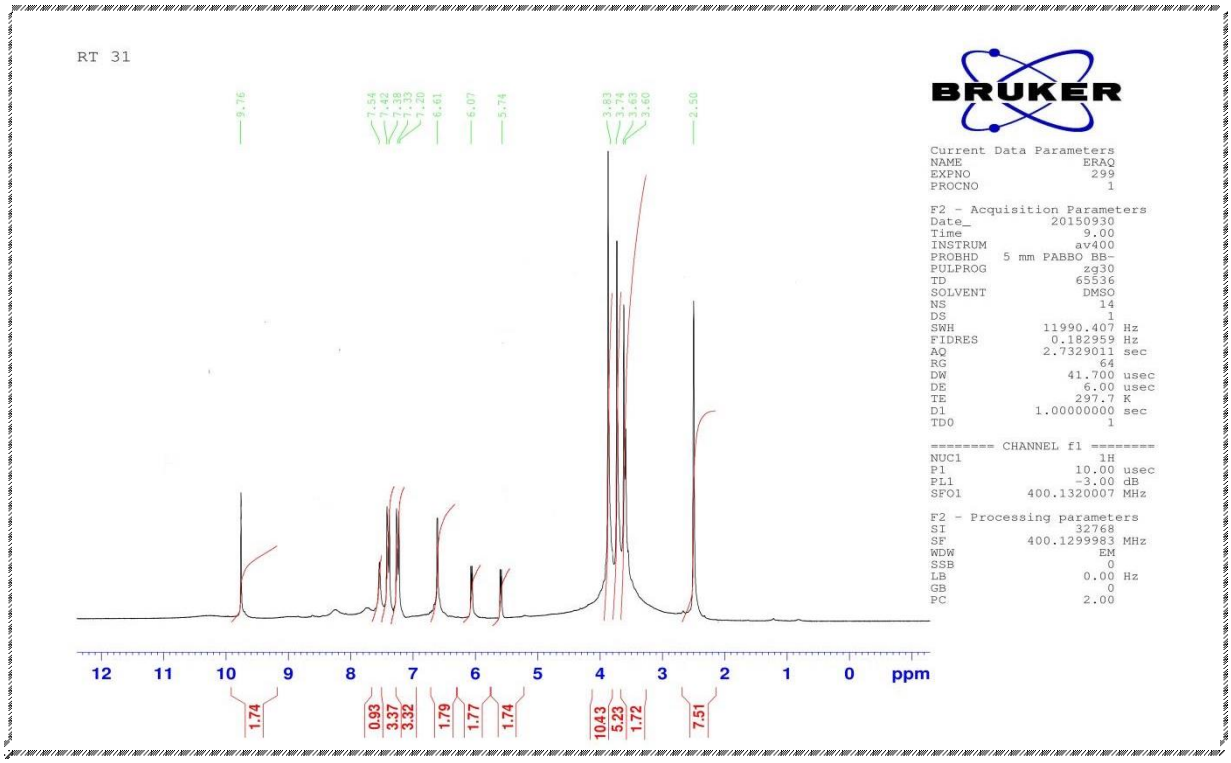

Fig. (4): ^{1}H-NMR spectrum for compound (2g)

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