Eco-Friendly Modification of Fused Pyrimidine Derivatives via Lemon Juice-Catalyzed Biginelli Reaction

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ABSTRACT

Biginelli reaction is one of the most important one-pot multicomponent organic reactions which used to afford especial type of heterocyclic compounds represented by pyrimidine derivatives via acidic conditions. Pyrimidine have been shown a wide and diverse applications in medical, pharmaceutical, biological and industrial fields. In this work our target is to prepare fused pyrimidine derivatives via Biginelli reaction with replacement the metallic acid catalyst by lemon juice as a natural acid catalyst with multiplier effect. First of all, the sulfathiazole underwent the diazotization reaction to give the diazonium salt (1) followed by reaction with malononitrile to obtained the aryl hydrazine propanedinitrile (2) which then reacted with hydrazine hydrate (98%) to afford 2,5-diamino pyrazole derivative (3). Finally , the last one underwent Biginelli reaction with dimedone and aromatic aldehydes in acidic media from lemon juice to achieve poly Biginelli products (4-7,) which illustrated by 1H-NMR, FT-IR and GC-Mass spectroscopy in addition to the theoretical biological study using the molecular Docking program.

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Keyword: Pyrimidine, Biginelli reaction, Lemon juice, Multicomponent reactions, hydrazine propanedinitrile

Introduction

The Biginelli reaction in being a multicomponent reaction (MCR) it is very simple, value-powerful, and highly efficient for building complex molecular via one-step (Ryabukhin et al., 2010). As a result, it has a great deals of attention due to their wide range applications in pharmaceutical industries ((Mochaddas et al., 2012 & Shaikh et al., 2012) as antihypertensive (Atwal et al., 1990), anticancer (Heda et al., 2009), anti-inflammatory (Jadhav et al., 2012) and antibacterial agents (Badadhe et al., 2011), as well as in green chemistry due to its capacity to decrease chemical waste by using unconventional methods such as grinding, microwaves, or ultrasound technique, as well as using natural juices (Pal et al., 2013) as an excellent alternatives to chemical catalysts like a lemon juice.

In recent years, green chemistry has emerged as a key scientific approach aimed at reducing the environmental impact of chemical reactions. Among the strategies of green chemistry, the use of natural, non-toxic catalysts has gained attention as an alternative to strong or expensive traditional catalysts. Lemon juice, rich in citric acid and other organic acids, has proven effective as an eco-friendly acidic catalyst in numerous organic reactions ((Patil et al., 2011&Cofelice et al., 2019).

Lemon juice is mainly composed of (Kumar & Pandit, 2014):

- Citric acid: A tricarboxylic acid responsible for its high acidity.
- Other organic acids such as malic acid and ascorbic acid.
- Secondary compounds like flavonoids and essential oils.

The acidity from these organic acids provides a natural acidic medium that accelerates chemical reactions, particularly Biginelli Reaction (Mohamed *et al.,* 2021), Acetylation (Chavhan et al., 2016), Benzoxazole Synthesis (Mahadevaswamy & Kariyappa , 2017), Schiff Bases (Patil et al., 2012), Knoevenagel (Deshmukh et al., 2012), Octahydroquinazolinone Derivatives (Malavattu et al., 2019) and Benzimidazole Synthesis (Malavattu et al., 2019).

Lemon juice represents an excellent example of applying green chemistry principles by providing a natural acidic medium that is highly effective in numerous organic reactions. Its use as a catalyst offers economic benefits, reduces environmental impact, and enhances reaction efficiency. Research suggests that its applications can be further expanded for broader industrial and laboratory-scale processes in the future (Das D., 2020).

In view of these fact, the aim of the present study is to obtained poly heterocyclic compounds represented by fused pyrimidines (4-7)via Biginelli reaction as one-pot three component reaction using the lemon juice as natural acid catalyst .

EXPERIMENTAL

Melting points (M.P.) were measured on Electrothermal Stuart SMP 10. melting point apparatus. Infrared (FT-IR) spectra were recorded as (KBr) disk using a Bruker, FT-IR spectrophotometer (Pye Unicom sp 2000). Nuclear Magnetic Resonance Spectrometer (H^1-NMR): Measurement of the nuclear magnetic resonance spectrum using a Bruker Bio Spin Gmbll Spectrophotometer 400MHz Turkey, using DMSO-d_6 as a solvent and TMS as an internal reference. Spectral regions were expressed in (ppm). The measurements were performed at Gaze Osman Paşa University, Turkey. Mass spectrometer (GC-MS): Mass spectra were measured using an Agilent GC-MS. The measurements were performed at Gaze Osman Paşa University, Turkey. Thin layer chromatography (TLC) was carried out on silica gel (120 mesh) with 13% gypsum coated plates (2x10) cm, activated for one hour at (110-120°C) before use and the plates were developed with iodine vapor, and also the assigned structure of the prepared compounds was corroborated by available physical and spectral methods.

Synthesis of 4-((3,5-diamino-1H-pyrazol-4-yl) diazenyl)-N-(thiazol-2yl) benzene sulfonamide (3): (El-Fahham et al., 1988)

In beaker (50ml) the sulfathiazole (0.01 mole) and HCl concentration (4 ml) was cooled on an ice bath (0-5℃) followed by adding NaNO2 (1gm /10 ml water), the precipitate of diazonium salt (1) was separated and added to an aqueous solution of malononitrile (0.1 mole /50 ml water) then adding CH3COONa (12.5 g) and crushed ice was added with stirring. The precipitate was filtrated off to obtain the compound (2), which then poured into round bottomed flask (100ml) and dissolved in methanol (15ml),after adding hydrazine hydrate(98%/ 0.1mole) the reaction mixture the refluxed for (10 minutes),cooling and acidify with acetic acid. The solid product then filtered off and mixed with water (20ml and let to settle for (24 hrs.), followed by filtration and recrystallization from ethanol to afford the building unite (3) .

Comp.(2): Orange powder, M.Wt.=232, M.P. ℃= dec.> 360, yield(%)=90, FT.IR (υcm^{-1}): NH(3221), C=N(1603),CN(2219).

Comp.(3): Olive green powder, M.Wt.=364, M.P. **℃**= 265-267, yield(%)=98, R_f =0.430, FT.IR (υcm^{-1}): NH2(3338), NH(3132), C=N(1627).

Synthesis of 4-((2-amino-9-aryl-6,6-dimethyl-8-oxo-1,2,4,5,6,7,8,9-octahydro pyrazolo [5,1-b] quina zolin-3-yl) diazenyl)-N-(thiazol-2-yl) benzenesulfo namide (4-7): (Jaseim et al., 2023)

In a round bottomed flask (50 ml), equimolar (0.002 mole) of dimedone, and aromatic aldehyde was mixed with (0.001 mole) of compound (3) in an acidic medium of lemon juice prepared immediately before the reaction, (1 ml) as a catalyst and solvent, then the reaction mixture was refluxed in a water bath at (70°C /1 hr). The resulting precipitate filtered off and washed thoroughly with ice water to remove the excess acid, dried and recrystallized from ethanol.

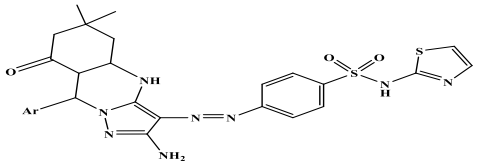


Table 1: physical properties and spectral data of compounds (4-7)

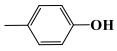
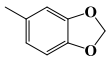
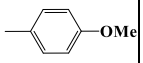
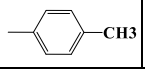
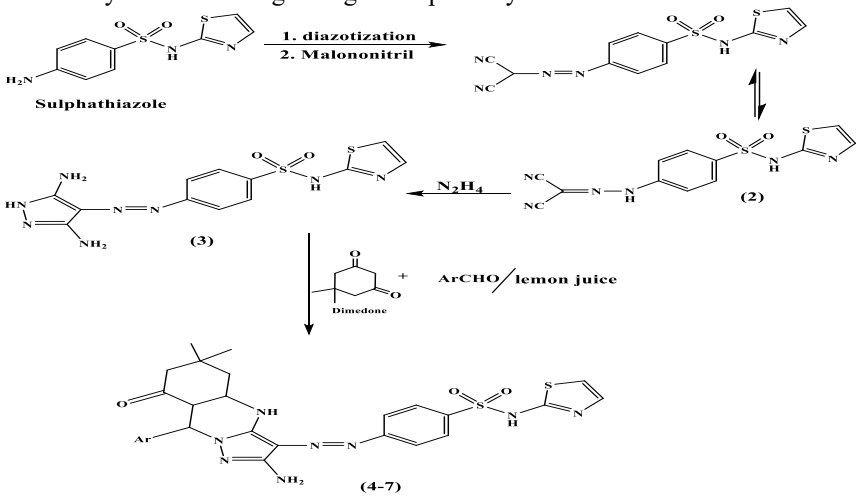
Comp. No.	Ar	M.P.(°C)	Yield(%)	R_f	FT-IR (υ cm^{-1})						
					NH_2	NH	CH_3		C=O	C=N	C=C arom.
							sym.	asym.			
4		230-232	86	0.48	3310	3236	2900	2950	1715	1518	1500
5		242-244	84	0.5	3305	3200	2890	2905	1625	1543	1520
6		224-226	80	0.52	3321	3210	2929	2957	1630	1555	1510
7		188-190	82	0.40	3315	3220	2910	2965	1705	1527	1527

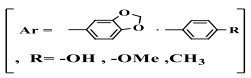
Table 2. (^{1}H-NMR) & Mass spectroscopy

Comp. No.	^{1}H-NMR(δppm)	MS(m/z)/ Base peak
4	Dimedone(m,0.98-2.87,10H); SO_2-NH(s,2.92,1H);OH(s,5.52,1H);NH_2(s,2.30,2H);Ar-H(m,6.64-7.86,11H); NH-pyrazol(s,9.42,1H).	592/71
5	Dimedone(m,1.01-2.90,10H);NH_2(s,2.41,2H); SO_2-NH(s,2.95,1H); CH_2-piperonal(s,5.56,2H);Ar-H(m,5.97-7.88,10H);NH-pyrazol(s,9.12,1H).	620 /71
6	Dimedone(m,0.99-3.70,10H);NH_2(s,3.26,2H);OCH_3(s,3.71,3H); SO_2-NH(s,5.58,1H);Ar-H(m,6.81-7.89,11H); NH-pyrazol(s,7.91,1H).	606 /83
7	Dimedone(m,0.67-2.72,10H);NH_2(s,2.87,2H); NH(s,5.60,1H);Ar-H(m,6.83-7.96,11H);SO_2- NH-pyrazol(s,12.78,1H).	590 / 43

Results And Discussion

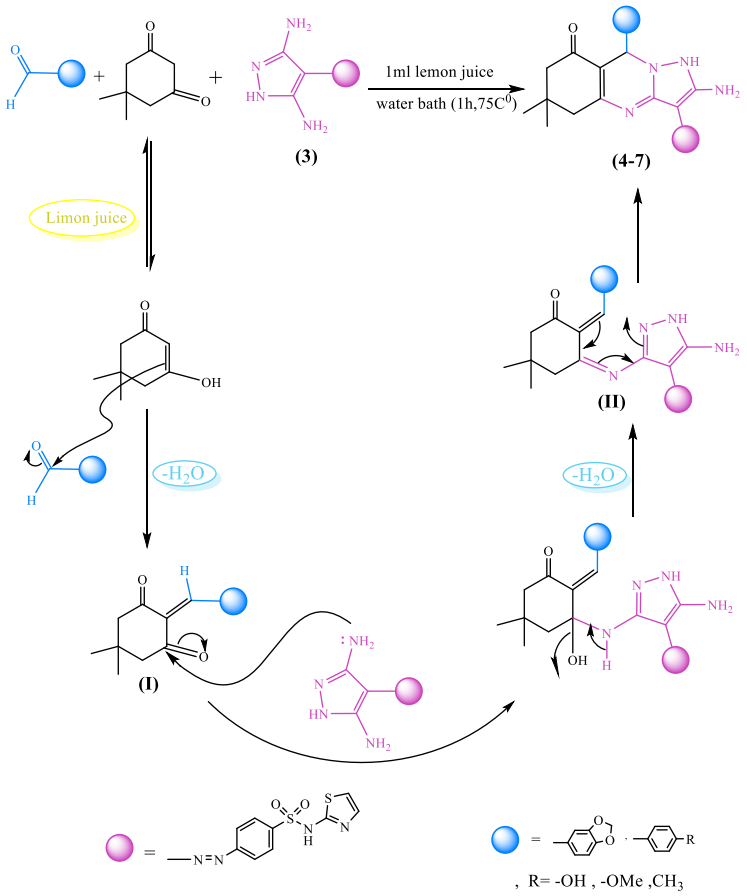
All prepared compounds were synthezide through the general pathway bellow:





Scheme 1: The synthetic pathway for compounds (1-7)

In this reaction we used lemon juice as an acidic catalyst to afford the poly heterocyclic Biginelli products with acceptable yields . Mechanistically, it is reasonable to assume that the reaction was proceeded firstly via Knovenagil reaction between the dimedone and the protonated aldehyde to afford the intermediate (I) with losing water molecule which then underwent nucleophilic addition reaction and also with losing another water molecule of amino-pyrazole group on the conjugated carbonyl group in compound (I) to afford the intermediate (II). The last one in turn proceeded through the intracyclization reaction to achieve the Biginelli poly heterocyclic product represented by compounds(4-7) as shown in Scheme (2), (Hügel, 2009; Wang et al., 2010; Loto et al., 2012).



Scheme 2: The Mechanism of Synthetic Compounds (4-7)

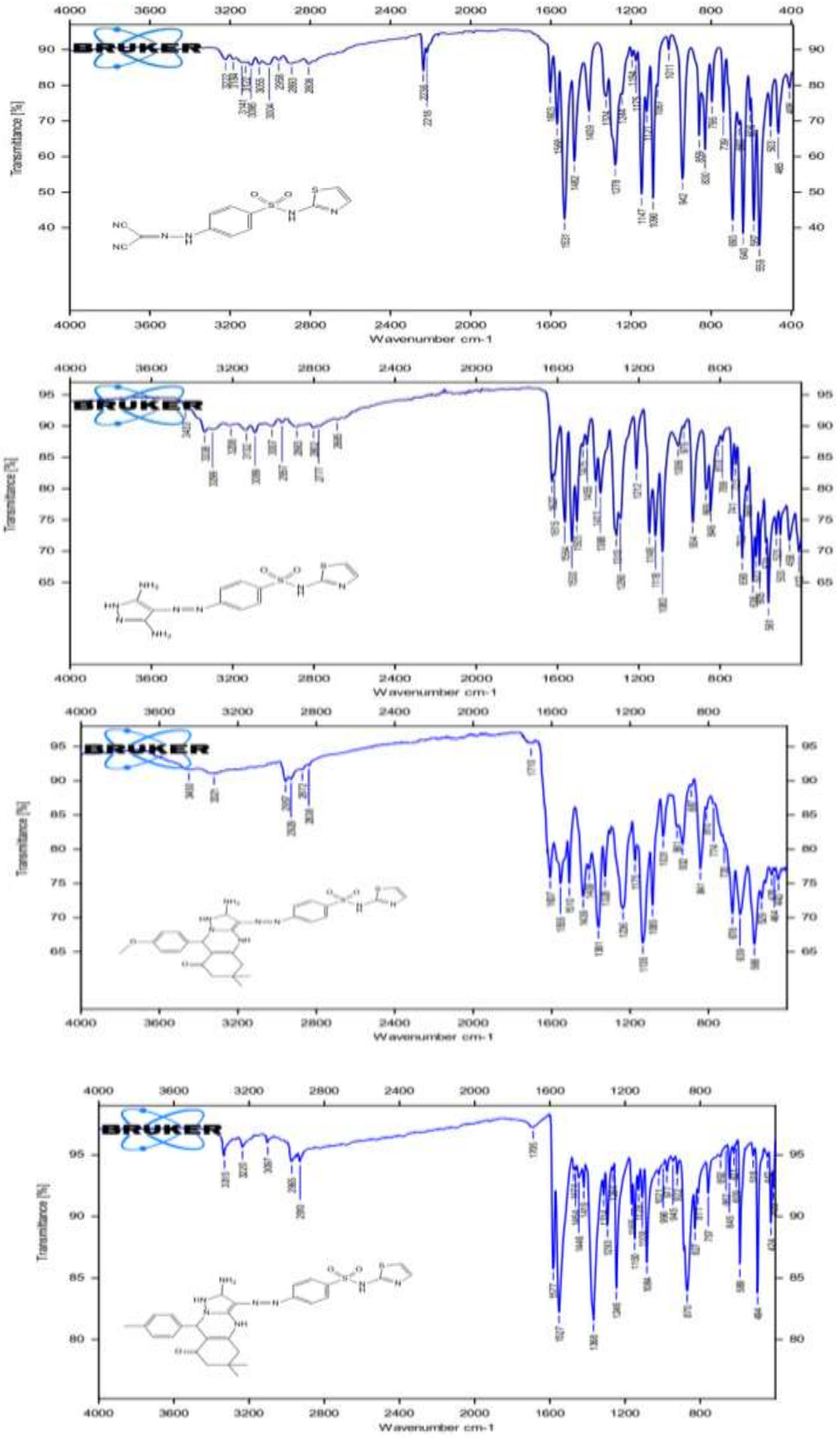
The structures of compounds (4-7) were confirmed by spectral methods represented by FT-IR as shown in Table (1). In FT-IR spectra all compounds show absorption bands at (3305-3321 cm^{-1}), (3200-3236 cm^{-1}), (1625-1715 cm^{-1}), (1500-1527 cm^{-1}) and (1518-1555 cm^{-1}) due to NH_2, NH, C=O, C=C (arom.) and C=N functional groups respectively. Whereas in Mass spectra all compounds show the (m/z) value equal to their molecular weight as the reaction ratio is (1:1:1) this result give great evidence for the right structure in addition to the identification by H^1-NMR spectroscopy which gave diagnosed and characteristic absorption peaks that enhance the proof of the synthetic formula of the prepared compounds, Table (2).

For more characterization, molecular docking was studied on the compounds (5& 6) as an essential evaluation in computational drug design to predict how to specific biological target [Bcl-2 protein (B-cell lymphoma 2) apoptosis regulator] these two compounds shown stable correlation according to their binding energy (-8.8036 and -8.4529) for compounds 5& 6 respectively. The theoretical binding energy for these compounds gave clear evidence of its ability to significantly inhibit the effectiveness of the enzyme mention above and also a preliminary indicator of the biological activity of these two compounds.

Conclusion

Advantages of using lemon juice as a natural acidic catalyst:

- ✓ Environmentally friendly: Reduces the use of harmful mineral acids or toxic solvents.
- ✓ Economical and readily available: A low-cost, natural resource.
- ✓ Mild reaction conditions: Often requires no extreme temperatures or pressures.
- ✓ High yields and short reaction times: Comparable or superior to traditional catalysts.
- ✓ Simplified product isolation: Reduces purification steps and chemical waste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Transmittance [%]
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4000
3600
3200
2800
2400
2000
1600
1200
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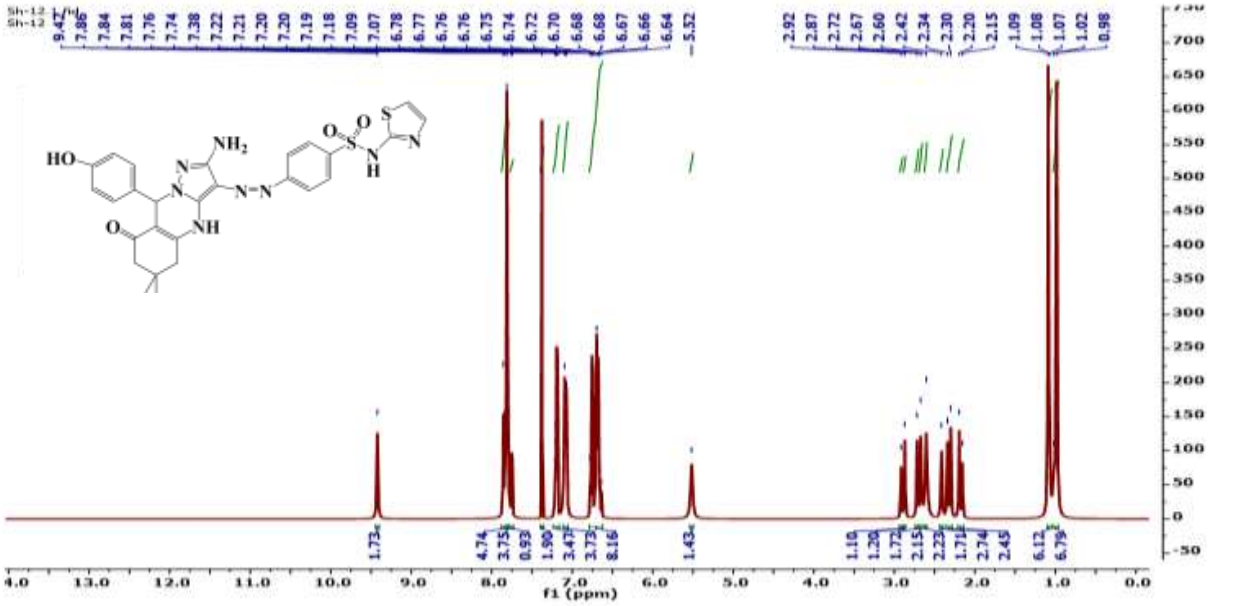
400


HO
NH2
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NH
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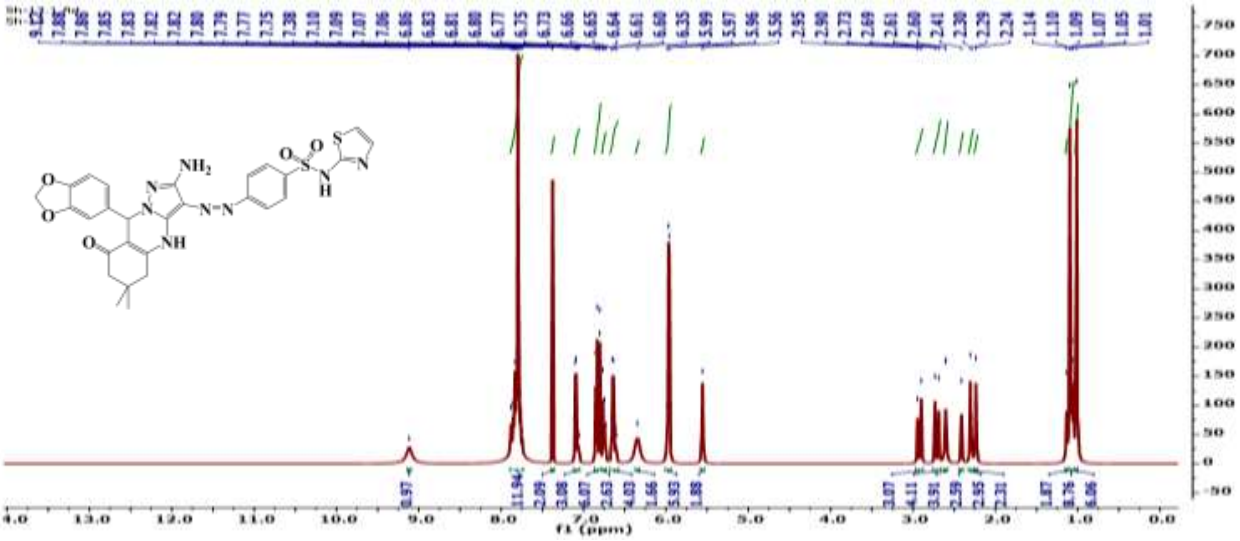
f1 (ppm)


O
O
NH2
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NH
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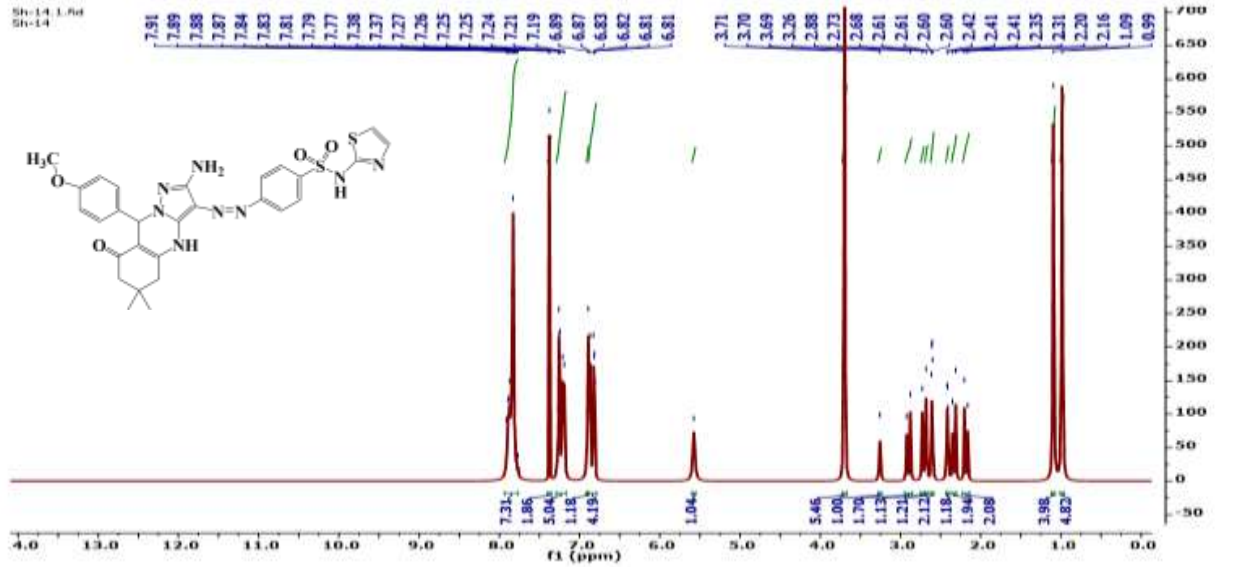
H3C
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NH
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N
H
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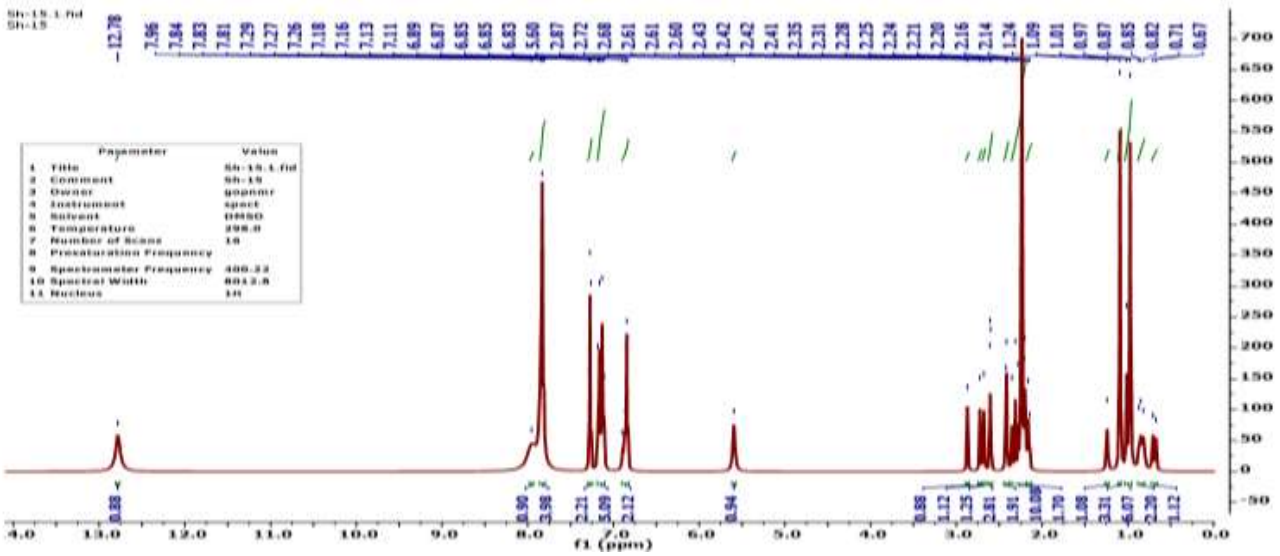
f1 (ppm)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Parameter Value
1 Title Sh-15 1.fid
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6 Temperature 298.0
7 Number of Scans 16
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9 Spectrometer Frequency 400.22
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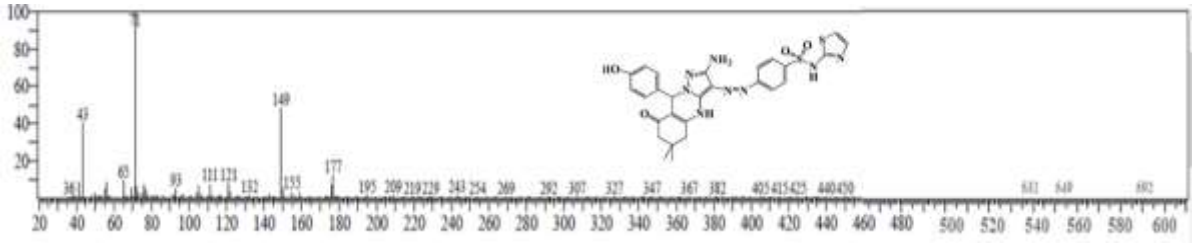

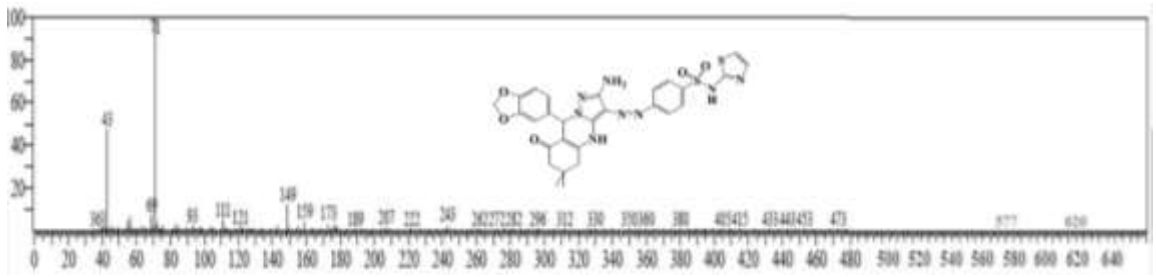

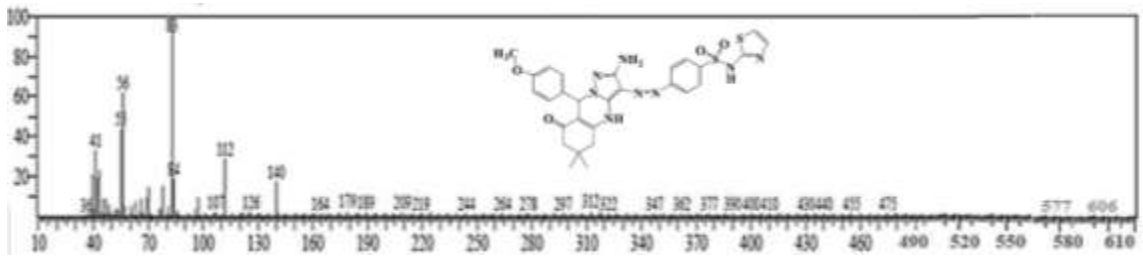

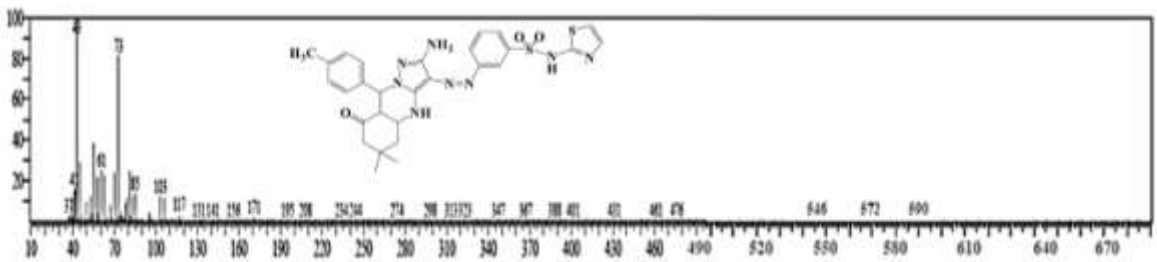

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