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The Synthesis and Biological Evaluation of Prodrug Amide Derivatives Based on Phenylene Dioxy Di Acetic Acid

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Abstract. Seven unused amides compounds (1a-7a) prodrug subordinates based on phenylene di oxy di acidic acid as well as ponder their antibacterial and DPPH radicals rummaging exercises The structure of synthesized compounds were explained through cutting edge spectroscopic strategies counting NMR, IR and UV. (4a-7a) The antibaterial effect of compounds 1a-7a were estimated on *Escherichia coli* (-) and *Staphylococcus aureus* (+),compound 6 show the simplification effective, inhibitory viability with hindrance values of 28 and 20 µg/ml for *Escherichia coli* (-) and *Staphylococcus aureus* (+), respectively. Compounds shown DPPH radicals rummaging movement compare to the ascorbic corrosive. As a conclusion, seven compounds have been synthesized and the compounds appeared potential against two microscopic organisms species and DPPH radicals. The discoveries of this ponder can upgrade the understanding of natural exercises of the amide compounds.

INTRODUCTION

A combination of drugs and their carrier molecule claimed to be prodrug [1]. These carrier atoms are managed through different courses. Within the body, they are metabolized to evacuate the carrier atom and discharge the dynamic medicate atom. The alterations of carrier particles performed location particular, metabolized at a specific tissue or by a specific protein [2]. These carrier particles can help the sedate to have more natural half-life, more medicate concentration at target location, focused on activity and amplified reliable sedate levels in vivo which are the impediments confronted by numerous drugs [3], carrier atoms have been created which are particular in their activity and have potential to be utilized in combination with sedate atoms [4]. Hydroquinone may be a phytochemical bioactive compounds display in numerous plant kingdom. Hydroquinone and its subsidiaries are auxiliary metabolites in numerous characteristic sources such as plants and microorganism. Hydroquinone can it discover in tea, coffee, natural product, brew, ruddy wine, and tobacco [5]. Dihydroxybenzenes and their offshoots are utilized in makeups as sterile, cancer prevention agents [6]. Hydroquinone have powerful tyrosinase restrained effects, which transform tyrosine to melanochrome and has been utilized for the handling of hyperpigmentary and melanosis unrest [7]. however although it is oxidized readily in watery solution leading role to fast browning. Arbutin, the of course occurring d-glucoside of hydroquinone is a robust inhibitor of melanin composition and has been announce to possess inhibitory activity on oil peroxidation [8] and is applied in the beauty products industry for its antiseptic and skin illumination effects [9,10].

EXPERIMENTAL

Synthesis of hydroquinone derivatives

Corrosive compound (1mole) was broken down in ethanol (10 ml), include two drops of thionyl chloride was kept beneath reflux for 2hrs. In a circular bottomed carafe amino compounds (2mole) were broken up in ethanol

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dissolvable, this was extra drop shrewd to the corrosive combination. The ensuing combination was spared beneath attractive stirrer for 2 hrs. A accelerate was gotten and decontaminated utilizing recrystallization prepare to deliver immaculate amide compound subordinates (1-7) [11]. The response steps were checked by TLC plats beneath {UV} (254 nm wave length).

Instruments and Apparatus

Solvents and chemicals were picked up from commercial sources and were connected without additionally refining. Infrared spectra on record utilize Bruker FTIR spectrophotometer. NMR spectra were recorded by Bruker Avance III 500 spectrometer (500 MHz for 1H NMR and 100 MHz for 13C NMR, individually utilizing DMSO-d6 or D2O as solvents). Chemical shifts were recorded in ppm. Aluminum demonstrative silica gel 60 F254 lamina were utilized for thin-layer chromatography (TLC), visualized underneath bright light (254-365 nm) to keep an eye on the responses. The clean action was indicated utilizing agar dissemination handle (materials). DPPH (materials).

Antibacterial Assay

Commonalty the bacterial methods of insight were found from the Microbial Sort Culture Bunch (babylon college, Iraq). The Gram negative (Escherichia coli) furthermore Gram positive (Staphylococcus aureus) were sub refined on wholesome agar. The check of seven compounds (1a-7a) were total in vitro by the agar well spread method. The standard arrangements (5 mg/mL) of the examination compounds were set through defrost 5 mg of examination compound in ethanol. All testers were cleaned through a 0.2 mm layer candidate and kept at 5°C unto additionally utilize. Microbial inoculums were intended since 24 hold cultures through fecundate 100 µL of every examination bacterial culture in 20 mL of cozy, heated, autoclaved Mueller Hinton agar, germ layers were set. Afterward addition, these were gush into disinfected put labels on Petri plates (150 mm × 20 mm). The 8 mm hole were pierce in the cling Petri plates with the support of a disinfected cork auger. By a micropipette, 100 mL of each examination compound (stock 5, mg/mL) was additional to the single hole. The packed plates were brood in an vertical site at 37°C for 24 h. The diameter of the area of outgrowth inhibition in all directions fully next nursery was calculated in mm, with ethanol as a negative hegemony below comparable states for evaluation. Process was carry out in two duplicate dishes for each creature. [14].

DPPH Radical Scavenging Activity

Positively tried seven compounds were for their antioxidant adequacy. The DPPH assess was done agreeing to the strategy that detailed by Aldulaimi (2019) [12,13]. The ordinary arrangement was planning by mix-up DPPH with methanol in a dull put and kept at 20oC until utilized. Two distinctive concentrations of amide compounds (10 and 25 µg/ml) were arranged in methanol. 3 ml of DPPH stock arrangement was included to 2 ml of the arranged arrangement of amino compounds with shaking. The blend kept at room temperature for 30 minutes to whole the response. The absorbance was calculated at 517nm for the combination by a spectrophotometer. Within the affirmed control, the tester was changed with ascorbic corrosive. The DPPH rummaging impact was decided by the following condition

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Scavenging activity (%) = (A blank – A sample)/ A blank X 100
A blank: Absorbance of blank
A sample: Absorption of samples
Experiments were carried out in reiterate, and the products were expressed in µg/ml

RESULTS AND DISCUSSION

Here in, we report the response of hydroquinone with 2, 2'-(1, 4-phenylenebis (oxy)) diacetic acid, which is went with by a response of hydroxyl bunches that were display in hydroquinone with alkyl halide of chloroacetic acid. Compound to create the corrosive compound (a) (Figure 1) that will act as beginning fabric to union the amide subordinates. The response continued beneath gentle conditions in ethanol at 55–60 C to create corrosive compound with surrender rate (80 %). Arrangement of compound (a) was demonstrated by FTIR range with a solid assimilation band comparing to hydroxyl gather (O-H) at 3266 cm-1 and retention band at 1648 cm-1 speaking to

the presence of carbonyl gather. The 1H-NMR band of compound (a) shown single fragrant top at δ 6.86 (s, H-2,H-3,H-5 and H-6, 4H) comparing to four fragrant protons, the chemical move was in assention with that detailed for hydroquinone ring [15]. Additionally the 1H-NMR range uncovered resonances of two CH2 bunches at δ 4.59 as single

2, 2'-(1, 4-phenylenebis (oxy)) bis (N-(1-hydroxy-1-phenylpropan-2-yl)-N-methylacet amid) (1a)

FTIR cm-1: 2984, 2937 and 2897 (, -CH, -CH2-, -CH3), 1648 cm-1 and 1627 cm-1 for (C=C). 1H-NMR (DMSO-d6, 500 MHz) δ (ppm): δ 6.86 for five proton of benzene ring, δ 6.6 and δ 6.7 doublet-doublet for four proton of benzene ring.13C-NMR (DMSO-d6, 100 MHz) δ (ppm): carbonyl group of amide at δ 168.88,115 for phenyl group of benzene ring, δ 65.23 for carbon ether group, δ 60.56 for methyl group connected with amide, δ 14.0 for carbon connected with methyl group .

2,2'-((2,2'-(1,4-phenylenebis(oxy))bis(acetyl))bis((2,3-dimethylphenyl)azanediyl)) dibenzoic acid (2a)

FTIR cm-1: 3307 (OH), 2984, 2937 and 2861 (-CH, -CH2-, -CH3), 1646(C=O), 1595 (C=C) .1H-NMR (DMSO-d6, 500 MHz) δ (ppm): δ 9.45 singlet for COOH, δ 6.66-7.89 for phenyl groups, δ 4.12 for O-CH2 groups. 13C-NMR (DMSO-d6 with 1% v/v TMS, 100 MHz) δ (ppm): δ 170.2 for (C=O), δ 168.7 for amide group, δ 65.2 for carbon of ether, δ 13.67 and 20.23 for methyl groups.

2, 2'-(1, 4-phenylenebis (oxy)) bis (N-acetyl-N-(4-hydroxyphenyl) acetamide) (3a)

FTIR cm-1: 2979, 2939 and 2814 (CH, CH2 and CH3), 1627.97 for amide group, 1609 cm-1 for (C=C). 1H-NMR (DMSO-d6, 500 MHz) δ (ppm): δ 6.86 for proton of phenyl group, δ 9.5 for phenol, δ 1.98 for methyl group of ketone, δ 4.13 for CH2 of ether. 13C-NMR (DMSO-d6 with 1% v/v TMS, 100 MHz) δ (ppm): δ 185 for carbonyl group, δ 168.8 for amide, δ 115-152 for carbon of phenyl, δ 65.2 for carbon of ether, δ 14.02 for methyl group.

You 2, 2'-(1, 4-phenylenebis (oxy)) bis (N-(1, 5-dimethyl-3-oxo-2-phenyl-2, 3-dihydro-1H-pyrazol-4-yl)acetamide) (4a)

FTIR cm-1: 3010, 2970 and 2910 (CH, CH2 and CH3), 1640 for amide group, 1608 (C=C). 1H-NMR (DMSO-d6, 500 MHz) δ (ppm): δ 1.0-2.2 for CH3 groups, δ 4.1 CH2, δ 6.5-7.7 for phenyl groups, δ 9.3 for amide. 13C-NMR (DMSO-d6 with 1% v/v TMS, 100 MHz) δ (ppm): δ 10.0, 14.0 for CH3, δ 112-150 for phenyl groups, δ 160 andδ 168 for two amide.

2, 2'-(1, 4-phenylenebis (oxy)) bis (N-(4-aminophenyl) acetamide) (5a)

FTIR cm-1: 3372, 3322 and 3204 cm-1 for primary and secondary amine, 3006, 2988 and 2914 (CH, CH2 and CH3), 1648.97 for amide group, 1601 for (C=C). 1H-NMR (DMSO-d6, 500 MHz) δ (ppm): δ 6.9 for proton of phenyl group, δ 4.5-4.7 for primary amine, δ and 6.5-6.8 for amide. 13C-NMR (DMSO-d6, 100 MHz) δ (ppm): δ 65 for carbon of ether, δ 114-123 for carbon of phenyl group, δ and 136,152 carbon connected with amine and oxygen atom, δ 168 ppm for carbonyl of amide.

7,7'-((2,2'-((2,2'-(1,4-phenylenebis(oxy))bis(acetyl))bis(azanediyl))bis(2-phenylacetyl))bis(azanediyl))bis(3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid) (6a)

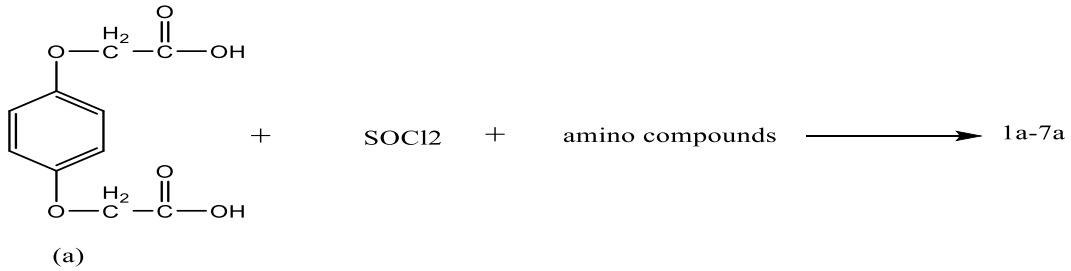
FTIR cm-1: 3350 for OH, 3006, 2988 and 2914 (CH, CH2 and CH3), 1650 for amide group, 1600 for (C=C).

1H-NMR (DMSO-d6, 500 MHz) δ (ppm): δ 1.2 for CH3, δ 3.6 for proton of ether, δ 6.6-6.8 for phenyl groups, δ 7.3 for amide. 13C-NMR (DMSO-d6 with 1% v/v TMS, 100 MHz) δ (ppm): δ 19.4 for CH3 group, δ 60–66.4 for CH2, δ 115 and 128 for phenyl groups, δ 152.1 and 152.3 for carbonyl group, δ 168.9 for amide.

7,7'-((2,2'-((2,2'-(1,4-phenylenebis(oxy))bis(acetyl))bis(azanediyl))bis(2-(4-hydroxy phenyl)acetyl))bis(azanediyl))bis(3,3-dimethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]octane-2-carboxylic acid) (7a)

FTIR cm-1: 3360 for OH and COOH, 1666 for amide group, 1611 for (C=C). 1H-NMR (DMSO-d6, 500 MHz) δ (ppm): δ 1.0-1.6 for CH3, δ 3.4 and 4.6 for CH2 ether and four rings, δ 6.7 for proton of phenyl groups, δ 7.3 for amide.13C-NMR (DMSO-d6, 100 MHz) δ (ppm): δ 14.11 for CH3, δ 60.6 and 65.3 for four ring and O-CH2, δ 115 for phenyl groups, δ 152 for carbon connected with oxygen, δ 168.9 for carbonyl groups .

The scavenging activity of synthesized compounds were examined at dissimilar concentricity (10 and 25 µg/mL). The results were presented in (Figure 3). In contrast,. The compounds have been estimated for their in vitro to the antioxidative action through by DPPH radicals scavenging activity. The outcome showed that all the compounds eligible to decrease the constant, lilac colour radical DPPH to the creamy colour DPPH-H. Additionally, compared to Ascorbic acid as a standard, they exhibited moderate antioxidant activity. The result showed that compound a displayed the highest antioxidant activity. According to Costa et al. (2013) [16], the existence of hydroxyl group contributes to the higher activity of compound a. However, the new compounds may act as an antioxidant agent due to the activity that was exhibited compared to the ascorbic acid. Moreover, in vitro antimicrobial activity was estimated for the synthesized compounds using disc diffusion and MIC. Table 1. The compounds appeared high activity against the two species of bacteria MIC value 200 and 100 µg/mL with inhibition zone 10-28 mm for Escherichia coli (-) and Staphylococcus aureus.



(a)

FIGURE 1. Structure of compound (a) and proposed synthetic route for compounds (1a-7a).

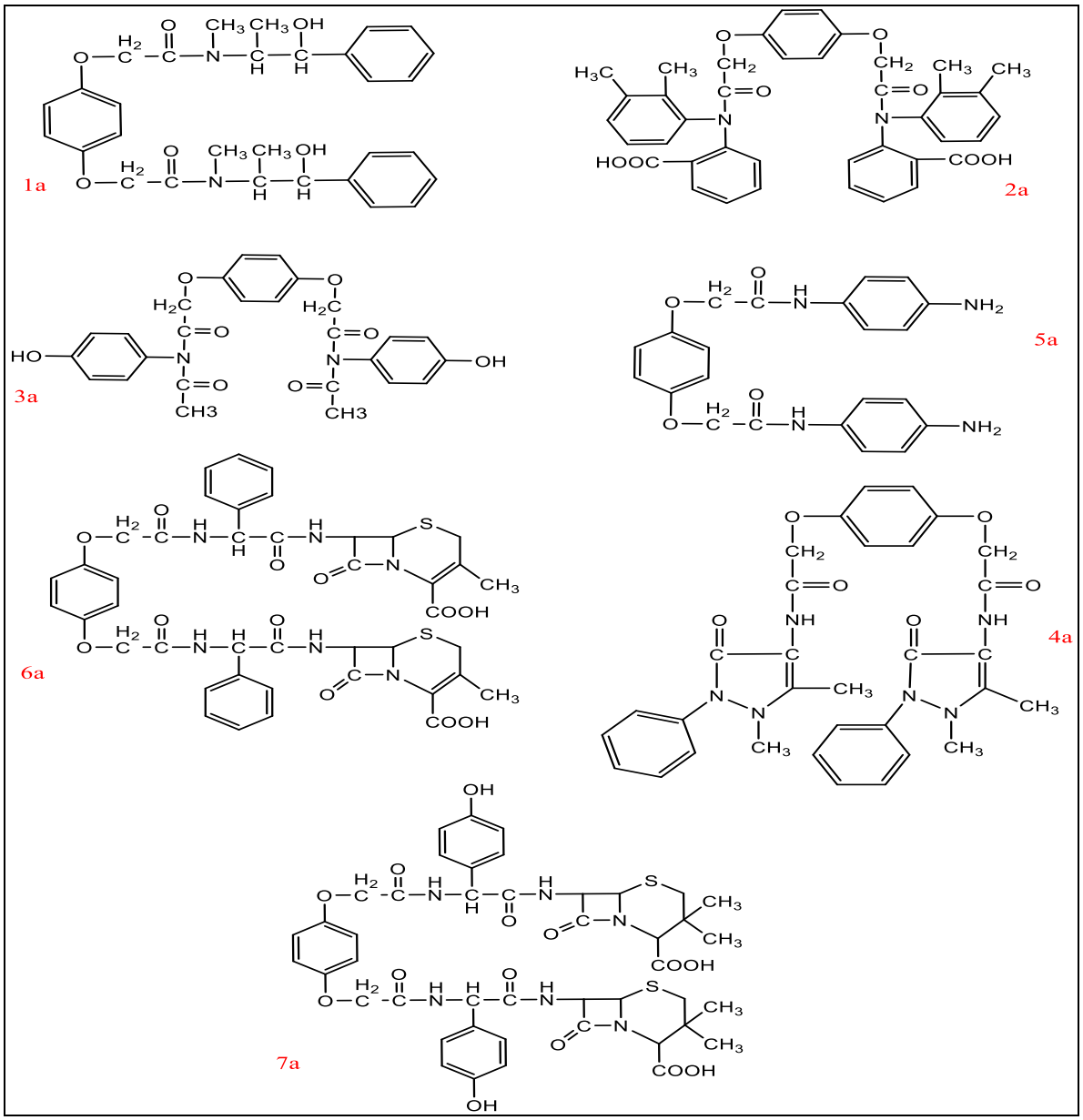


FIGURE 2. Structure of compounds (1a-7a).

TABLE 1. The microbial cultures.

Comp.	Zone of the inhibition by (mm), concentration (µg/mL)	
	G+ Staphylococcus	G- Escherichia coli
	5	5
Ethanol	0	0
5a	10	12
6a	20	28
4a	12	20
7a	0	5

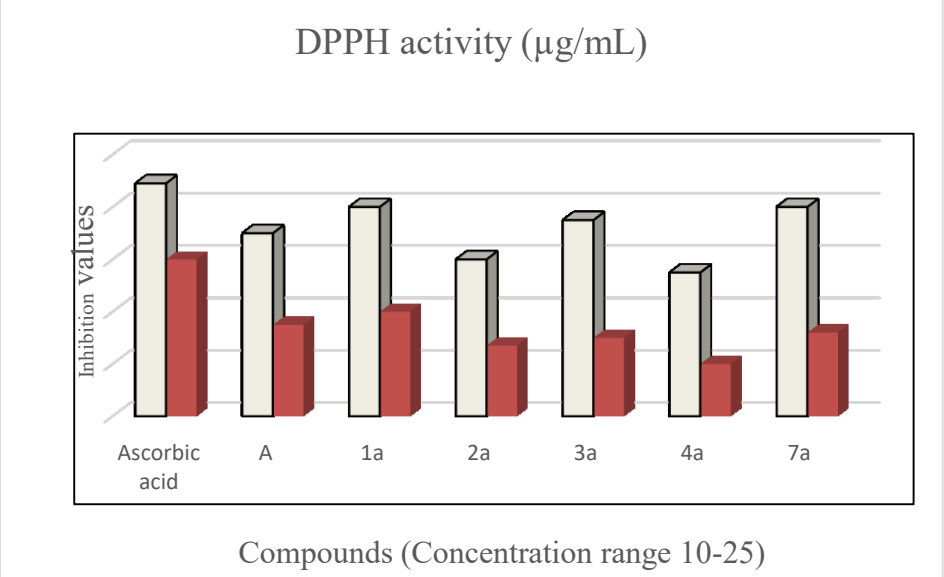


FIGURE 3. DPPH inhibitor activity of synthesized compounds.

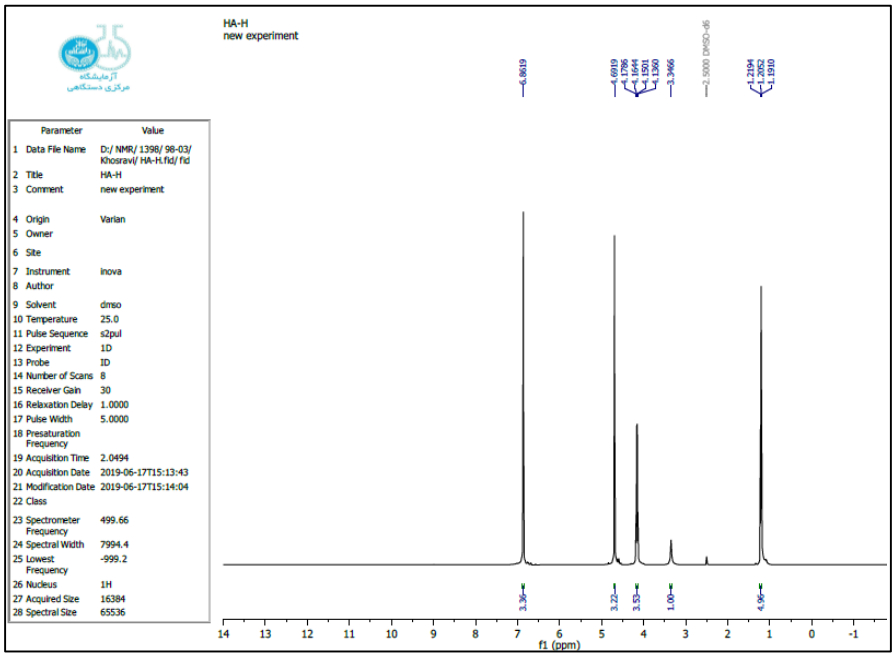


FIGURE 4. 1H-NMR range of 1a.

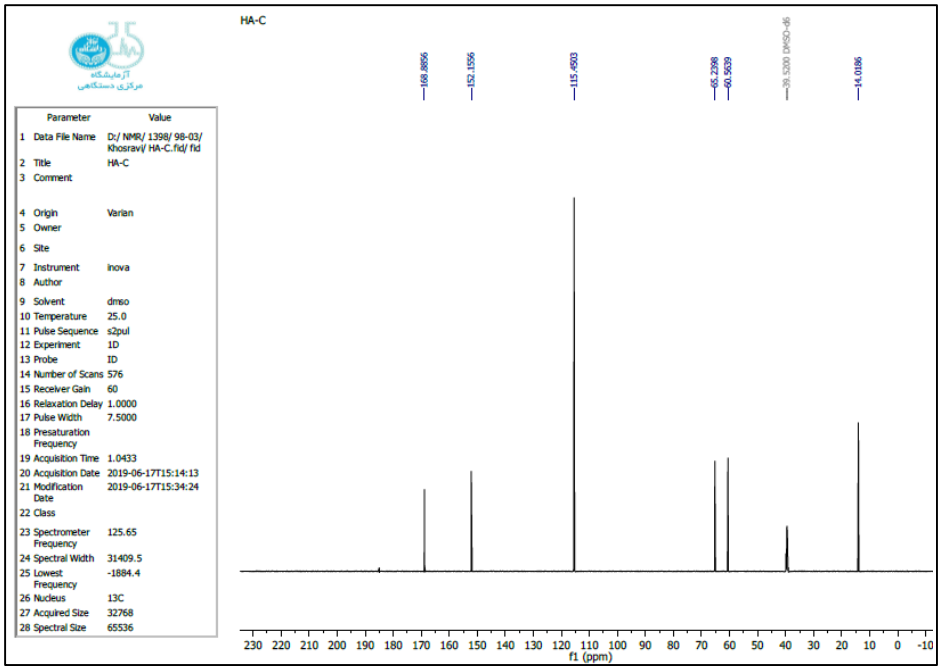


FIGURE 5. 13C-NMR range of 1a.

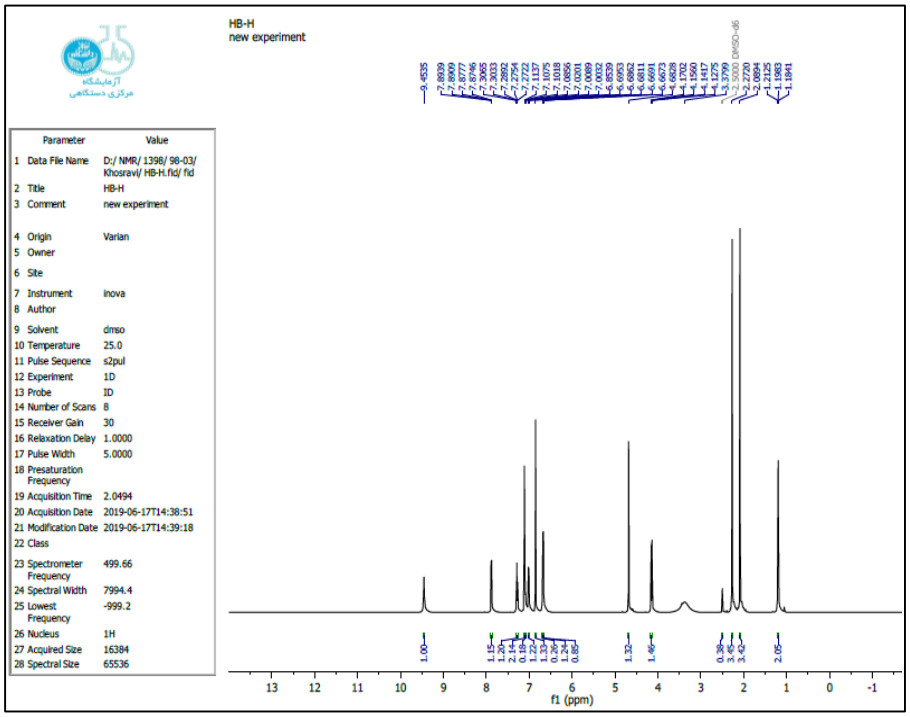


FIGURE 6. 1H-NMR range of 2a.

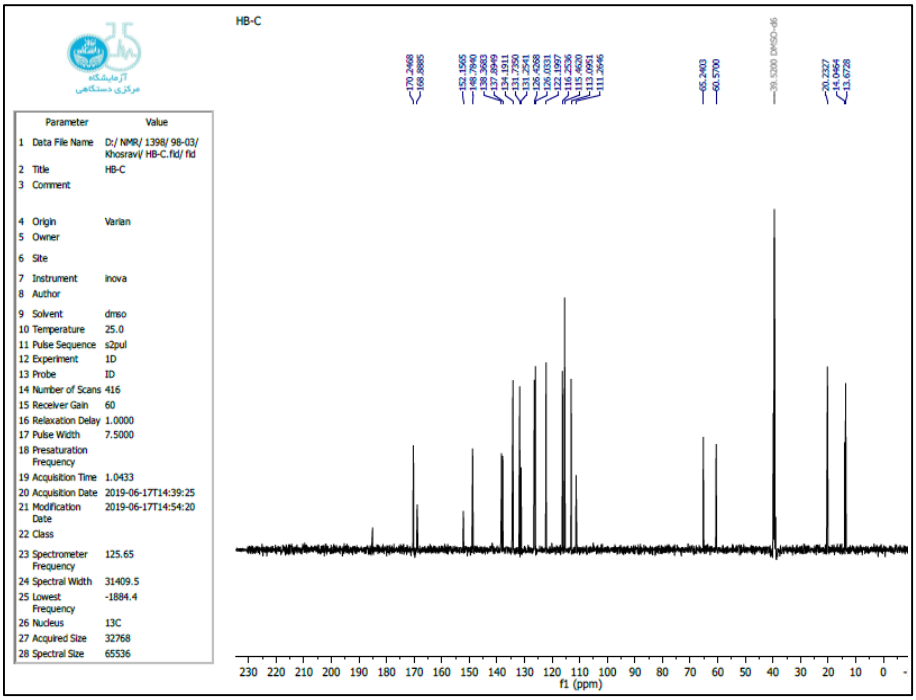


FIGURE 7. 13C-NMR range of 2a.

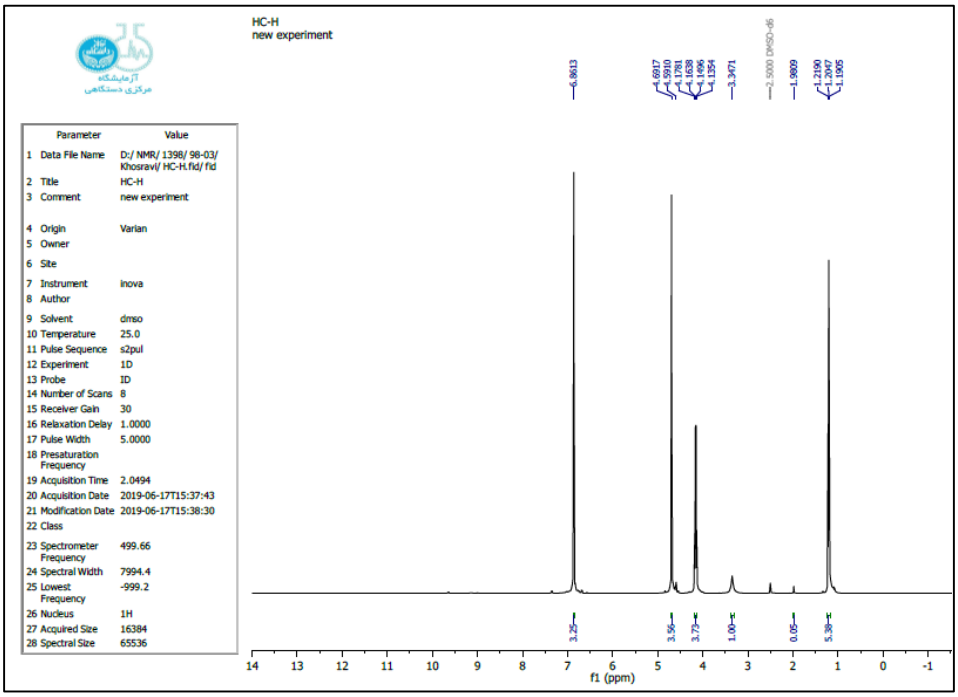


FIGURE 8. 1H-NMR range of 3a.

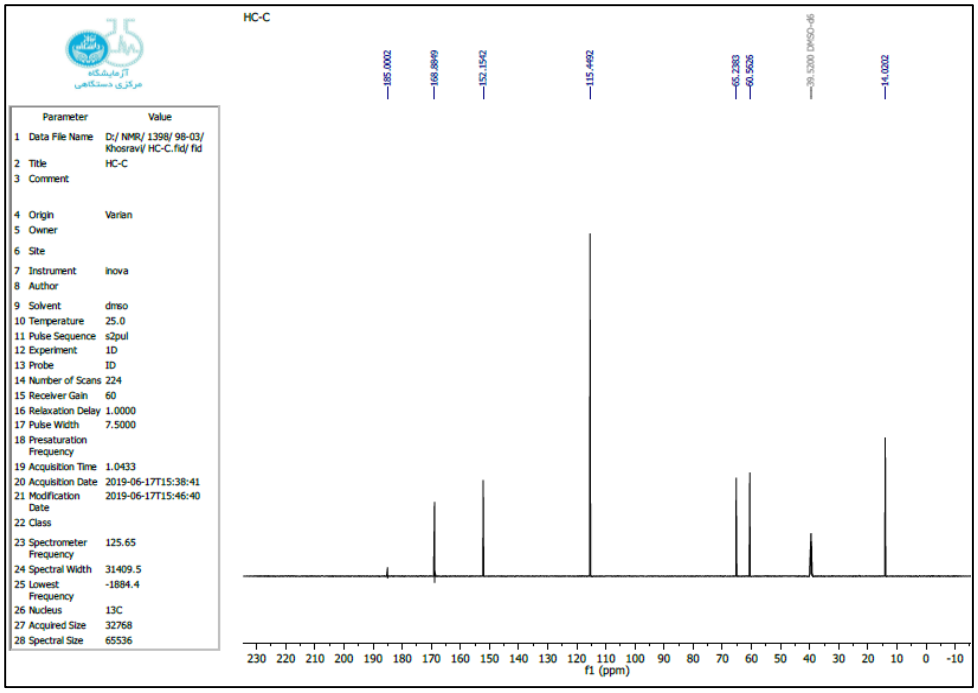


FIGURE 9. 13C-NMR range of 3a.

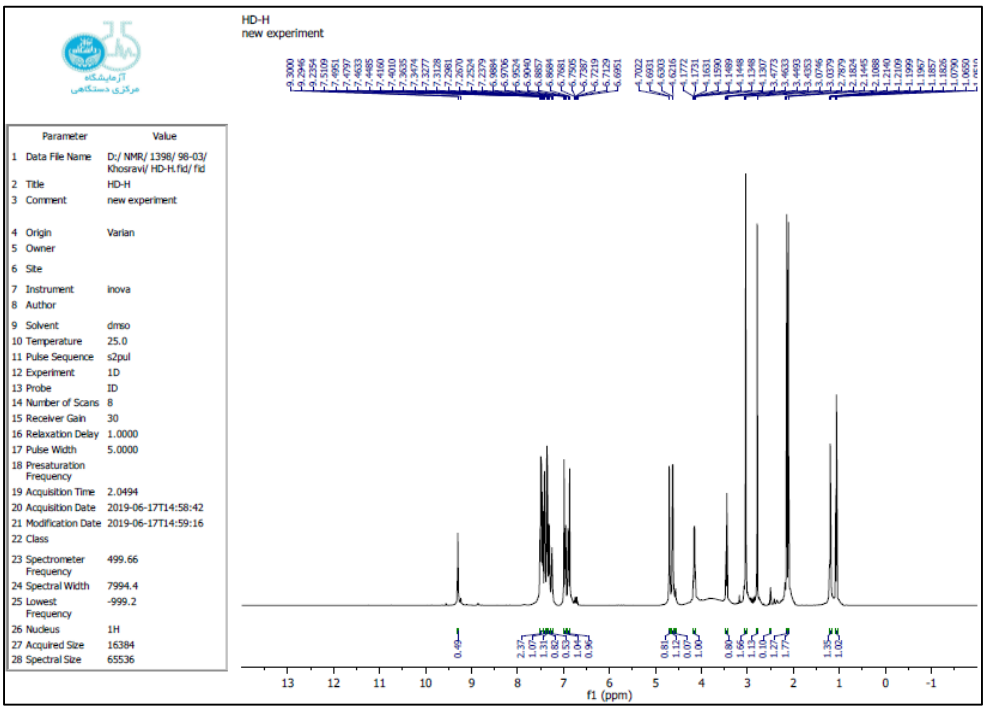


FIGURE 10. 1H-NMR range of 4a.

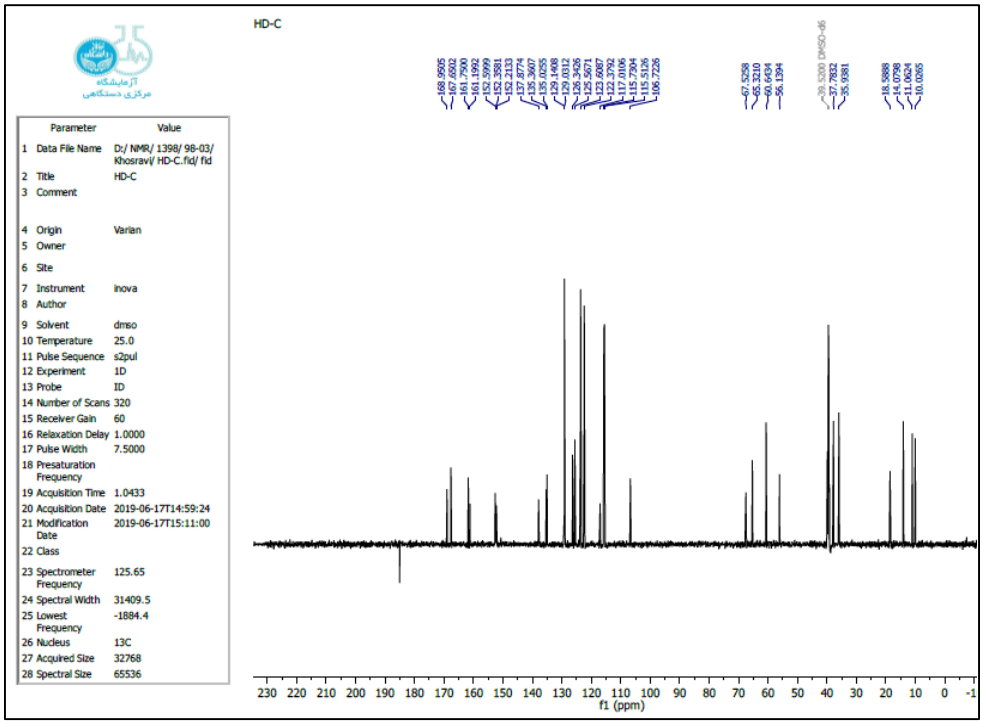


FIGURE 11. 13C-NMR range of 4a.

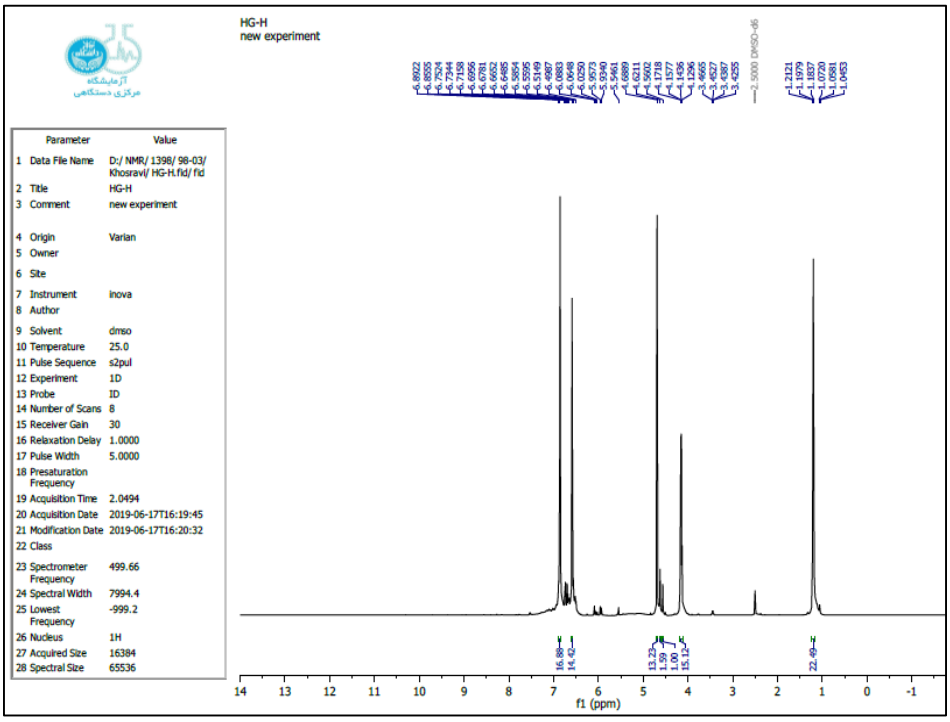
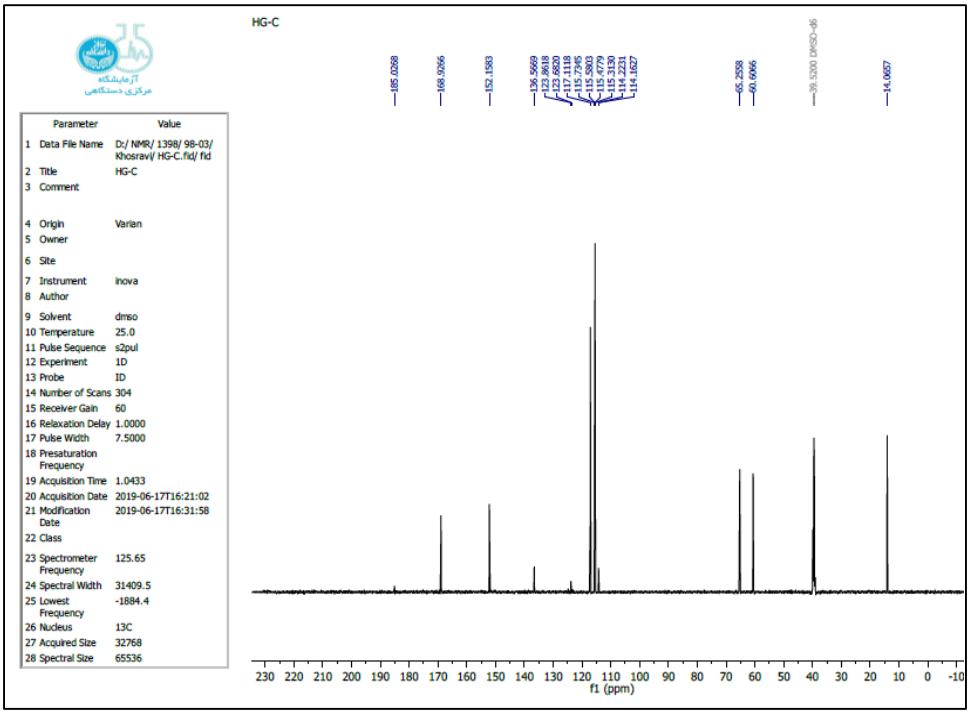


FIGURE 12. 1H-NMR range of 5a.



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8 Author	
9 Solvent	dmso
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11 Pulse Sequence	s2pul
12 Experiment	1D
13 Probe	ID
14 Number of Scans	304
15 Receiver Gain	60
16 Relaxation Delay	1.0000
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18 Presaturation Frequency	
19 Acquisition Time	1.0433
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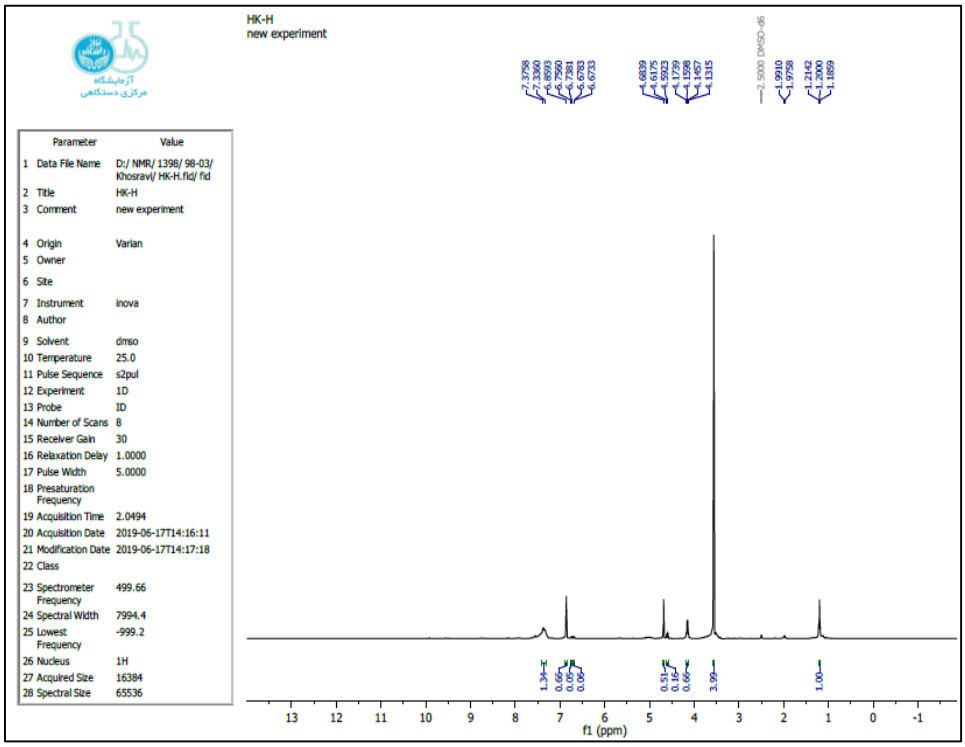
FIGURE 13. ^{13}C-NMR range of 5a.



Parameter	Value
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6 Site	
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8 Author	
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28 Spectral Size	65536

FIGURE 14. 1H-NMR range of 6a.

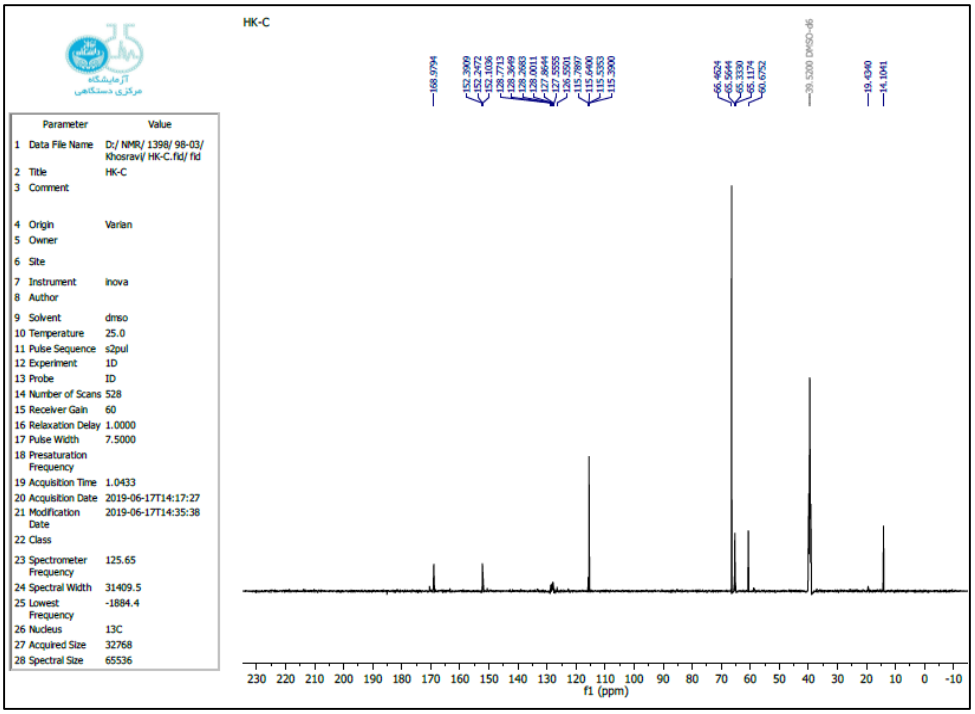

FIGURE 15. 13C-NMR range of 6a.

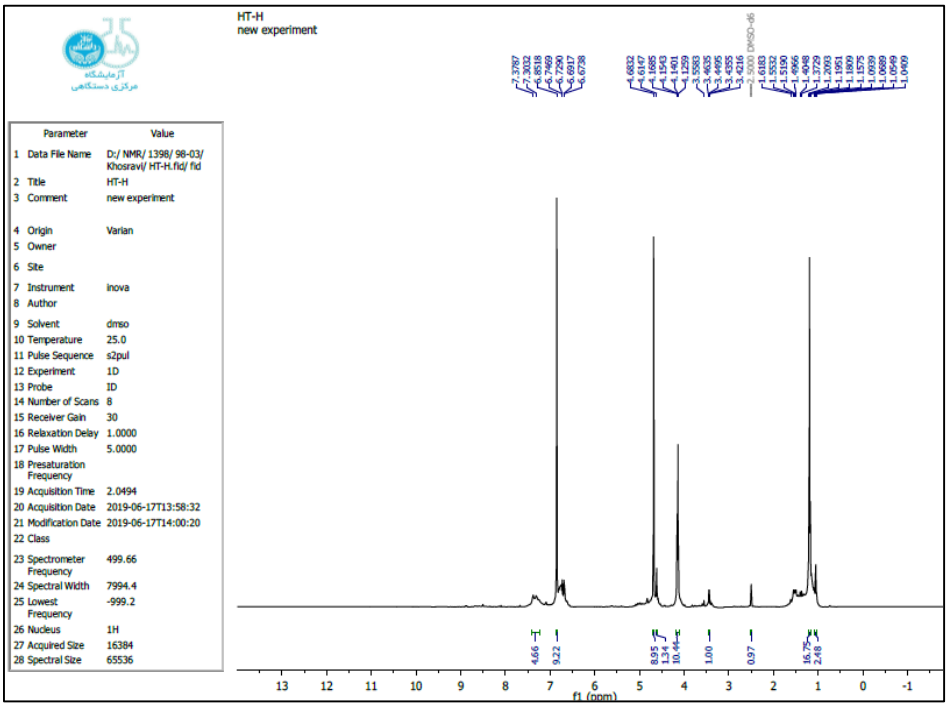

FIGURE 16. 1H-NMR range of 7a.

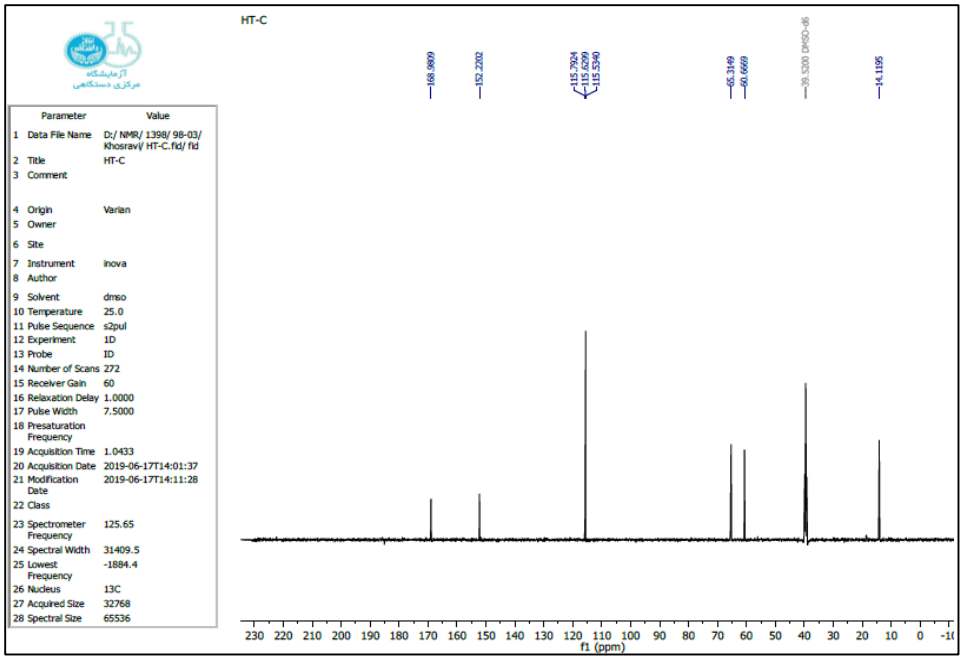

FIGURE 17. 13C-NMR range of 7a.

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