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Solvent-Free One-Pot Synthesis of Butyl N-[(2-Hydroxy-1-naphthyl)(aryl)methyl]carbamate Derivatives and Their Biological Evaluation

Sadeq H Saleh Azzam[1] *, Sami Q.S. Abdullah[1,2], Maher A Al Maqtari[1] and Mona Saad Al-Ezzi[2]

[1]**Department of Chemistry, Faculty of Sciences, Sana'a University, Sana'a, Yemen,**
[2]**Department of Chemistry, Faculty of Sciences, Dhamar University, Dhamar, Yemen**

*Corresponding author: s.azzam@su.edu.ye, azam.sadeq@gmail.com

Abstract

We report a highly efficient method for synthesizing carbamatoalkyl naphthols *via* one-pot, three-component condensation involving 2-naphthol, aldehydes, and butyl carbamates. This reaction, facilitated by cerium ammonium nitrate, can be performed under solvent-free conditions at 80°C and generally occurs within a short time frame. The resulting compounds were thoroughly characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry. Additionally, the antimicrobial properties and biocompatibility of the newly synthesized compounds were evaluated using laboratory tests. The findings indicated that these compounds exhibited significant biological activity compared to standard antibiotics, and their hemocompatibility was confirmed.

Article Info

Keywords:
Carbamatoalkyl naphthol's, Cerium ammonium nitrate, One-pot synthesis, Solvent-free condition.

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1. INTRODUCTION

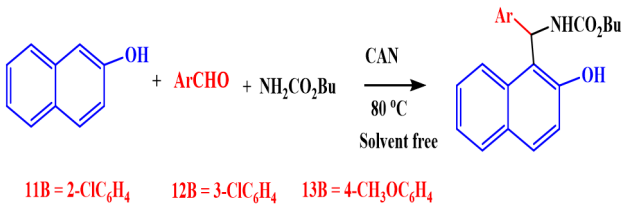
The synthesis of complex organic molecules with various functional groups is pivotal in medicinal chemistry because these compounds frequently exhibit significant biological activity. Carbamatoalkyl naphthols represent a vital class of compounds recognized for their wide-ranging pharmacological characteristics, including anti-inflammatory, antioxidant, and antimicrobial activities. Developing efficient and sustainable synthetic methods for these molecules is essential to explore their potential as therapeutic agents [1].

Multicomponent reactions are integral to organic synthesis [2], medicinal chemistry [3], and material science [4]. This atom-efficient method involves combining three or more reactants in a single operational step to produce the final product [5], allowing for the rapid production of extensive libraries of organic molecules. A considerable number of notable multicomponent reactions have been identified from the Strecker $alpha$-aminonitrile synthesis to the Groebke–Blackburn–Bienaymé reaction [6].

Carbamatoalkyl 2-naphthols, which are significant intermediates of biologically active compounds, can be easily synthesized *via* a three-component reaction that includes 2-naphthol, methyl carbamate [7–9], and aromatic aldehydes [10, 11]. However, relatively few studies have focused on their syntheses. The 1,3-aminooxygenated functional motif is present in numerous natural products and drugs [12–15]. Naturally occurring compounds such as sedridine, allosedridine, febrifugine, nikkomycin Z, and negamycin, which possess a 1,3-aminooxygenated moiety, exhibit antifungal and antibacterial properties [16]. Additionally, marketed drugs such as ritonavir and lopinavir—approved antiretroviral treatments for HIV/AIDS, haloperidol [17–19], venlafaxine (an antipsychotic), desvenlafaxine (antidepressants) [20], vildagliptin (an antidiabetic) [21], and tramadol (a synthetic analgesic) [22], also contain a 1,3-aminooxygenated motif. The extensive list of commercially available bioactive compounds contains a 1,3-aminooxygenated motif. An extensive list of bioactive molecules featuring 1,3-aminooxygenation highlights the

importance of exploring additional valuable and pharmaceutically relevant compounds that contain this functional group.

Naphthalene derivatives have been recognized for their various biological activities, including anti-inflammatory [23], antibacterial [24–26], cardiovascular [27], antiproliferative, and antiviral properties [28]. One category of these compounds includes 1-amidoalkyl-2-naphthols, which contain a significant 1,3-aminooxygenated moiety in their structures along with an amide bond. Cerium ammonium nitrate (CAN) has become increasingly important in organic reactions owing to its many benefits, including high reactivity, easy accessibility, simple handling, and stability across different solvents [29]. This study highlights the catalytic effectiveness of CAN for the efficient three-component synthesis of carbamatoalkyl naphthols (11B-13B) under solvent-free conditions (**Scheme 1**).



scheme 1. Three-component synthesis of carbamatoalkyl naphthols catalyzed by CAN.

2. MATERIALS AND EXPERIMENTAL METHODS

2.1. Experimental

All reagents were of analytical grade, obtained from the Shanghai Chemical Reagent Company, and used without further purification. Some materials were supplied by the Faculty of Science at Sana'a University, whereas others were purchased from reputable companies both inside and outside Yemen. All chemicals used in this study were of high quality and produced by Schreck GmbH, a German company. The melting points were determined using an RD-II micromelting point apparatus. Infrared spectra were collected using a Varian Scimitar 2000 series Fourier transform instrument. ^{1}HNMR and ^{13}C NMR spectra were recorded on an Agilent 300-MHz instrument in DMSO-d_6, with TMS as the internal standard. Mass spectrometry analysis was performed using an Agilent 1100 Series LC/MSD VL ESI instrument.

2.2. Method for the Synthesis of Carbamatoalkyl Naphthols (B)

The standard synthesis procedure included the combination of β-naphthol (5 mmol), an aldehyde (5 mmol), and a carbamate (5.5 mmol) in a reaction vessel. Subsequently, cerium ammonium nitrate (CAN) (0.1 mmol) was added to the mixture. The reaction was stirred magnetically in a preheated water bath set at 80 ℃. Once the reaction was complete, as monitored by thin-layer chromatography (TLC), the mixture was allowed to cool to ambient temperature. It was then washed with a 1:1 (v/v) water/ethanol solution, and the resulting product was recrystallized from a 2:3 (v/v) water/ethanol mixture. The conditions and components used to prepare the compounds are listed in **Table 1.**

2.3. Spectral measurements

At the Spectroscopy Laboratory, Faculty of Science, Sana'a University, the compounds were analyzed using infrared (IR) spectroscopy, with measurements conducted in the wavenumber range of 400–4000 cm^{-1} using F-IR-4800S (Shimadzu, Japan) equipment. The compounds were characterized by ^{1}HNMR 300 MHz, ^{13}CNMR 75 MHz, and MS at the Microanalysis Center, Faculty of Science, Cairo University, Egypt.

2.4. Biological Screening

The newly synthesized compounds (11B, 12B, and 13B) were tested for antimicrobial activity in *vitro* at various concentrations. The testing included two gram-negative bacteria, *Salmonella* and *Escherichia coli*, as well as two gram-positive bacteria, *Staphylococcus aureus* and *Bacillus subtilis*. In addition, two fungal species, *Aspergillus flavus* and *Candida*, were screened. A modified Kirby-Bauer disk diffusion method was used for this purpose.

employing clinical isolates. All microbial strains were obtained from the Microbiology Laboratory, in the Department of Microbiology, Sana'a University, Sana'a City, Yemen. As test organisms, these bacterial strains were cultured on nutrient agar for 24 h to enhance their viability, followed by adjusting their turbidity to 0.5 McFarland standard using sterile saline. The prepared bacterial suspensions were carefully spread on Mueller-Hinton agar plates. [30]. The prepared fungal suspension was carefully spread to Sabouraud dextrose agar plates. Using sterile techniques, each compound was dissolved in dimethyl sulfoxide, and a 1 mg/ml solution was prepared. This solution was then used to prepare different concentrations, including 6.2, 12.5, 25, 50, 75, and 100 μg/ml.

2.5. Hemolytic Activity and Compatibility with Human Red Blood Cells

To evaluate the compatibility of compounds derived from *P. somniferus*, fresh red blood cells (RBCs) were obtained from a healthy volunteer. Blood samples were col-

Table 1. Synthesis of Carbamatoalkyl Naphthol's in the Presence of CAN Without Solvent.

Compound	ArCHO	Solvent (mL)	n (1) : n (2) : n (3)	CAN (mmol)	Time (h)	Yield (%) [b]
1	4-$CH_3C_6H_4$	Free	1:1:1	1.0	2	6
2	3-$CH_3C_6H_4$	-	1:1:1	1.0	3	8
B11	2-ClC_6H_4	-	1:1:1	1.0	1	94
B12	3-ClC_6H_4	-	1:1:1	1.0	1	90
B13	4-$CH_3OC_6H_4$	-	1:1:1	1.0	1	85

lected in EDTA tubes, and 3 mL was used for erythrocyte isolation. The sample was centrifuged at 14,000 rpm for 5 min to create a pellet, which was subsequently washed three times using phosphate-buffered saline (PBS). Finally, 9.8 ml of PBS was added to 200 μL of the pellet [31].

The test substance was prepared by dissolving 1000 μg/ml in 0.5 mL of dimethyl sulfoxide (DMSO). Subsequently, saline solution (0.5 mL) was added. Various concentrations of the solutions were obtained. The erythrocyte suspension was then mixed with the different test sample concentrations and incubated at 37 ℃ for 1 h. Following incubation, the mixture was centrifuged for 10 min at 2500 rpm. The supernatant was collected and distributed into a 96-well plate, and hemoglobin release was measured at 540 nm. DMSO and Triton X-100 were used as the negative and positive controls, respectively. The percentage of hemolysis was calculated using the following formula:

%Hemolysis = [{(sample absorbance) _ (negative control absorbance)}O {(positive control absorbance) _ (negative control

The analysis was performed at Alpha International Specialized Laboratory in Dhamar, Yemen.

3. RESULTS AND DISCUSSION

This is a model for green and efficient multicomponent synthesis. The combination of β-naphthol, aldehyde, and carbamate under CAN catalysis favored the formation of 1-carbamatoalkyl-2-naphthols *via* electrophilic aromatic substitution. CAN is a Lewis acid that activates the aldehyde carbonyl and enables nucleophilic attack by β-naphthol and the subsequent addition of carbamate [29]. Advantages of this process are the relatively mild reaction conditions (80℃ water bath), low catalyst loading (0.1 mmol CAN), shorter reaction times (typically 50–60 min), high atom economy, and environmentally friendly work-up without the need for organic solvents during the reaction step. It is green chemistry principle-compatible and does not require toxic reagents or demanding conditions. Firstly, the reaction was carried out to prepare the target compounds using 4-methylbenzaldehyde and 3-methylbenzaldehyde as substrates. However, the product yields in both cases were low 6% and 8%, respectively (Table 1).

Reaction completion was monitored by TLC, which typically showed a single spot indicating high conversion. The target carbamatoalkyl naphthols were obtained in high yields (85–95%), considering the nature of the aldehyde and carbamate used. The yield of the product with aryl aldehydes containing electron-withdrawing groups (EWGs) is higher than that with aryl aldehydes bearing electron-donating groups (EDGs). This can be explained by the electron-withdrawing groups on aryl aldehydes, which enhance reactivity by stabilizing intermediates (such as o-QMs or iminium ions) and increasing electrophilicity. This directly correlates to higher product formation rates and yields, which facilitates the formation of intermediates, and increase electrophilicity, making them more reactive toward nucleophiles. In contrast, EDGs destabilize the intermediate, decrease electrophilicity, and lower reactivity. Therefore, aryl aldehydes with EWGs are more reactive, which accounts for their better product yields than aryl aldehydes with EDGs. The final product purity was excellent after recrystallization, as confirmed by spectroscopic techniques such as IR, ^{1}H NMR, ^{13}C NMR, and MS. The product generally appeared as a yellow to brown solid with a distinct melting point, indicating a pure and high-quality compound.

The spectrum data analysis for the newly obtained compounds is shown below:

Butyl[(2-Chlorophenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-carbamate (11B)

Brown crystals; (203-204 °C).

IR (KBr): 3422, 3198, 3075, 2959,1737, 1623, 1583, 1432, 1341, 1069, 749, 605 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm = 10.21 (s, 1H, NH), 7.92-7.12 (m, 10H, ArH), 6.84 (d, 1H, J = 7.8 Hz, CH), 4.02 (s, 1H, OH), 2.63 (t, 2H, CH_2), 1.62 (qu, 2H, CH_2), 1.34 (se, 2H, CH_2), 0.85 (t, 3H, CH_3) ppm.

^{13}C NMR (75 MHz, DMSO-d_6): δ ppm = 174.12, 153.01, 145.26, 132.90, 131.98, 130.12, 129.72, 128.72, 126.82, 126.43, 124.82, 122.85, 118.38, 67.63, 49.99, 30.75, 18.63, 13.65 ppm; MS (EI, 70 Ev): M/Z (%) 383 [(M^{+1}), 230, (100%)].

Butyl[3)-Chlorophenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-carbamate (**12B**)

Brown yellowish crystals;(201-202 °C).

IR (KBr): 3432, 3221, 3056, 2957, 1735, 1613, 1520, 1432, 1334, 1051, 750, 671 cm^{-1}; ^{1}H NMR (300 MHz,

DMSO-d_6): δ ppm = 9.93 (s, 1H, NH), 7.93-7.22 (m, 10H, ArH), 6.87 (d, 1H, J = 7.6 Hz, CH), 3.93 (s, 1H, OH), 2.95 (t, 2H, CH_2), 1.58 (qu, 2H, CH_2), 1.28 (se, 2H, CH_2), 0.86 (t, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ ppm = 167.15, 153.54, 138.41, 132.90, 131.98, 130.12, 129.72, 128.72, 126.82, 126.43, 124.82, 122.85, 118.38, 63.81, 49.99, 30.75, 18.40, 13.64 ppm; MS (EI, 70 eV): m/z (%) 383 [(M^{+1}), 230 (100%)].

Butyl[-2) Hydroxy- naphthalen-1-yl) -(4-methoxy-phenyl)-methyl]-carbamate (13B))

Brown crystals; (208-209 °C).

IR (KBr): 3432, 3213, 3060, 2958, 1734, 1620, 1517, 1431, 1332, 1059, 748, 625 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm = 9.94 (s, 1H, NH), 7.82-7.03 (m, 10H, 1H, OH), 2.51 (t, 2H, CH_2), 2.25 (qu, 2H, CH_2), 1.61 (se, 2H, CH_2), 0.81 (t, 3H, CH_3) ppm.

^{13}C NMR (75 MHz, DMSO-d_6): δ ppm = 173.77, 152.94, 141.26, 134.88, 132.37, 129.84, 128.99, 126.55, 125.84, 123.14, 122.75, 120.51, 118.64, 68.76, 46.05, 27.65, 21.47, 14.64 ppm; MS (EI, 70 eV): m/z (%) 379 [(M^{+1}), 143(100%)].

3.1. Biological Activity

The newly synthesized compounds 11B, 12B, and 13B were evaluated in *vitro* for their antimicrobial activity against two gram-negative bacteria, *Pseudomonas aeruginosa* and *Escherichia coli*, and two gram-positive bacteria, *Staphylococcus aureus* and *Bacillus subtilis*. In addition, their antifungal activities against *Aspergillus flavus* and *Candida albicans* were assessed. Reference agents, including the fungicide Nystatin and the bactericides Gentamicin, Vancomycin, Tetracycline, and Doxycycline, were used to benchmark the effectiveness of the tested compounds under identical conditions. The antimicrobial activity was quantified by measuring the zone of inhibition (mm) and calculating the percentage activity index. The results are presented in **Table 2 and Figure 1**.

The results shown in **Table 2** and **Figure 1** indicate that compounds 11B, 12B, and 13B demonstrated significant antimicrobial activity at all tested concentrations against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Candida albicans*, and *Aspergillus flavus*, surpassing that of the reference drugs. The presence of the hydroxyl group in these compounds may improve their antimicrobial properties by promoting the generation of reactive oxygen species **(ROS)**, which damage microbial membranes. Compounds 11B and 12B exhibited similar antimicrobial activities, with minor differences due to the varying positions of the chlorine groups. Compound 13B showed a slightly higher antimicrobial activity than 11B and 12B, likely because of the attached phenoxy group. This demonstrates that the phenoxy group enhances the antimicrobial effects of the (**YP51**) by enhancing the inhibitory effect of the enzyme and increasing oxidative stress.

3.2. Hemolysis Test Procedure

The hemolytic effects of the compounds 11B, 12B, and 13B were assessed at various concentrations in the concentration range of 125 to 1000 g/mL on human red blood cells (hRBCs) under physiological conditions (pH 7.4, 37 ℃) was evaluated against DMSO and TX100 [32] as the negative and positive controls, respectively, and the results are shown in **Figure 2** and **Table 3.**

Red blood cells are usually a useful tool for toxicity studies of the compounds being studied, as they membrane properties, due to their well-characterized membrane properties and are accessible. In practice, the findings indicated a slight lack of hemolytic effect of compounds 11B, 12B, and 13B at concentrations below 500 μg/mL compared to the 100% lysis of the positive control TX100, with no significant differences up to 750 μg/mL; however, cell lysis was observed at the highest tested concentration (1000 μg/mL).

Furthermore, the hemolytic effect of compounds 11B, 12 B, and 13B were below 750 μg/mL, which is considered a high dose. It is below the permissible range (<4.5%) [33], and although dose-dependent hemolysis is a common observation, the mechanism underlying this phenomenon remains unclear. Consequently, compounds 11B, 12B, and 13B may be considered nontoxic to hRBCs at low and moderate concentrations.

Continuing our efforts to discover and develop new routes for synthetic approaches to novel antimicrobial agents, the search for antimicrobial agents from natural sources, especially medicinal plants, has gained significant momentum. Plants such as *Boswellia sacra*, *Mirabilis jalapa*, and *Lawsonia inermis* have shown promising antimicrobial, antioxidant, and therapeutic properties, as documented in recent studies [34–36]. These findings highlight the potential of phytochemicals as a rich source of bioactive compounds. In countries such as Yemen, where foodborne infections and microbial diseases are still common due to poor hygiene practices and limited public awareness [37–39], both natural and synthetic strategies need to be prioritized. The current study adds to this effort by demonstrating the green, solvent-free synthesis of new carbamatoalkyl naphthols with strong antimicrobial activity and good biocompatibility. Therefore, integrating plant-based research with chemical synthesis can, play a crucial role in meeting the growing demand for effective and accessible antimicrobial therapies in resource-limited regions.

4. CONCLUSION

These results indicate that CAN serves as an effective catalyst for one-pot three-component condensation involving 2-naphthol, aromatic aldehydes (especially those

Table 2. Preliminary antibacterial activity of the synthesized compound.

Organic compounds at different concentrations	Inhibition Zone (mm) Microorganism					
	Bacteria				fungal species	
	Gram-positive		Gram-negative			
	Salmonella	E. coli	S. epidermidis	B. Subtilis	Candida	Aspergillus
11B 100%	20	20	30	27	46	40
11B 50%	15	18	25	25	30	30
11B 25%	15	15	20	21	25	30
11B 12.5%	11	15	20	20	23	26
11B 6.5%	11	13	20	20	20	25
12B 100%	15	15	21	25	35	40
12B 50%	13	17	20	22	30	32
12B 25%	13	17	20	20	27	30
12B 12.5%	12	18	18	23	25	28
12B 6.5%	10	15	16	20	20	22
13B 100%	23	15	27	23	44	55
13B 50%	19	13	22	19	35	40
13B 25%	23	17	22	17	32	33
13B 12.5%	18	15	20	15	30	30
13B 6.5%	23	16	20	15	25	30
Gentamycin	20	26	0	0	-	-
vancomycin	0	19	10	10	-	-
Tetracycline	26	13	16	0	-	-
Doxycycline	20	22	0	30	-	-
Nystatin	-	-	-	-	16	14

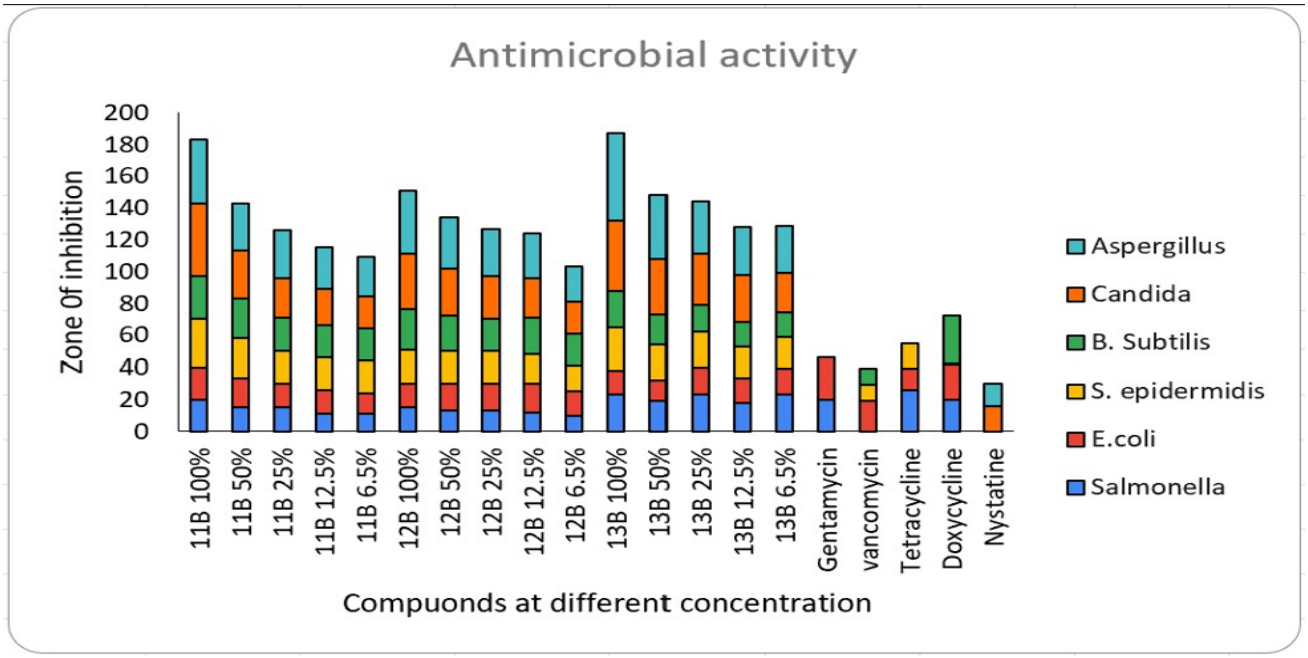


Figure 1. Antibacterial activity of synthesized compounds.

containing electron-withdrawing groups), and methyl butyl carbamates. This method offers several notable advantages, including the use of a cost-effective and readily available catalyst, mild reaction conditions, straightforward workup procedures, and high yields (85-94%). This study expands current methodologies for the synthesis

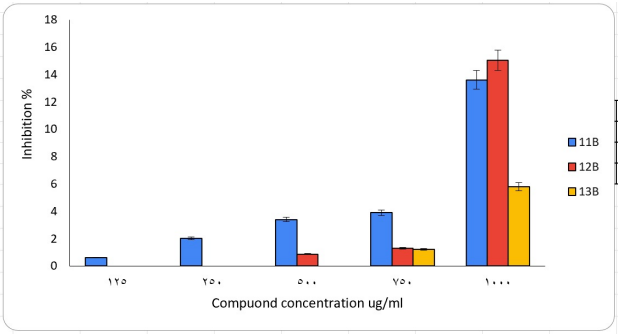


Figure 2. Percentage of hemolysis of hRBCs caused by the compounds under the test.

Table 3. Hemolytic activity compounds of on human erythrocyte cells.

Compounds at different concentrations (g/mL)					
	125	250	500	750	1000
11B	0.61	2.02	3.4	3.9	13.6
12B	0.00	0.00	0.86	1.31	15.05
13B	0.00	0.00	o.25	1.2	5.8

of target compounds. Furthermore, these compounds demonstrated greater compatibility with human cells and tissues at medium and low concentrations. Their biocompatibility appears to be influenced by factors such as shape, pH, size, and surface chemistry. Additionally, the compounds exhibited superior antimicrobial activity compared to that of standard antibiotics.

5. CONFLICT OF INTEREST

The authors declare no competing financial interests.

6. ETHICAL COMPLIANCE

All procedures performed in studies involving human participants were in accordance with the ethical standards.

7. SUPPORTING INFORMATION

Data supporting this publication are available under he references.

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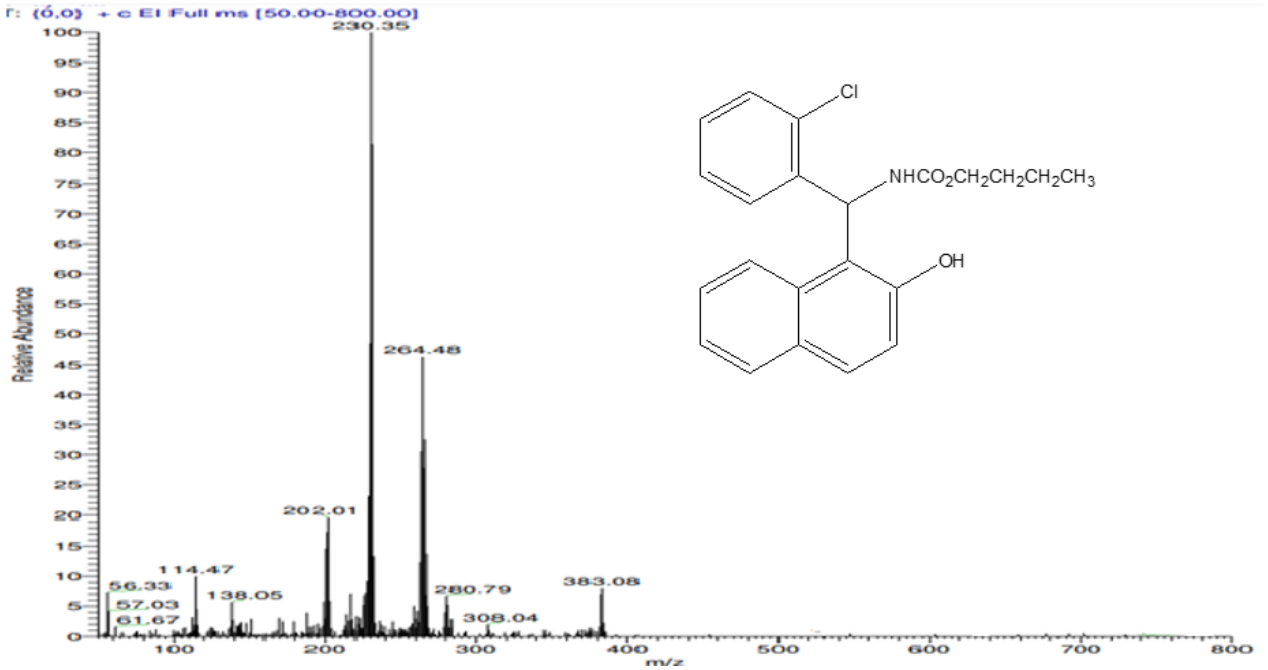
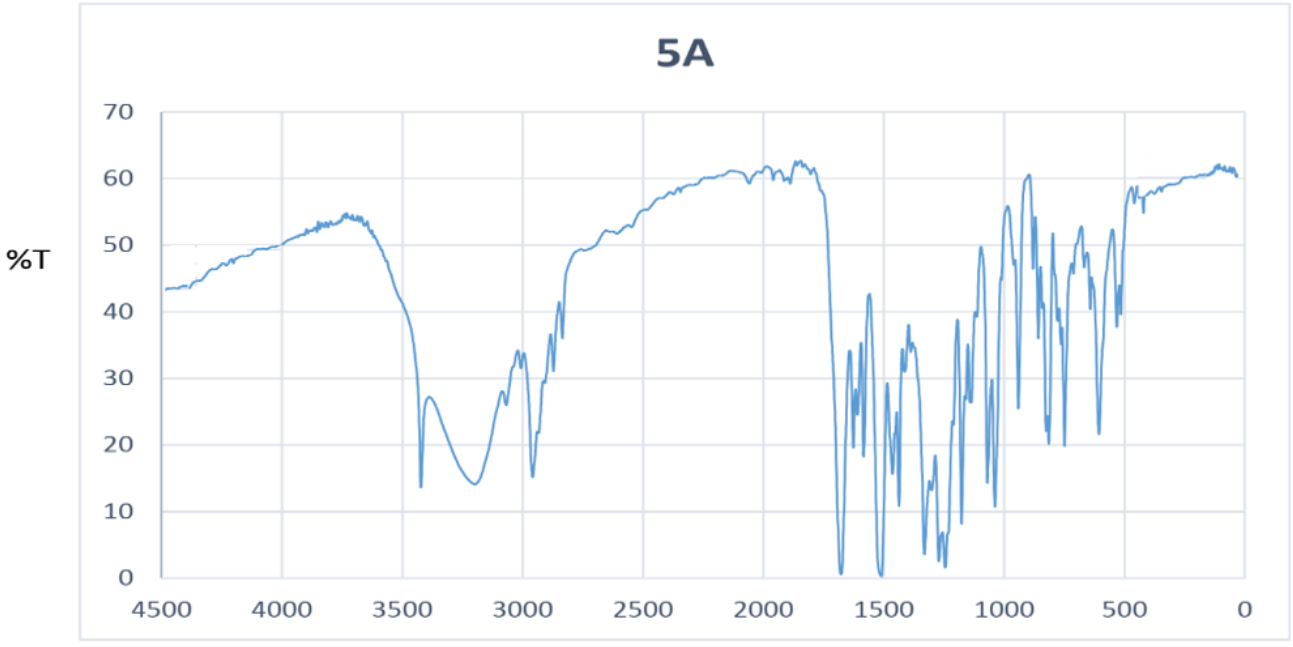
SUPPLEMENTARY INFORMATION MATERIALS

SPECTRAL ANALYSIS OF THE SYNTHESIZED NEW COMPOUNDS, INCLUDING MS, FT-IR, ^{1}H NMR, ^{13}C NMR:

1. **Butyl[(2-Chloro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-carbamat(11B)**





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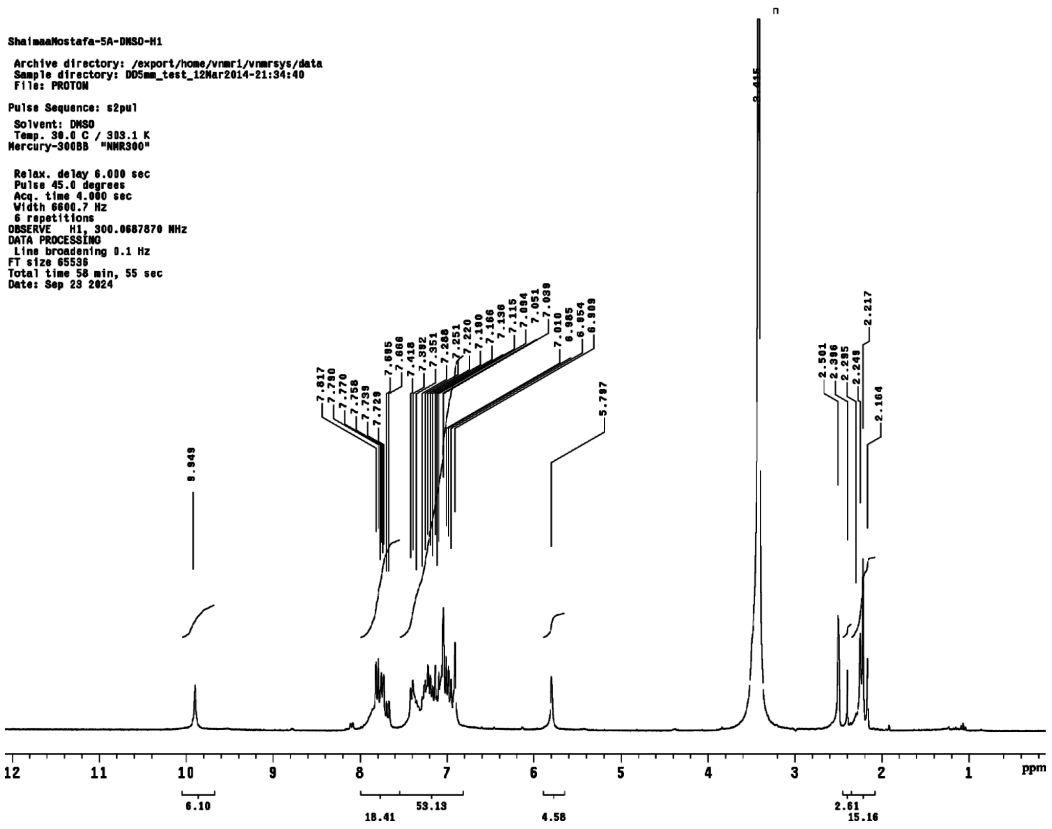
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Mercury-300BB "NMR300"
Relax. delay 6.000 sec
Pulse 45.0 degrees
Acq. time 4.000 sec
Width 6666.7 Hz
6 repetitions
OBSERVE H1, 300.0687870 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 58 min, 55 sec
Date: Sep 23 2024
8.049
7.817
7.790
7.770
7.758
7.739
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7.685
7.666
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7.382
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7.018
6.985
6.954
6.908
5.797
3.415
2.501
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2.217
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ppm
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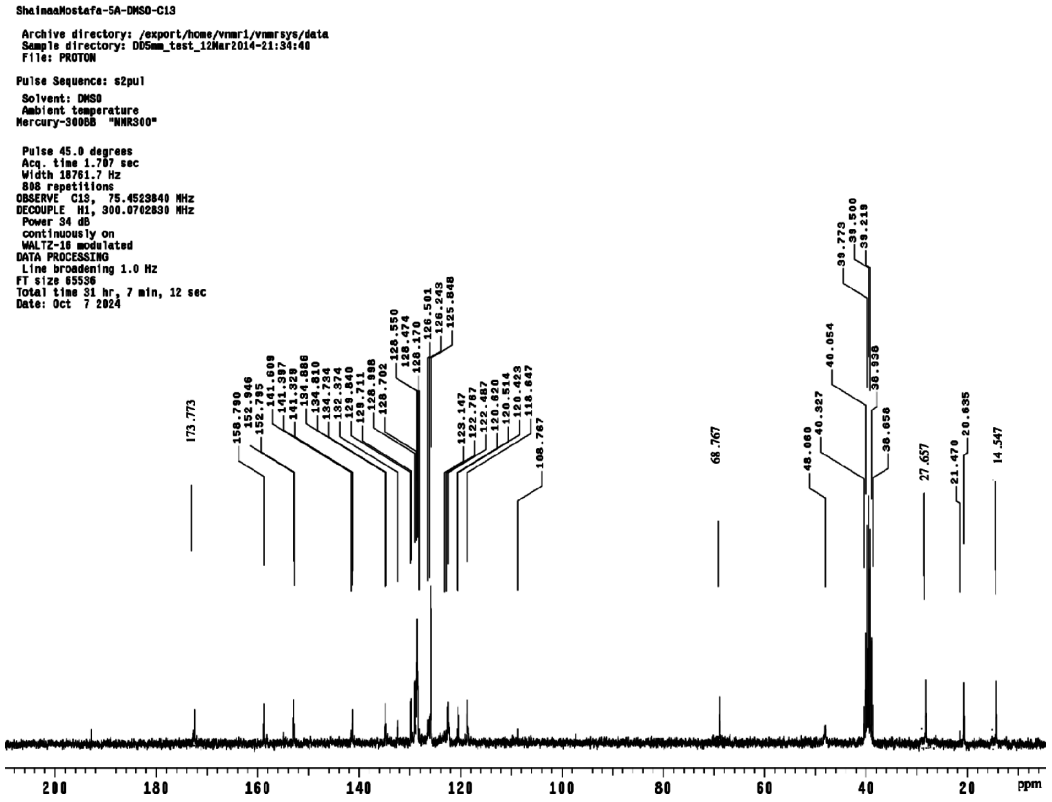
18.41
53.13
4.58
2.61
15.16

A5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Solvent: DMSO
Ambient temperature
Mercury-300BB "NMR300"
Pulse 45.0 degrees
Acq. time 1.707 sec
Width 18761.7 Hz
898 repetitions
OBSERVE C13, 75.4523840 MHz
DECOUPLE H1, 300.0702830 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 31 hr, 7 min, 12 sec
Date: Oct 7 2024
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152.946
152.795
141.669
141.397
141.238
134.886
134.810
134.734
132.374
129.840
129.711
128.398
128.702
128.550
128.474
128.170
126.591
126.243
125.848
122.147
122.787
122.487
120.620
120.514
120.423
118.647
108.767
68.767
39.773
39.560
39.348
39.218
40.054
38.938
38.656
40.060
40.327
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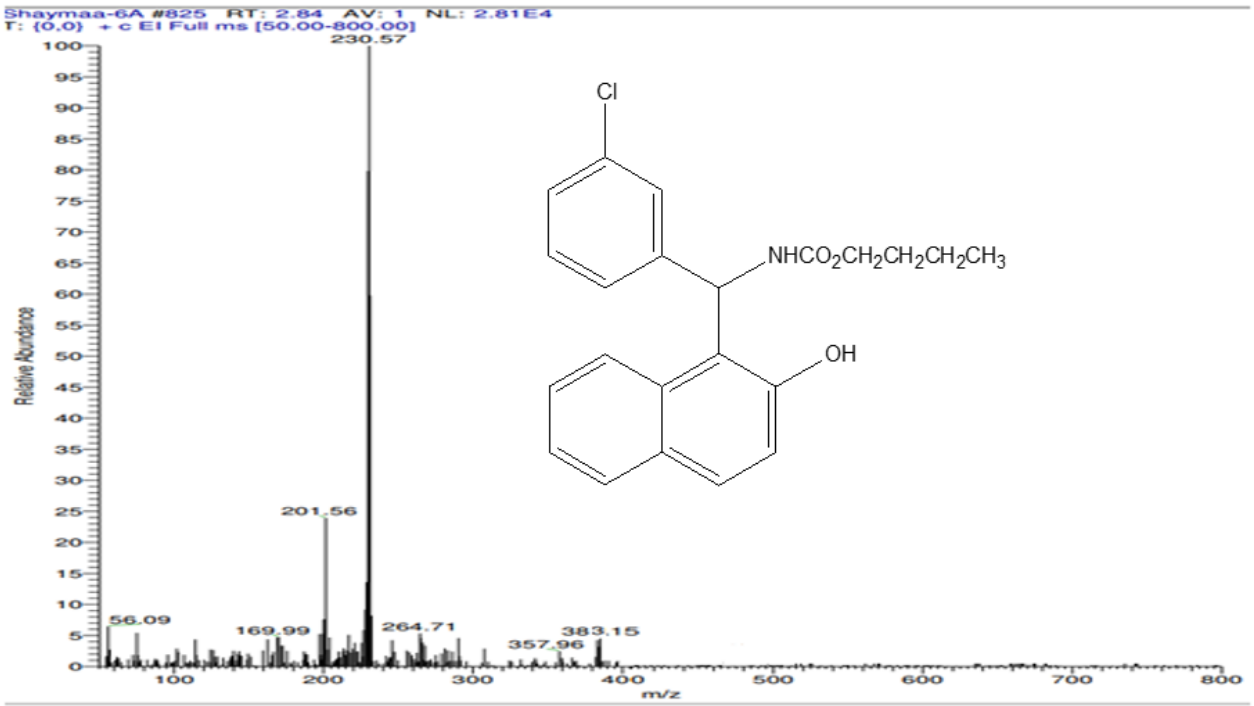
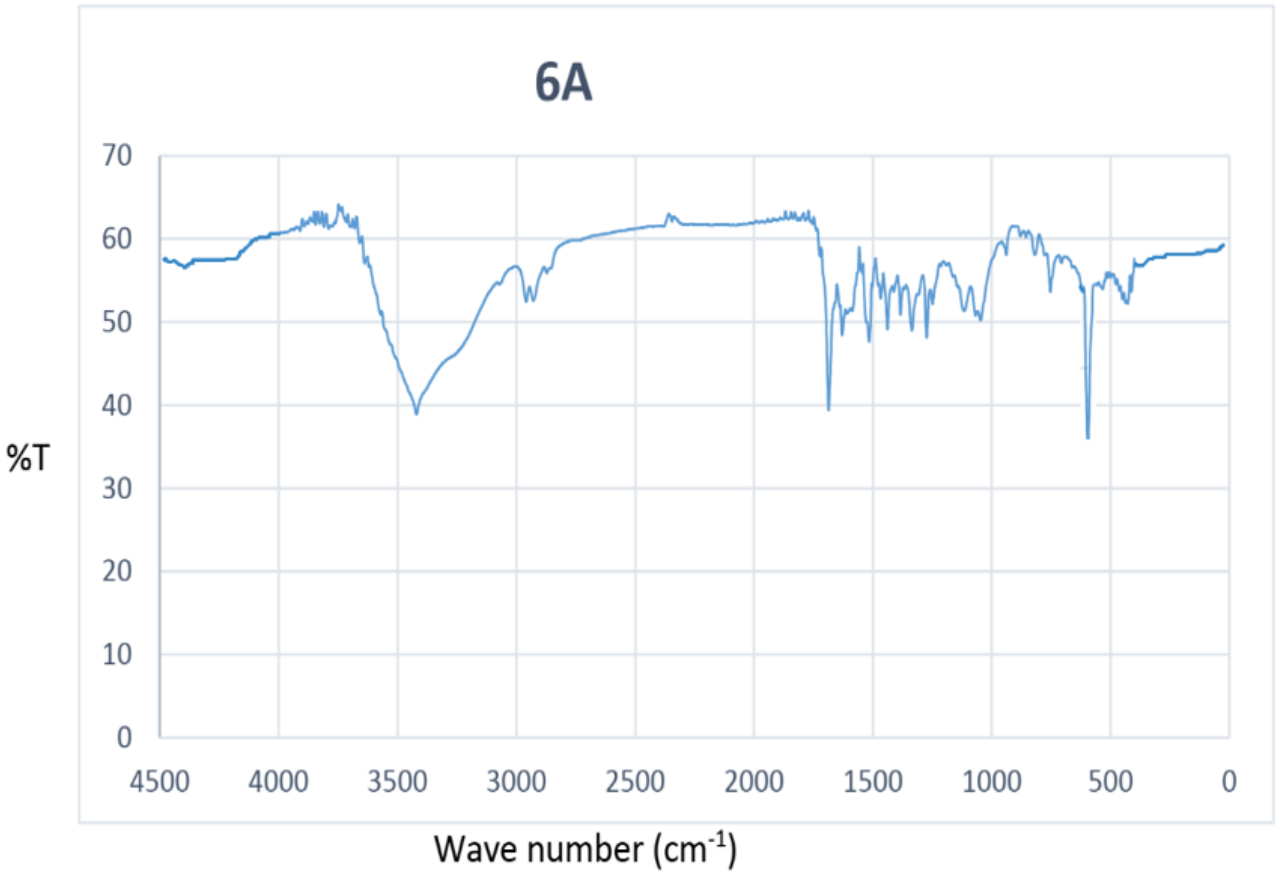
ppm

2. **Butyl[(3-Chloro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-carbamat(12B)**





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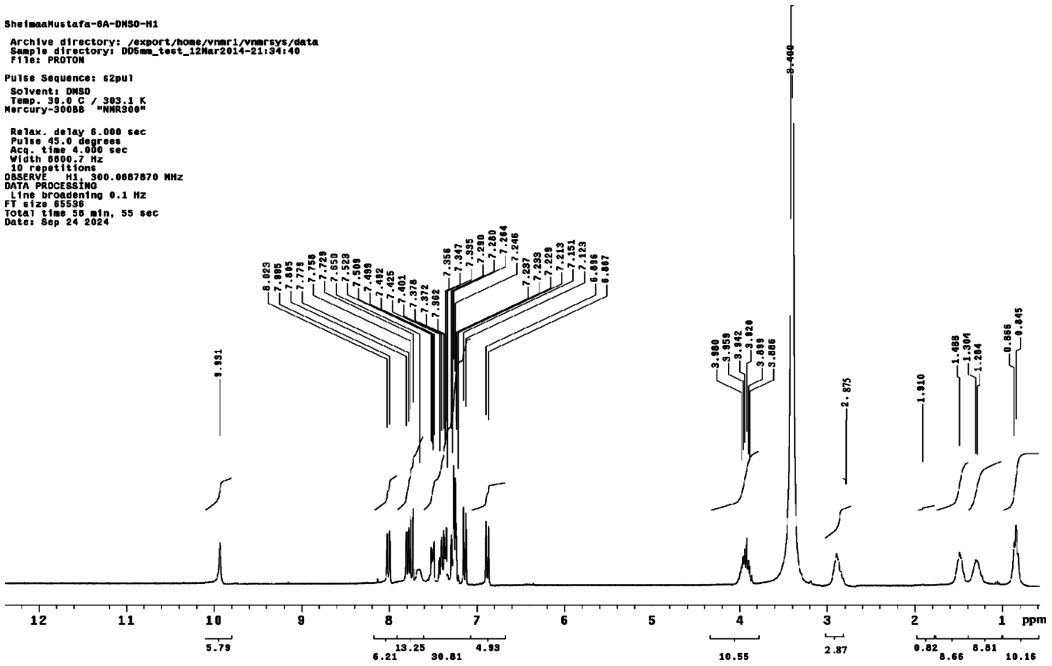

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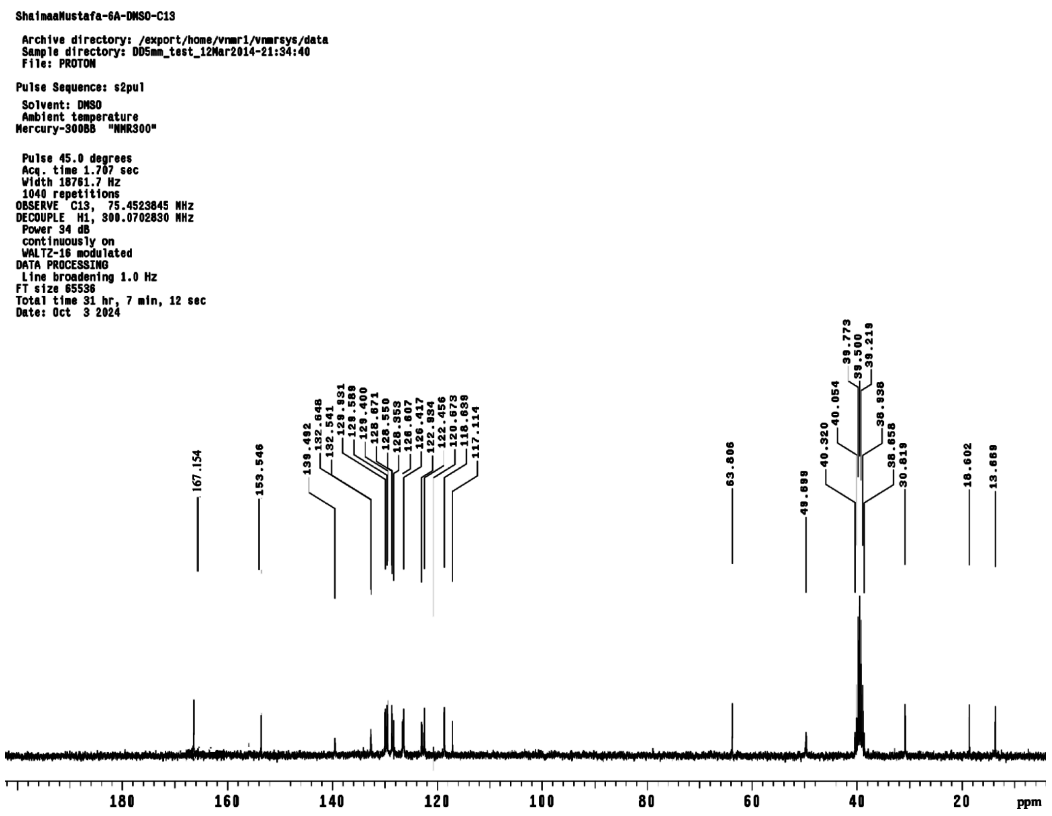

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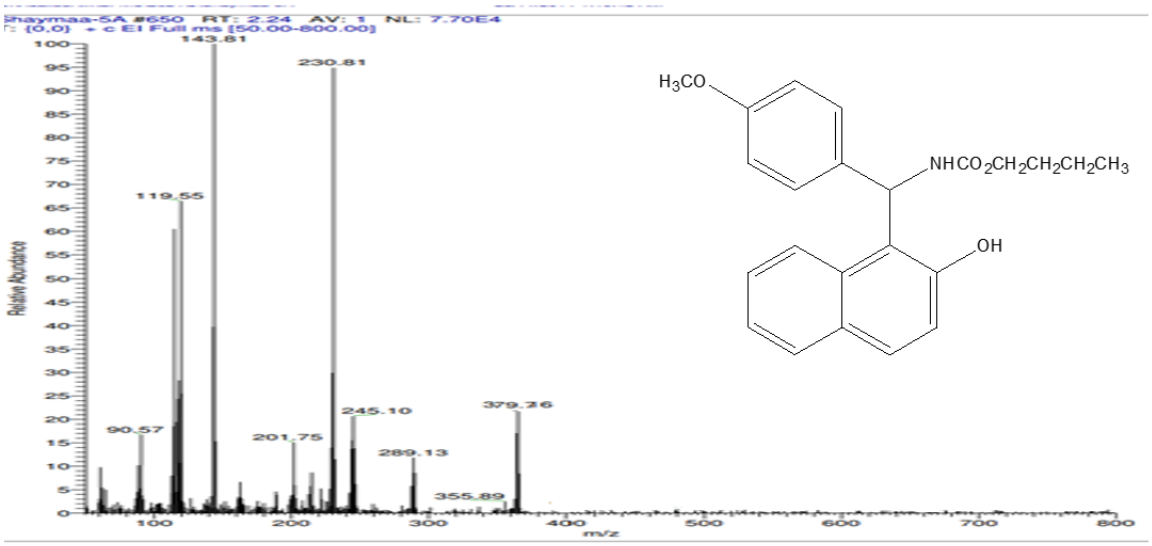
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119.55
90.57
201.75
245.10
289.13
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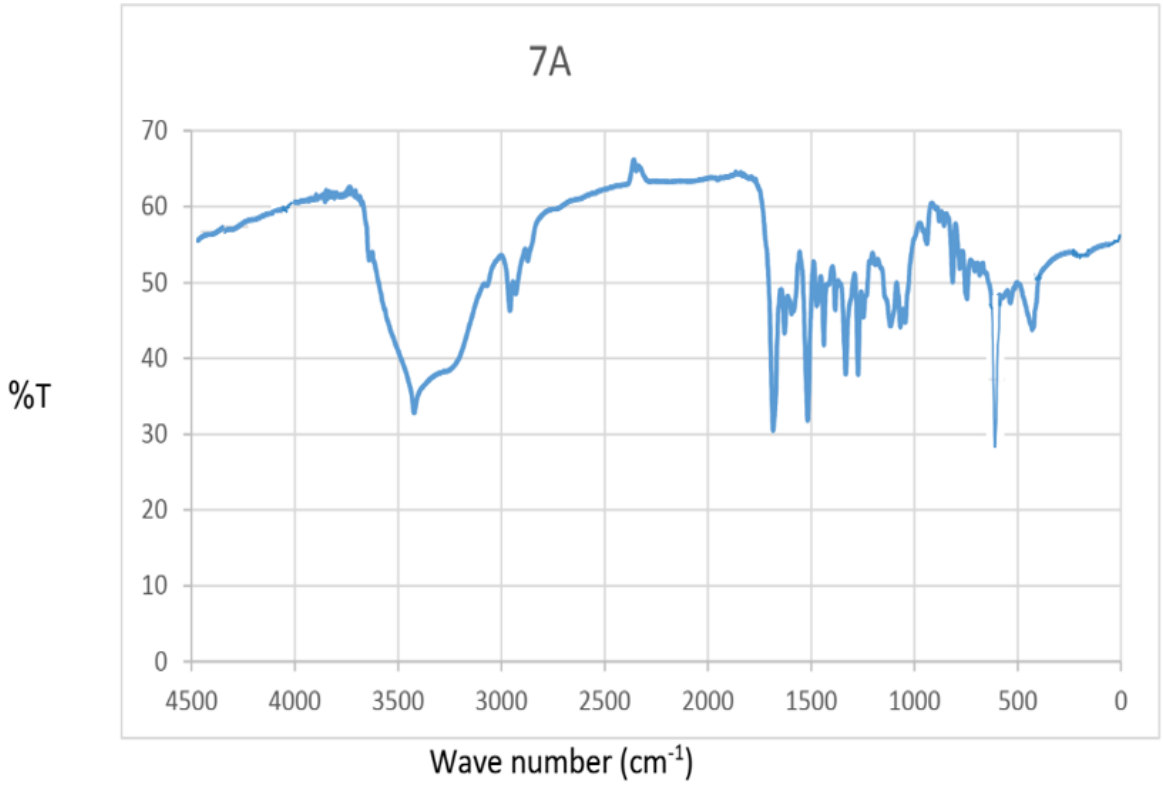
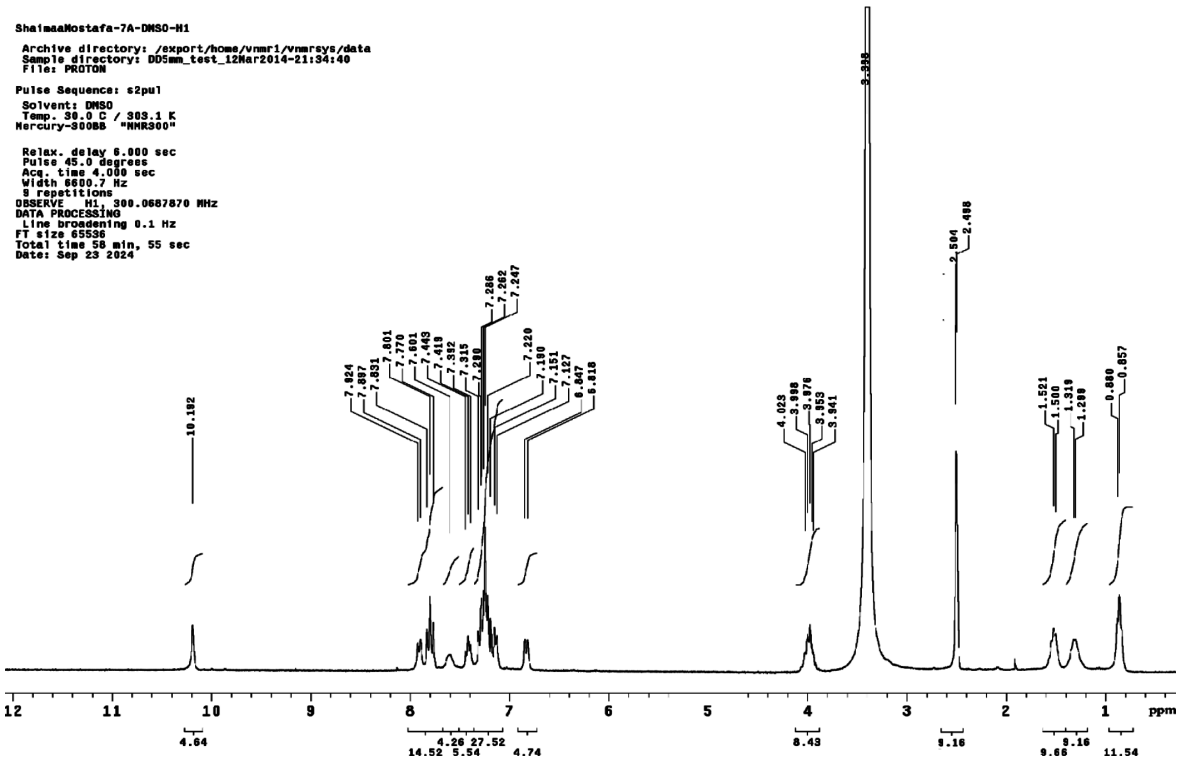
355.89
Relative Abundance
m/z
H3CO
NHCO2CH2CH2CH2CH3
OH


7A
%T
Wave number (cm-1)

A7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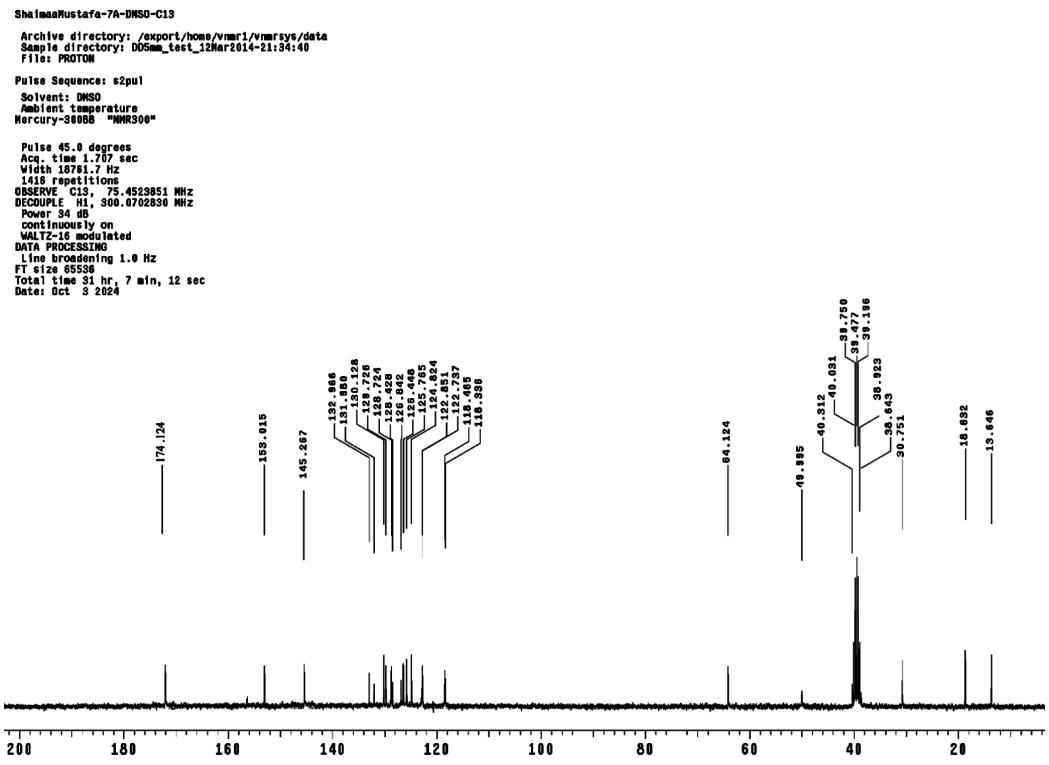
Solvent: DMSO
Temp. 30.0 C / 303.1 K
Mercury-300BB "NMR300"
Relax. delay 6.000 sec
Pulse 45.0 degrees
Acq. time 4.000 sec
Width 6600.7 Hz
8 repetitions
OBSERVE H1, 300.0687870 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 58 min, 55 sec
Date: Sep 23 2024
ppm

A7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Solvent: DMSO
Ambient temperature
Mercury-300BB "NMR300"
Pulse 45.0 degrees
Acq. time 1.707 sec
Width 18761.7 Hz
1418 repetitions
OBSERVE C13, 75.4523851 MHz
DECOUPLE H1, 300.0702830 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 31 hr, 7 min, 12 sec
Date: Oct 3 2024