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Original Research

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SDBS is Highly Alternative as a Green and Efficient Catalyst for the One-Pot Four-Component Synthesis of Imidazole Derivatives

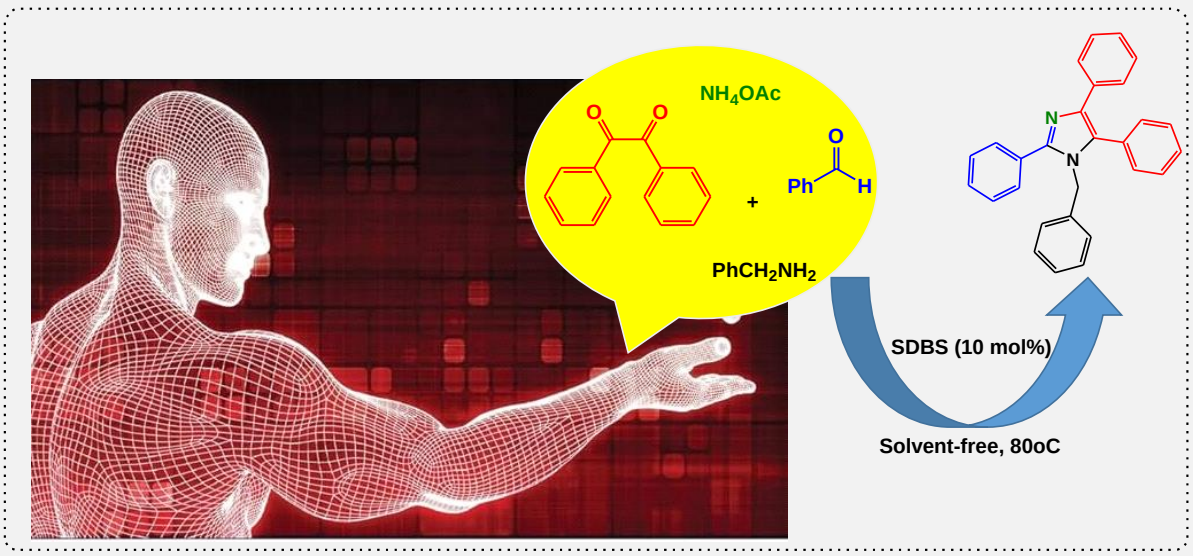
Alberto Sanchez-Mendoza*, Ivana Lago

[1]Faculty of Chemical Sciences, Complutense University of Madrid, Spain

[2]Faculty of Basic Sciences, Department of Chemical Chemistry, Complutense University of Madrid, Spain

Corresponding author-mail: Albertosanchezm@yahoo.com

ABSTRACT: Imidazoles are drugs with various biological properties such as antifungal, anti-inflammatory, analgesic, anti-tuberculosis, anti-depressant, anti-cancer and anti-viral. In this research, new derivatives of imidazoles were synthesized using anionic surfactant Sodium dodecylbenzene sulfonate (SDBS) as a catalyst From the four-component and three-component reaction of benzyl with aromatic benzaldehydes and first-type aliphatic and aromatic amines and ammonium acetate in the presence of SDBS as a catalyst in solvent-free conditions and at a temperature of 80 °C, derivatives of tetrasubstituted was synthesized with high yield. The structure of the synthesized compounds was confirmed using spectroscopic data. Among the features of this method are high yield, simple and mild conditions, one-pot reaction and no need for solvent.



KEYWORDS: Imidazole, Antifungal, Analgesic, Anionic Surfactant SDBS, Solvent-free.

Introduction

Heterocycle chemistry is one of the most important topics in the synthesis of organic chemistry [1]. Diazoles are flat ring molecules with the molecular formula $C_3H_4N_2$, which consist of three carbon atoms and two nitrogen atoms [2]. Diazoles are divided into two categories according to the position of nitrogen atoms in the ring: a) 1,2-diazoles (pyrazole) b) 1,3-diazoles (imidazole). Imidazole is a five-membered planar ring with the formula $C_3H_4N_2$, where nitrogens are placed in positions 1 and 3 [3]. This unusual

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aromatic ring is classified in the category of alkaloids and is one of the common substructures found in many natural compounds and substances that exhibit medicinal properties [4]. Amino acid histidine, histamine and biotin can be mentioned among these compounds. Imidazole derivatives such as ketoconazole, cimetidine and etomidate are used in the treatment of many systemic fungal infections and drug therapy[5] . The structure of these compounds is shown in **Figure 1**.

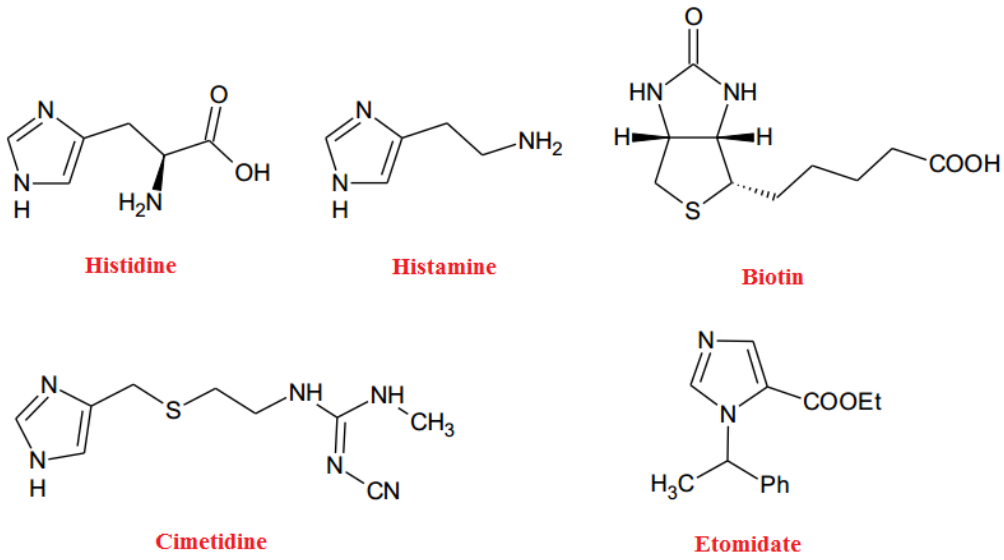

Figure 1. Structure of triazole compounds.

Biotin is necessary for the growth of cells, the metabolism of fatty acids, fats and amino acids. It also helps to keep blood sugar level stable and transfer carbon dioxide in the body [6]. Biotin consists of an ureido (tetrahydroimidazolone) ring fused to a tetrahydrothiophene ring. Various imidazole derivatives were discovered in 1840 [7]. In 1858, Heinrich Dibas succeeded in synthesizing imidazole for the first time. He has used the reaction of glyoxal and formaldehyde in ammonia to prepare imidazole. Due to the fact that the gain of the Dibas method was low, today, by modifying the reaction conditions, this method is used to prepare imidazole derivatives [8]. For example, for the preparation of Lufin (2,4,5-triphenyl-1-H-imidazole), the Dibas synthesis method has been used in the presence of microwave radiation. In this reaction, benzyl, benzaldehyde and ammonia in acetic acid are used [9]. Recent advances in organometallic catalysts, coordination chemistry and green chemistry have increased the range of imidazoles in the synthesis and application of its derivatives as ionic liquids and stable N-heterocyclic carbons [10]. Imidazolium salts, in which the imidazole ring is present as a cation, are obtained from the alkylation of the ring nitrogen. These salts have been used as ionic liquids [11].

Surfactants are surface active reagents that have the ability to be absorbed or placed on the surface when they are not dissolved in a solvent at low concentration [12]. In this way, they specifically change the physical properties of these surfaces [13]. The term interface is commonly used to describe the boundary of liquid/liquid, liquid/solid and liquid/gas systems [14]. This absorption behavior can be attributed to the nature of the solvent and to the chemical structure of the surfactant, which has a polar group and a non-polar group (amphiphile) inside a molecule [15]. Surfactants, which are an important and diverse class of

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chemicals, accumulate with a large number of useful dual-process phenomena due to their dual nature [16]. They are used in a large number of industrial products such as emulsions, inks, detergents and wetting agents [17]. In addition, surfactants have many applications in the fields of catalysis, electrochemistry, preparation of new nanomaterials, organic synthesis, liquid/liquid extraction, and green chemistry. The scientific and accepted classification of surfactants is based on their separation in water [18]. In this way, surfactants are divided into four categories, which are:

1- Anionic surfactants

2- Cationic surfactants

3- Nonionic surfactants

4- Amphoteric surfactants

Surfactants that are separated into an amphiphilic anion and a cation in water, and the cation is an alkali metal or a fourth-type ammonium salt, are called anionic surfactants [19,20]. This category is the most commonly used surfactants, which include alkylbenzenesulfonates (detergents), soaps (fatty acids), lauryl sulfates (foaming agents), dialkylsulfosuccinate (wetting agent) and lignosulfonates (dispersants) [21]. Anionic surfactants comprise about 50% of industrial production. Surfactants are widely used as catalysts in the synthesis of organic materials and catalyze many reactions [22].

In this article, new derivatives of imidazoles were synthesized using anionic surfactant SDBS as a catalyst. Among the features of this method, we can mention the conditions without reaction solvent, easy separation of the product from the catalyst, short reaction time and good yield of the product.

■ Results and Discussion

The review of scientific literature shows that the use of SDBS catalysts has not been reported in the four-component and three-component reactions for the synthesis of imidazoles. In this project, derivatives of tetrasubstituted imidazoles are reported from the reaction of benzyl with aromatic aldehydes and aliphatic or aromatic amines of the first type and ammonium mastate in the presence of SDBS as a catalyst in solvent-free conditions at 80 °C with high yield.

The FT-IR spectrum of the imidazole compound taken as a KBr tablet is shown in **Figure 2**. The stretching absorption of phenyl groups is observed at 1506-1599 cm^{-1}, the stretching absorption of CH_2 of aromatic rings at 3037 cm^{-1} and the corresponding stretching absorption of OH group at 3500 cm^{-1}.

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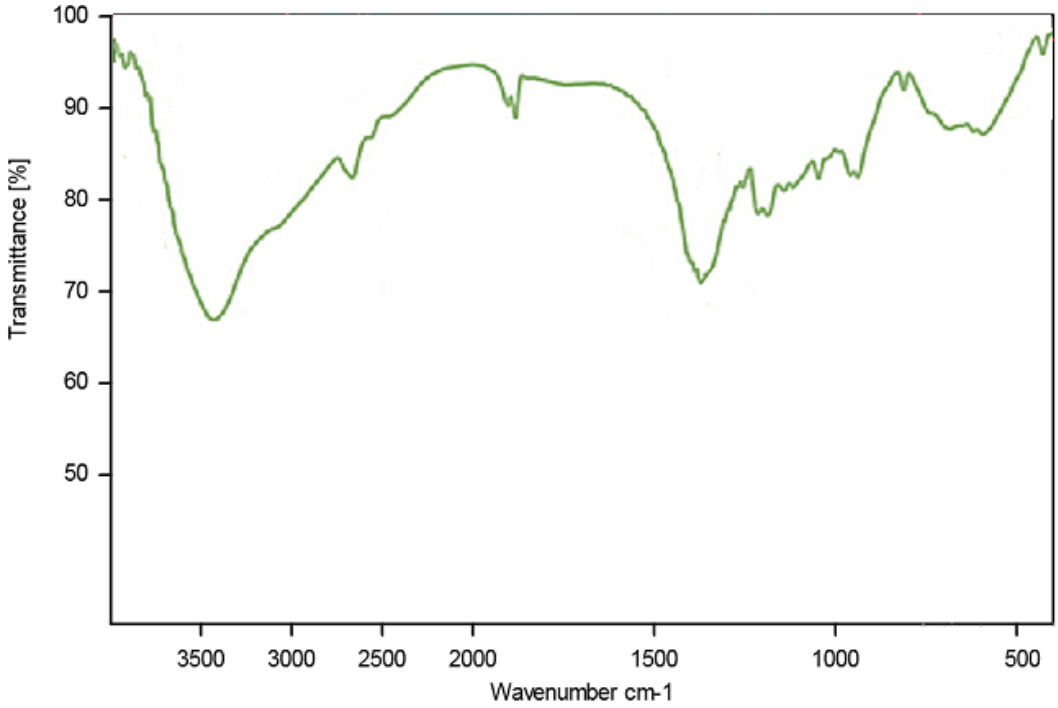

Figure 2. FT-IR spectra for imidazole compound.

To optimize the reaction conditions, the reaction of benzyl with benzaldehyde and benzylamine and ammonium mastate has been used as the base reaction. In this reaction, the effects of solvent, catalyst and temperature on yield and reaction time were investigated in **Table 1**. The reaction did not take place without a catalyst. In the condition without solvent, the best result and the product with high yield were produced. The reaction is not performed in the non-polar solvent of chloroform due to the insolubility of ammonium mastate in the solvent. The reaction was carried out in ethanol and DMF solvents, but it is not a suitable method due to the low yield and long time required for the reaction. The amount of 10 mol% was used as a catalyst in solvent-free conditions and a temperature of 80 °C. The investigations showed that in solvent-free conditions, at temperatures below 80 °C, the yield of the reaction decreases and the reaction time increases, and at higher temperatures, the yield and reaction time remain constant.

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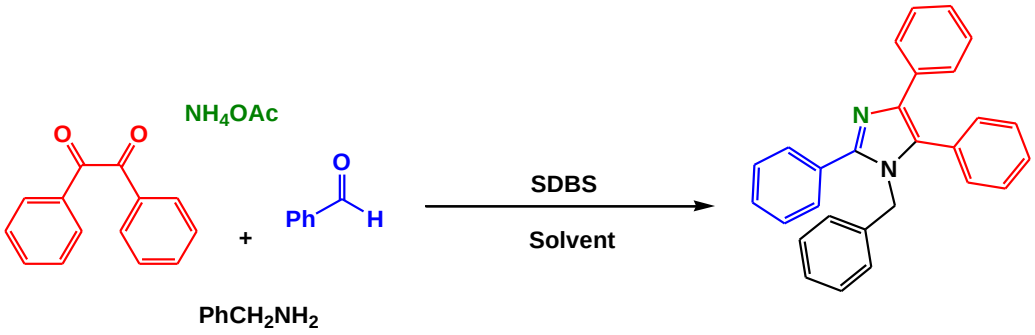
Table 1. Optimizing reaction conditions for imidazole synthesis [a]



Entry	Catalyst (mol%)	Solvent (Tem °C)	Temp (°C)	Yield (%) [a]
1	--	----	120	No
2	5	----	80	51
3	**10**	**----**	**80**	**98**
4	15	-----	80	77
5	10	------	120	98
6	10	THF	80	81
7	10	DMF	80	79
8	10	DMSO	80	63
9	10	$MeOH/H_2O$	80	75
10	10	$CHCl_3$	80	39
11	10	MeOH	80	71
12	10	H_2O	80	55
13	10	-----	----	28
14	10	------	50	36

After optimizing the reaction conditions, various derivatives of tetrasubstituted imidazoles in positions 1, 2, 4, and 5 were synthesized. These compounds were synthesized during a four-component reaction of benzyl, aromatic aldehydes, ammonium mastate and aromatic or aliphatic amines in the presence of SDSAB as a catalyst in solvent-free conditions and at a temperature of 80°C. The results are shown in **Table 2**. The investigations show that aldehydes with electron-withdrawing groups such as NO_2 and Cl increase the yield of the reaction compared to aldehydes with electron-donating groups such as CH_3. In the case of benzaldehyde, with the steric crowding in the molecule, the reaction efficiency decreases compared to aldehydes with the same electron-withdrawing group, without steric hindrance, and the time for this reaction increases. Aliphatic and aromatic amines with electron-withdrawing and electron-donating groups perform this reaction well and have a high reaction yield.

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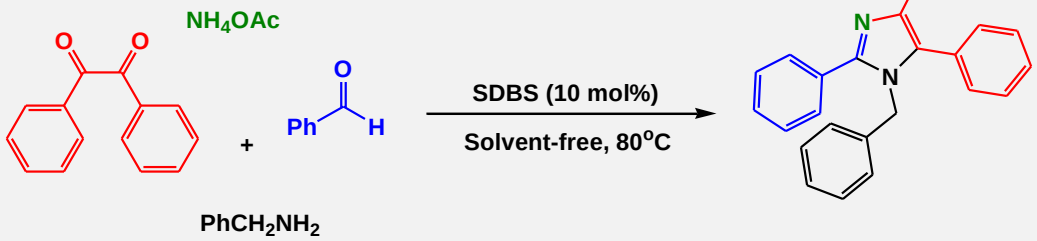
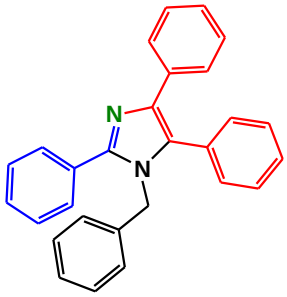
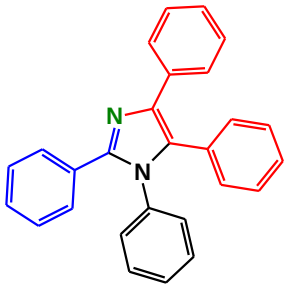
Table 2. Reaction yield of substituted imidazole derivatives [a]



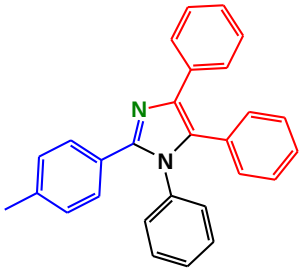
8 Examples
88-98%



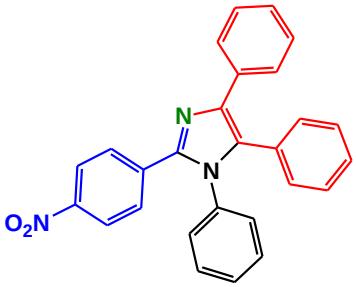
3a (98%)



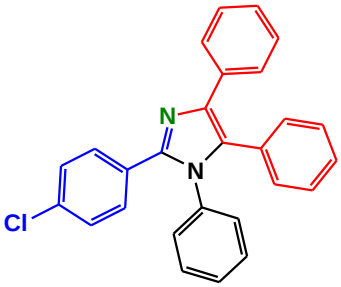
3b (95%)



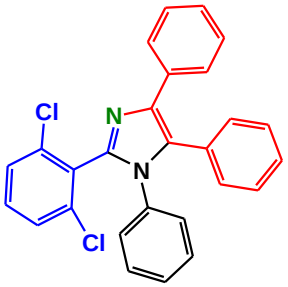
3c (89%)



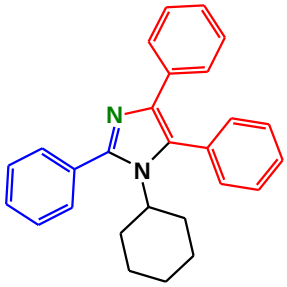
3d (96%)



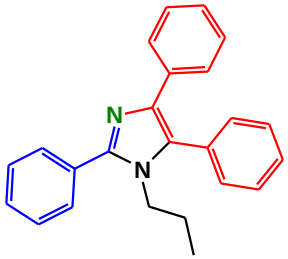
3e (94%)



3f (88%)



3g (91%)



3h (89%)

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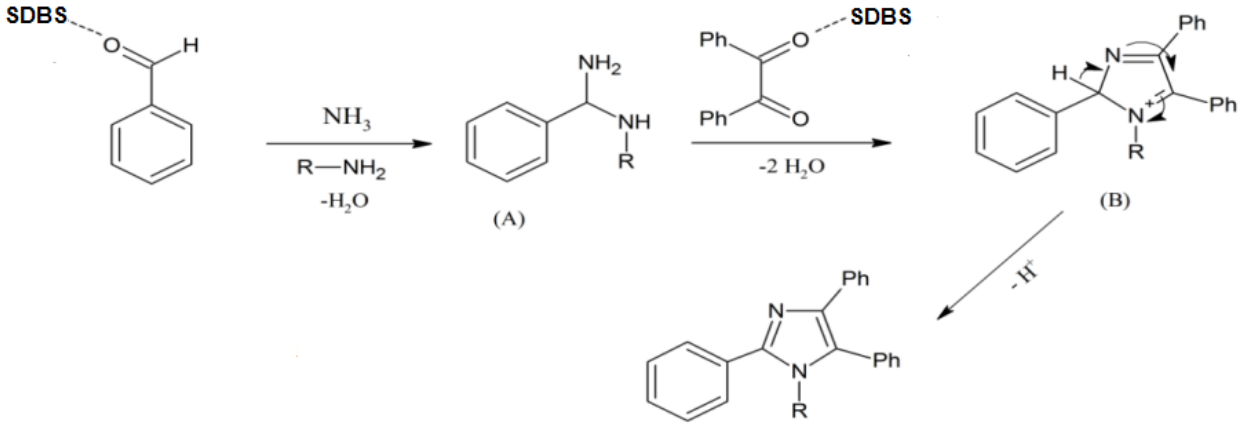
Considering that the reaction is carried out in solvent-free conditions, SDBS does not play a role as a surfactant. It seems to act as an ionic liquid and cause a homogeneous environment of the reaction mixture. SDBS activates the carbonyl aldehyde group for nucleophilic attack, and then compound A is obtained. In the next step, compound A reacts with the benzyl carbonyl group activated by SDBS and creates compound B by losing two moles of water, and then this compound combines with Loss of H^+ produces imidazole. The proposed mechanism of this reaction is shown in **scheme 1**.



Scheme 1. Plausible mechanism.

■ Conclusion

In this research work, we succeeded in synthesizing various derivatives of tetrasubstituted imidazoles in the form of multicomponent and one-pot reactions using SDBS as a catalyst in solvent-free conditions and at a temperature of 80°C. The following are the features of this method:

1- One-pot reaction, which does not need to separate the intermediates and carry out the reaction in the next steps, which leads to a decrease in the yield of the reaction.

2- Conducting the reaction in solvent-free conditions, organic solvents are toxic and destructive to the environment.

3- The simplicity of the reaction conditions, there is no need to use destructive acid catalysts.

4- High reaction efficiency

5- Short reaction time, most of these reactions are completed in 60 minutes.

■ Experimental

All the chemicals used were of research grade and were used without further purification. The melting points of all compounds were determined on a Toshniwal apparatus. The purity of compounds was checked on thin layers of silica Gel– G coated glass plates and n-hexane: ethyl acetate (8 : 2) as eluent. IR spectra were recorded on a Shimadzu FT IR–8400S spectrophotometer using KBr pellets.1H and 13C NMR

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spectra were recorded in $CDCl_3$ using TMS as an internal standard on a Bruker spectrophotometer at 400 and 125 MHz respectively.

General Procedure for Synthesis of Imidazole

A mixture of benzyl (1 mmol), benzaldehyde derivatives (1.1 mmol), aliphatic or aromatic amines of the first type (1.1 mmol), ammonium mastate (1.5 mmol) and SDBS (10 mol%) was stirred in a test tube in an oil bath. After the end of the reaction, which was determined by TLC, the reaction mixture was cooled. The obtained product was washed with water and dried to remove excess ammonium mastate and catalysts. The crude product was crystallized in a mixture of water and ethanol for further characterization.

Supporting Information

1-(4-Methylphenyl)-2,4,5-triphenyl-1H-imidazole (3c):

White solid; m.p. 182-184 ºC (lit. 183-185 ºC); 1H NMR (400 MHz, CDCl3) δ 7.60 – 7.58 (m, 2H), 7.45 – 7.43 (m, 2H), 7.25 – 7.14 (m, 11H), 7.04 (d, J = 8.0 Hz, 2H), 6.92 – 6.90 (m, 2H), 2.31 (s, 3H).

1-cyclohexyl-2,4,5-triphenyl-1H-imidazole (3g):

White solid; m.p. 168-169 ºC (lit. 167-169 ºC); 1H NMR (400 MHz, CDCl3) δ 7.63 – 7.61 (m, 2H), 7.48 – 7.41 (m, 10H), 7.16 – 7.08 (m, 3H), 3.97 (tt, J = 12.1, 3.3 Hz, 1H), 1.85 (d, J = 12.8 Hz, 2H), 1.68 – 1.43 (m, 6H), 1.09 – 0.99 (m, 2H).

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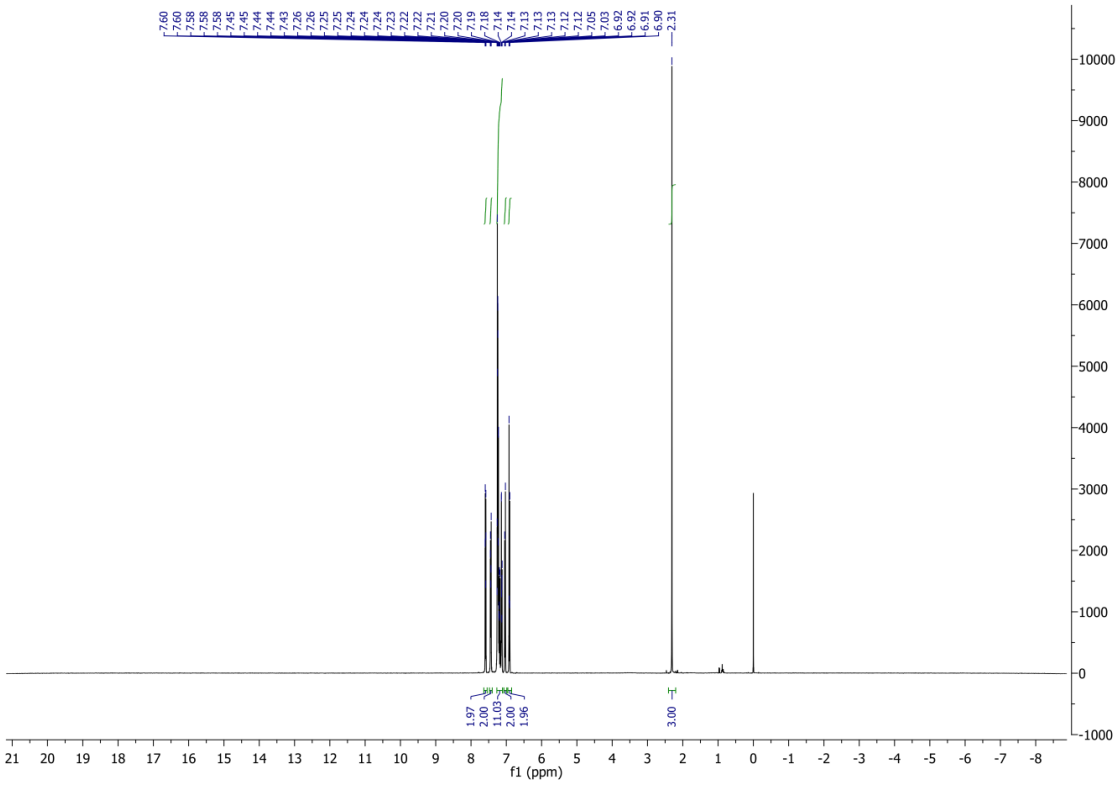
Copies of ^{1}H spectra of synthesized compounds:



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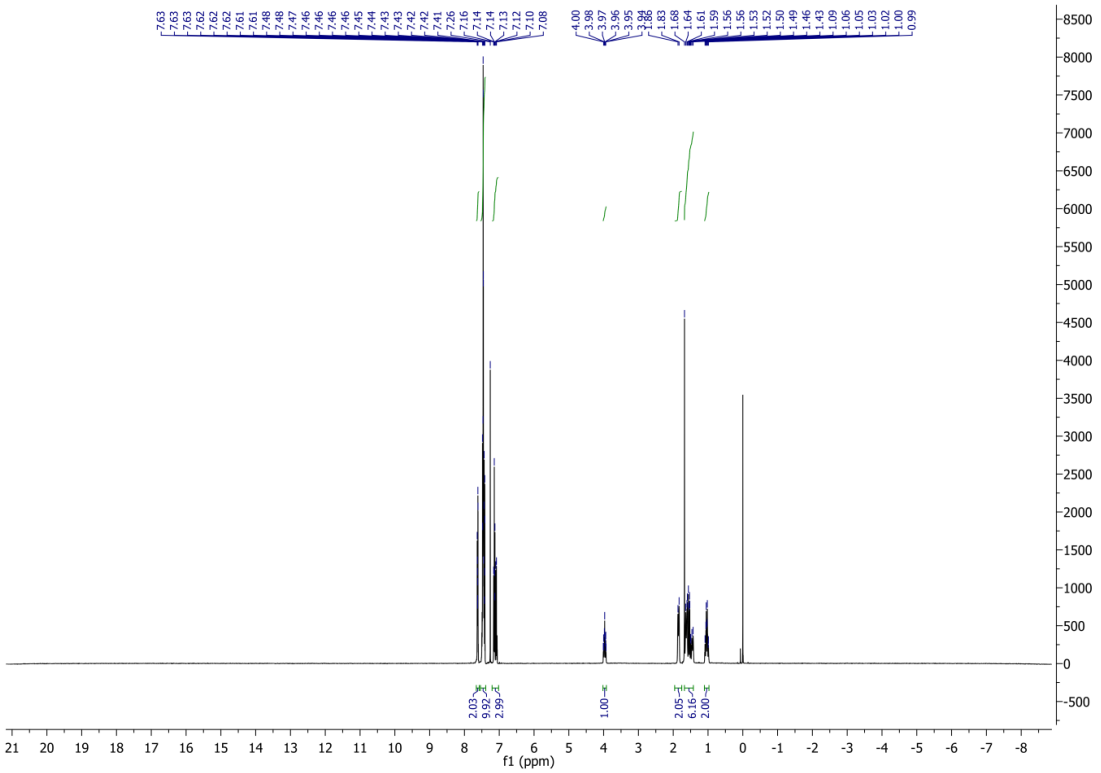

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