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Submission Number:	051603	
Application Number:	PCT/TR2023/051603	
Date of Receipt:	20 December 2023	
Receiving Office:	Turkish Patent and Trademark Office (Turkpatent)	
Your Reference:	22135-1	
Applicant:	IHSAN DOGRAMACI BILKENT UNIVERSITESI	
Number of Applicants:	2	
Title:	MECHANOCHEMICAL SYNTHESIS OF HISTAMINE H1-RECEPTOR ANTAGONISTS	
Documents Submitted:	221351-appb-000004.pdf (22135-1_application body_EN.pdf)	1460219
	221351-appb.xml	965
	221351-fees.xml	2250
	221351-requ.xml	7469
	221351-vlog.xml	1126
Submitted by:	GIZEM TEKE KARSLI (Customer ID: user_TR_TEKE-KARSLI_GIZEM_4620)	
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0	**For receiving Office use only**	
0-1	International Application No.	**PCT/TR2023/051603**
0-2	International Filing Date	**20 December 2023 (20.12.2023)**
0-3	Name of receiving Office and "PCT International Application"	**RO/TR**

0-4	**Form PCT/RO/101 PCT Request**	
0-4-1	Prepared Using	**ePCT-Filing Version 4.12.006 MT/FOP 20231213/1.1**
0-5	**Petition**	
	The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	**Turkish Patent and Trademark Office (Turkpatent) (RO/TR)**
0-7	**Applicant's or agent's file reference**	**22135-1**
I	**Title of Invention**	**MECHANOCHEMICAL SYNTHESIS OF HISTAMINE H1-RECEPTOR ANTAGONISTS**
II	**Applicant**	
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III-6	**Applicant and/or inventor**	
III-6-1	This person is	**Inventor only**
III-6-3	Inventor for	**All designated States**
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IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	**Agent**
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V	**DESIGNATIONS**	
V-1	**The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.**	
VI-1	**Priority Claim**	**NONE**
VII-1	**International Searching Authority Chosen**	**Turkish Patent and Trademark Office (Turkpatent) (ISA/TR)**

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VIII	**Declarations**	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	**Check list**	Number of sheets	Electronic file(s) attached
IX-1	Request (including declaration sheets)	**5**	✓
IX-2	Description	**27**	✓
IX-3	Claims	**4**	✓
IX-4	Abstract	**1**	✓
IX-5	Drawings	**16**	✓
IX-6a	Sequence listing part of the description	-	-
IX-7	TOTAL	**53**	
	Accompanying Items	Paper document(s) attached	Electronic file(s) attached
IX-8	Fee calculation sheet	-	✓
IX-20	**Figure of the drawings which should accompany the abstract**	**0**	
IX-21	**Language of filing of the international application**	**English**	
X-1	**Signature of applicant, agent or common representative**	**/GIZEM TEKE KARSLI/**	
X-1-1	Name (LAST, First)	**TEKE KARSLI, GIZEM**	
X-1-3	Capacity (if such capacity is not obvious from reading the request)	**Agent**	

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10-1	**Date of actual receipt of the purported international application**	**20 December 2023 (20.12.2023)**
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	**ISA/TR**
10-6	**Transmittal of search copy delayed until search fee is paid**	

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11-1	**Date of receipt of the record copy by the International Bureau**	

PCT (ANNEX - FEE CALCULATION SHEET)

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0-1	International Application No.	PCT/TR2023/051603		
0-2	Date stamp of the receiving Office			

0-4	**Form PCT/RO/101 (Annex) PCT Fee Calculation Sheet**			
0-4-1	Prepared Using	**ePCT-Filing Version 4.12.006 MT/FOP 20231213/1.1**		
0-9	**Applicant's or agent's file reference**	**22135-1**		
2	**Applicant**	**IHSAN DOGRAMACI BILKENT UNIVERSITESI**		
12	**Calculation of prescribed fees**	Fee amount/multiplier	Total amounts (CHF)	
12-1	Transmittal fee **T**	➪		
12-2-1	Search fee **S**	➪	**1713**	
12-2-2	International search to be carried out by	**TR**		
12-3	International filing fee (first 30 sheets) **i1**	**1330**		
12-4	Remaining sheets	**23**		
12-5	Additional amount **(X)**	**15**		
12-6	Total additional amount **i2**	**345**		
12-7	i1 + i2 = **i**	**1675**		
12-12	Electronic Filing reduction (Image) **R**	**-200**		
12-13	Total International filing fee (i-R) **I**	➪	**1475**	
12-17	Fee for restoration of priority rights **RP** Number of requests for restoration of priority rights	**0**		
	Total amount of fees for restoration of priority rights			
12-19	**TOTAL FEES PAYABLE (T+S+I+P+RP)**	➪	**3188**	
12-21	**Mode of payment**	**Other : No payment for the time being**		

DESCRIPTION

MECHANOCHEMICAL SYNTHESIS OF HISTAMINE H1-RECEPTOR ANTAGONISTS

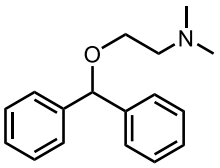
Technical Field of the Invention

The present invention relates to mechanochemical synthesis of histamine antagonists which are benzhydryl ethers and unsymmetrically disubstitutes piperazines and salts thereof. Said antihistamine active pharmaceutical ingredients can be diphenhydramine hydrochloride, cyclizine hydrochloride and diphenylpyraline hydrochloride.

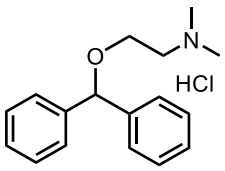
State of the Art

H_1-blockers (antihistamines) are commonly used to treat the symptoms of allergic reactions. They are found in many over-the-counter products for cold, flu, and allergy products as well as sleep aids and products to treat motion sickness. Many prescription medications containing H_1-blockers are used to treat seasonal allergies, allergic reactions, depression, nausea and vomiting, motion sickness, and vertigo. While first-generation H_1 antihistamines have a central effect and, thus, are also used as sedatives, second-generation H_1 antihistamines have less central effects and are primarily used as antiallergic drugs. Diphenhydramine hydrochloride, cyclizine hydrochloride and diphenylpyraline hydrochloride are first generation antihistamines.

Diphenhydramine hydrochloride (2-(Diphenylmethoxy)-N,N-dimethylethan-1-amine hydrochloride, DPH) is a well-known histamine antagonist that possesses antihistaminic, antitussive, sedative, antimotion-sickness, antiemetic, and anticholinergic effects. Diphenydramine, which is particularly used to treat allergies, insomnia, vomiting, dizziness, nausea and sypmtoms of cold [1] [2]. It is used in the drugs under the trade names of Dimedrol®, Allergina®, Valdren® or Benadryl®.

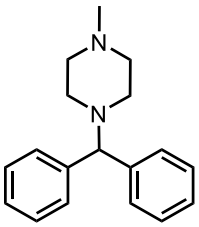


Diphenhydramine

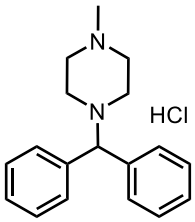


Diphenhydramine hydrochloride

Cyclizine hydrochloride (1-benzhydryl-4-methylpiperazine hydrochloride, CYC) is also an antihistamine which is a piperazine derivative with histamine H_1-receptor antagonist activity. It is sold as a drug under a number of brand names such as Marezine®, Vald®, Nausicalm® and it is utilized to treat and prevent nausea, vomiting and dizziness due to motion sickness or vertigo.

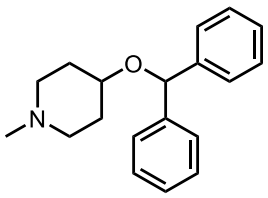


Cyclizine

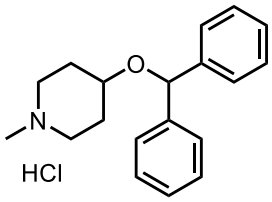


Cyclizine hydrochloride

Diphenylpyraline hydrochloride (4-(benzhydryloxy)-1-methylpiperidine hydrochloride, DPP) is another first-generation antihistamine in the diphenylpiperidine class with anticholinergic effects. It is marketed in Europe for the treatment of allergies and sold as a drug under brand names such as Allergen®, Arbid®, Belfene®, Diafen®.



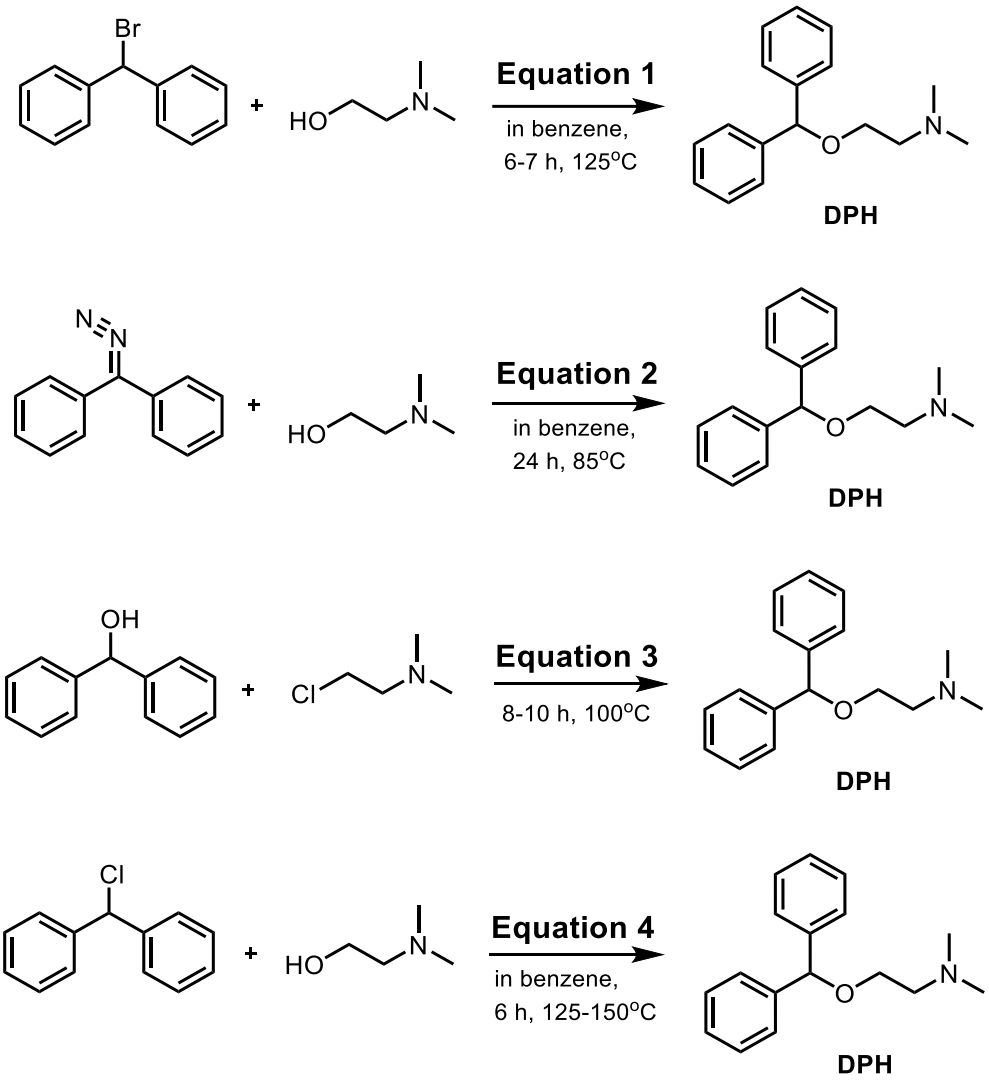
Diphenylpyraline



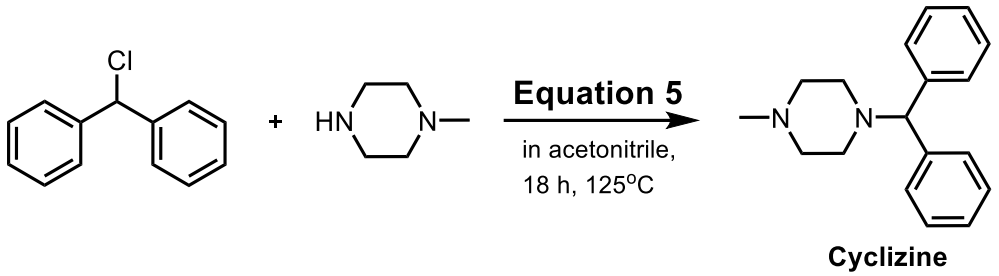
Diphenylpyraline hydrochloride

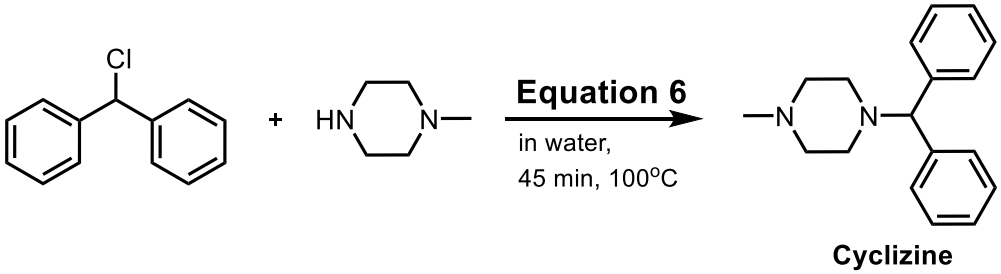
The first reported synthesis of DPH assigned to Parke, Davis & Co (Equation 1), which describes the reaction of bromodiphenylmethane with dimethylaminoethanol in benzene at 120 ^{o}C in the presence of anhydrous sodium carbonate [3]. Another synthesis in the prior art which is assigned to Merck & Co. (Equation 2) involves the reaction of 1,1'-(diazomethanediyl)dibenzene and dimethylaminoethanol in an inert solvent in the presence of inorganic base [4]. The other methods of state of art

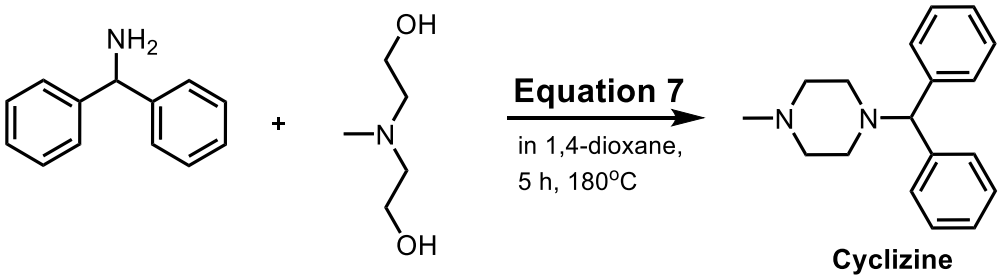
assigned to Searle & Co. (Equation 3) and Nopco Chem. Co. (Equation 4) present similar pathways as described above but with the usage of chlorinated substrates [5], [6].



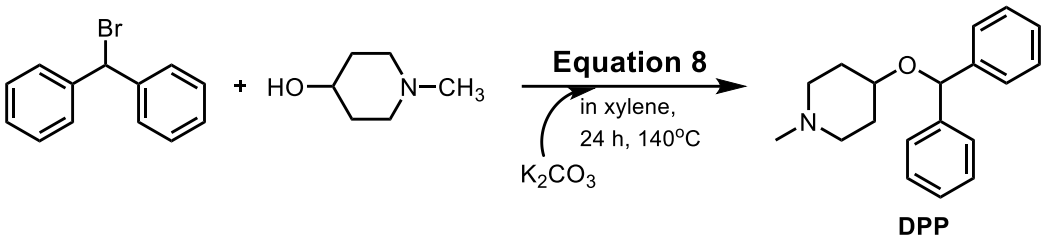
In the prior art, two conventional synthetic pathways were developed for cyclizine: one of them includes refluxing the mixture in acetonitrile for 18 h (Equation 5) [7], and the other one uses flow reactor in the presence of water (Equation 6) [8]. In the other perspective, Tsuji et al. synthesized cyclizine by the reaction of N-methyldiethanolamine and aminodiphenylmethane in 1,4-dioxane at 180°C for 5 h, however with very poor yield of 14% (Equation 7) [9].

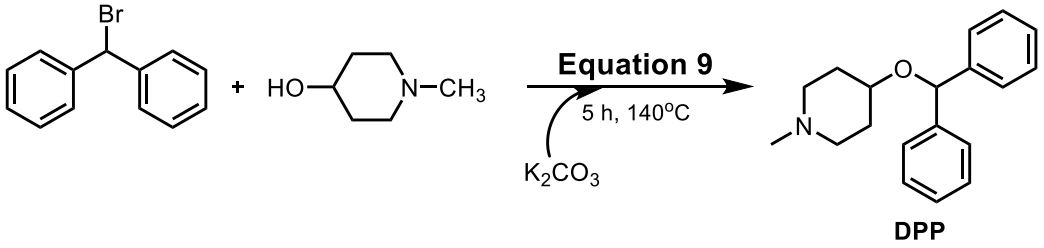


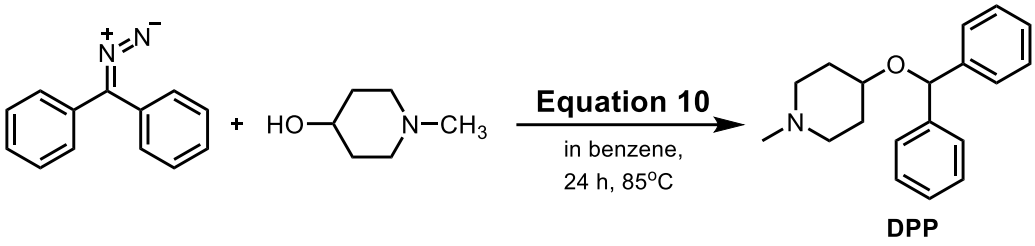


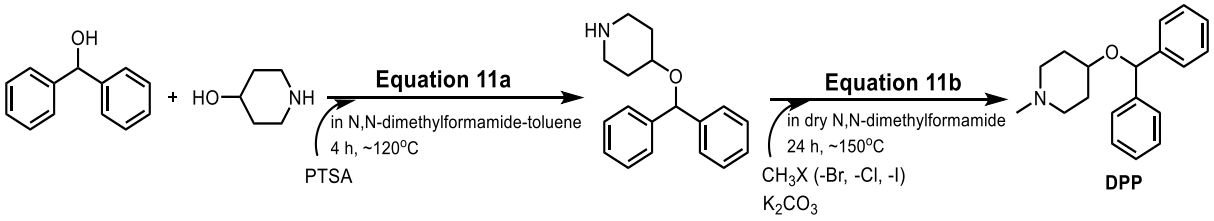


In the state of art, synthesis of diphenylpyraline (DPP) is based on the coupling of 4-hydroxy-1-methylpiperidine with benzhydrylbromide in the presence of potassium carbonate [10]. The reaction was refluxed in xylene at 140°C for 24 hours (Equation 8). Weis et al. showed the synthesis of DPP by etherification of 1-methylpiperidin-4-ol with halodiphenylmethanes or diphenyldiazomethanes (Equation 9) [11]. Synthesis assigned to Merck & Co. involves the reaction of 1,1'-(diazomethanediyl)dibenzene and 4-hydroxy-1-methylpiperidine in benzene (Equation 10) [4]. Method assigned to Lapa et al. presents a two-step reaction. It includes the reaction of diphenylmethanol and 4-hydroxypiperidine refluxing in N,N-dimethylformamide-toluene mixture in the presence of toluene-4-sulfonic acid (Equation 11a) and then refluxing the product formed in Equation 11a in N,N-dimethylformamide in the presence of potassium carbonate and alkyl halide around 150°C for 24 hours (Equation 11b) [12].







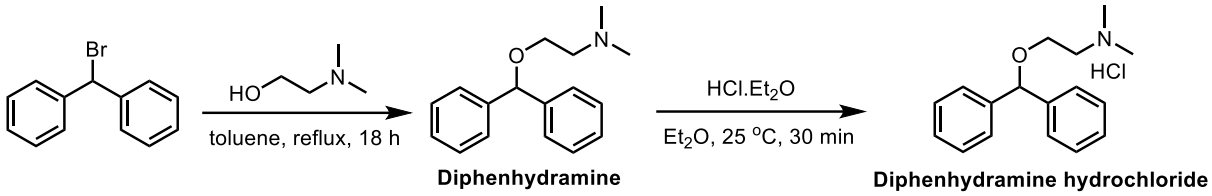


As it can be seen above, the reactions for synthesis of DPH, CYC and DPP in the state of art are mostly followed at high temperatures with hours of reaction times. However, the antihistaminic drugs described above are widely used and synthesized in large amounts worldwide.

Mechanochemistry refers to chemical reactions induced by mechanical energy. It has attracted increased attention because of advantages such as being a solution-free, energy saving, high-productivity and low-temperature process. Mechanochemistry offered not only a possibility to eliminate the need for bulk solvent use, and reduced the generation of waste, but it also unlocked the door to a different reaction environment for the synthesis of active pharmaceutical ingredients (APIs). In industry, still only wet chemistry methods are utilized for the synthesis of APIs which requires heating to high temperatures in toxic solvents for long hours as it was shown in aforementioned equations. However,

mechanochemical synthesis of APIs can be achieved by using ball mills both at room temperature and cryo conditions or by grinding with a simple pestle and a mortar. Besides, if needed mechanochemical synthesis of APIs can be achived by using planetary mills, twin-screw extrusion etc. These different techniques broadens the synthesis pathways for massive industrial synthesis of APIs. Especially, twin-screw extrusion is used to carry out continuous production of a wide range of chemical reactions and is primarily preferred in industrial processes [13]–[15].

The conventional synthesis of diphenhydramine hydrochloride (Equation 12) is carried out using toxic solvents (i.e. toluene [16], benzene [3]), high temperatures which leads high energy consumption and longer reaction times.



Equation 12

The state of the art was first invented by George Rieveschl in 1947 and this method is still the main option for massive diphenhydramine hydrochloride synthesis and production (Equation 1). The disadvantages for this technique are being costly and time consuming.

The limitations and disadvantages of the methods for synthesis of histamine antagonist active pharmaceutical ingredients (APIs) in the state of art such as reaction conditions with high temperatures, longer reaction times, using toxic solvents and more chemicals (e. g. bases, catalysts), multistep processes and work-ups, high generation of waste, high energy consumption made it necessary to improve a cost-effective, green and faster synthesis method for histamine antagonist active pharmaceutical ingredients (APIs) such as diphenhydramine hydrochloride, cyclizine hydrochloride and diphenylpyraline hydrochloride.

Brief Description and Objects of the Invention

The present invention discloses mechanochemical synthesis method of histamine antagonist active pharmaceutical ingredients (APIs), especially diphenhydramine hydrochloride, cyclizine hydrochloride and diphenylpyraline hydrochloride which are

antihistamines. In the present invention; diphenhydramine (DPH), cyclizine (CYC) and diphenylpyraline (DPP) is mechanochemically synthesized and then, hydrochloride salts of these active pharmaceutical ingredients (APIs) is formed. Mechanochemical synthesis of these active pharmaceutical ingredients (APIs) is performed by using ball-milling, cryomilling and grinding with mortar and pestle. Grinding with these three techniques offered to proceed the mechanochemical reactions, incorporating the mechanical force to drive chemical transformations by the direct absorption of mechanical energy instead of heating. In milling technique, the system is shaken at a desired frequency and this movement makes balls collide and mixes the reactants, reducing their particle size and activating the reactants mechanically. In comparison with the conventional methods, changing the frequencies enables us to eliminate the necessity of heating to favor the reactions. Grinding via ball mill in cryo conditions offered a way to proceed solid state reactions especially for the synthesis of cyclizine hydrochloride and diphenylpyraline hydrochloride since the starting materials; bromodiphenylmethane (MP: 35-39 ^{o}C), N-methyl piperazine (MP: -5.57 ^{o}C) and N-methyl-4-piperidinol (MP: 31 ^{o}C) have low melting points. So, they freeze before the reaction starts which creates liquid-free reaction media. Moreover, in this invention no solvent, no base and no catalyst is used to ease the reactions because mechanical input is highly sufficient to continue the synthesis. The synthesis of the APIs subjected to the present invention is achieved in minutes by using grinding techniques while conventional pathways takes hours to complete. Moreover, mechanochemical method provides one-step synthesis eliminating multistep processes and work-ups which are characteristics of conventional synthetic procedures. These APIs are in antihistamine class of drugs which treats symptoms of allergies such as hives, hay fever (allergic rhinitis), conjunctivitis, reactions to insect bites and sings, nausea, motion sickness, insomnia and many more.

One of the objects of the present invention is to provide a faster method for synthesis histamine antagonist APIs; especially diphenhydramine hydrochloride, cyclizine hydrochloride and diphenylpyraline hydrochloride by performing the reactions only in minutes in one to two steps by the help of mechanical forces to drive the reactions at high frequencies. These APIs are obtained with highest yields mostly between 10 to 20 min in the present invention. Performing the mechanochemical synthesis only in 1 to 5 minutes gave moderate to satisfactory yields.

Another object of the present invention is to provide a green method for synthesis of antihistamine APIs; diphenhydramine hydrochloride, cyclizine hydrochloride and diphenylpyraline hydrochloride. In the present invention the synthesis is performed by utilizing less toxic solvents, chemicals, and energy, and thus a green method is provided.

Another object of the present invention is to provide a cost-effective method for synthesis of antihistamine APIs; diphenhydramine hydrochloride, cyclizine hydrochloride and diphenylpyraline hydrochloride. In the present invention the synthesis is performed by using less chemicals (e.g., no solvents, no bases and no catalysts are needed to favor the reaction and only low amount of solvent for work-up processes is needed). It is also an energy efficient technique since it requires less usage of electricity to operate the ball mill in comparison to the conventional counterparts which require hours of heating in reflux.

According to the present invention, the mechanochemical reactions between reactants are performed in the absence of solvent at room temperatures or at -196 ^{o}C which can be achieved directly by a milling device. Thus, the method of the invention is green. Also, the said antihistamines are synthesized in minutes and less energy is spent. Besides that, the total cost is also diminished, because the addition of other chemicals such as bases (i.e., sodium carbonate) or catalysts to ease the reaction process as in the prior art is no longer needed. So, the invention is cost, energy and time effective synthetic method and a new environmental benign alternative for conventional synthesis of diphenhydramine and its derivatives. Mechanochemistry used in the present invention offers not only a possiblity to eliminate the need for bulk solvent use, and reduce the generation of waste, but it also unlocks the door to a different reaction environment.

Description of the Figures

FIGURE 1 ESI-MS spectrum of DPH after 1 min ball milling at 25 ^{o}C .

FIGURE 2 ESI-MS spectrum of DPH after 5 min ball milling at 25 ^{o}C.

FIGURE 3 ESI-MS spectrum of DPH after 5 min grinding with pestle & mortar at 25 ^{o}C.

FIGURE 4 ESI-MS spectrum of DPH after 1 hour ball milling at 25 ^{o}C.

FIGURE 5 ESI-MS spectrum of DPH after 1 hour ball milling at -196 ^{o}C.

FIGURE 6 ^{1}H NMR spectra of commercial reagents a) dimethylamino ethanol, b) bromodiphenylmethane, c) commercial reference DPH HCl, d) ^{1}H NMR spectrum of DPH HCl after 1 hour ball milling at 25 ^{o}C in $CDCl_3$ (+5 drops of methanol-d_4).

FIGURE 7 a) ^{1}H NMR spectrum of DPH HCl reference b) ^{1}H NMR spectra of DPH ball milled at 25 ^{o}C for 1 min, c) 5 min, d) 10 min, e) 20 min and f) 1 hour in $CDCl_3$ (+5 drops of methanol-d4).

FIGURE 8 ^{1}H NMR spectra of DPH a) after 5 min ball milling in ZrO_2 vessel at 25 ^{o}C, b) after 5 min ball milling in SS vessel at 25 ^{o}C, c) ^{1}H NMR spectrum of DPH after 5 min grinding with pestle and mortar at 25 ^{o}C in $CDCl_3$ (+5 drops of methanol-d_4).

FIGURE 9 ^{1}H NMR spectra of DPH a) after 1-hour cryomilling, and b) after 1 hour ball milling at 25 ^{o}C in $CDCl_3$ (+5 drops of methanol-d_4).

FIGURE 10 a) ^{13}C NMR spectrum of commercial reference DPH HCl. ^{13}C NMR spectra of b) DPH HCl and c) DPH after 1 hour ball milling at 25 ^{o}C in $CDCl_3$ (+5 drops of methanol-d_4).

FIGURE 11 ^{1}H NMR spectrum of DPH after 1 hour ball milling at 25 ^{o}C in $CDCl_3$ (+5 drops of methanol-d_4).

FIGURE 12 ^{13}C NMR spectrum of DPH after 1 hour ball milling at 25 ^{o}C in $CDCl_3$ (+5 drops of methanol-d_4).

FIGURE 13 ESI-MS spectrum of DPH HCl after 60 min ball milling at -196 ^{o}C.

FIGURE 14 ESI-MS spectrum of CYC after 5 min ball milling at 25 ^{o}C.

FIGURE 15 ESI-MS spectrum of CYC after 10 min ball milling at 25 ^{o}C.

FIGURE 16 ESI-MS spectrum of CYC after 20 min ball milling at 25 ^{o}C.

FIGURE 17 ESI-MS spectrum of CYC after 5 min ball milling at -196 ^{o}C.

FIGURE 18 ESI-MS spectrum of CYC after 10 min ball milling at -196 ^{o}C.

FIGURE 19 ESI-MS spectrum of CYC after 20 min ball milling at -196 ^{o}C.

FIGURE 20 ESI-MS spectrum of CYC after 60 min ball milling at -196 ^{o}C.

FIGURE 21 ESI-MS spectrum of CYC after 5 min ball milling in SS vessel at 25 ^{o}C.

FIGURE 22 ESI-MS spectrum of CYC after 5 min ball milling in SS vessel at -196 ^{o}C.

FIGURE 23 ESI-MS spectrum of CYC after 5 min grinding with pestle & mortar at 25 ^{o}C.

FIGURE 24 ^{1}H NMR spectra of starting materials a) bromodiphenylmethane and b) N-methyl piperazine. ^{1}H NMR spectra of CYC ball milled at -196 ^{o}C for c) 5 min, d) 10 min, e) 20 min and f) 1 hour in $CDCl_3$ (+5 drops of methanol-d_4).

FIGURE 25 ^{1}H NMR spectra of starting materials a) bromodiphenylmethane and b) N-methyl piperazine. ^{1}H NMR spectra of CYC ball milled at 25 ^{o}C for c) 5 min, d) 10 min, e) 20 min and f) 1 hour in $CDCl_3$ (+5 drops of methanol-d_4).

FIGURE 26 ^{1}H NMR spectra of CYC after 5 min ball milling in ZrO_2 vessel at 25 ^{o}C, 5 min ball milling in ZrO_2 vessel at -196 ^{o}C, 5 min ball milling in SS vessel at 25 ^{o}C, and 5 min ball milling in SS vessel at -196 ^{o}C, compared with spectrum of CYC after 5 min grinding with pestle and mortar at 25 ^{o}C in $CDCl_3$ respectively (+5 drops of methanol-d_4).

FIGURE 27 ^{1}H NMR spectrum of CYC after 5 min ball milling at -196 ^{o}C in $CDCl_3$ (+5 drops of methanol-d_4).

FIGURE 28 ^{13}C NMR spectrum of CYC after 5 min ball milling at -196 ^{o}C in $CDCl_3$ (+5 drops of methanol-d_4).

FIGURE 29 ESI-MS spectrum of CYC HCl after 60 min ball milling at -196 ^{o}C.

FIGURE 30 ^{1}H NMR spectrum of CYC HCl after 60 min ball milling at -196 ^{o}C in MeOD.

FIGURE 31 ^{13}C NMR spectrum of CYC HCl after 60 min ball milling at -196 ^{o}C in $CDCl_3$.

FIGURE 32 ESI-MS spectrum of DPP after 10 min ball milling in ZrO_2 vessel at 25 ^{o}C.

FIGURE 33 ^{1}H NMR spectrum of DPP after 10 min ball milling in ZrO_2 vessel at 25 ^{o}C in MeOD.

FIGURE 34 ^{13}C NMR spectrum of DPP after 10 min ball milling in ZrO_2 vessel at 25 ^{o}C in MeOD.

FIGURE 35 ESI-MS spectrum of DPP HCl after 10 min ball milling in ZrO_2 vessel at 25 ^{o}C.

FIGURE 36 ^{1}H NMR spectrum of DPP HCl after 10 min ball milling in ZrO_2 vessel at 25 ^{o}C in MeOD.

FIGURE 37 ^{13}C NMR spectrum of DPP HCl after 10 min ball milling in ZrO_2 vessel at 25 ^{o}C in MeOD.

Detailed Description of the Invention

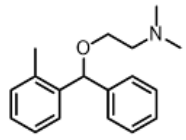
The present invention relates to mechanochemical synthesis method of hydrochloride salts of histamine antagonist active pharmaceutical ingredients (APIs), especially representatives of first-generation antihistamine active pharmaceutical ingredients which are hydrochloride salts of diphenhydramine (DPH), cyclizine (CYC) and diphenylpyraline (DPP). In the present invention; diphenhydramine (DPH), cyclizine (CYC) and diphenylpyraline (DPP) is mechanochemically synthesized and then, hydrochloride salts of these active pharmaceutical ingredients (APIs) is formed. Mechanochemical synthesis of these active pharmaceutical ingredients (APIs) is performed by using ball-milling, cryomilling and grinding with mortar and pestle.

In the present invention, ball milling is prefered to be used since ball milling has proven effective for promoting chemical reactions by transmission of mechanical force, many of these syntheses can be proceed solvent-free thereby revealing an increased sustainability compared to their solvent-based counterparts. Therefore, in our approach, mechanochemical reactions are carried out in a ball mill at room temperature (25 ^{o}C) and by cooling with liquid nitrogen from the integrated cooling system (-196 ^{o}C). Experiments are performed in both zirconia and stainless-steel milling vessels (25 mL volumetric capacity) with complementary ball materials (six milling balls, 10.06 mm in diameter). Moreover, mechanochemical synthesis of these

APIs are achieved by grinding the reactants with a pestle and a mortar at room temperature (25 ^{o}C)

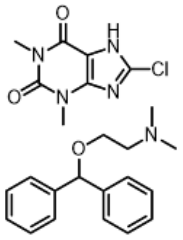
All the antihistamines sythesized by the synthesis method of the invention can be successfully used in the treatment of severe allergic reactions, nausea, hives, hay fever (allergic rhinitis), conjunctivitis, reactions to insect bites and sings, motion sickness, insomnia.

In the present invention, other derivatives of phenhydramine which are shown below can also be synthesized by using the method of the invention:



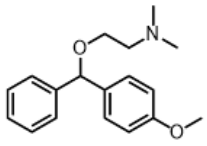
Orphenadrine

N,*N*-dimethyl-2-(phenyl(*o*-tolyl)methoxy)ethan-1-amine



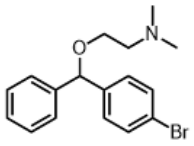
Dimenhydrinate

(Combination drug of diphenhydramine & 8-Chlorotheophylline)



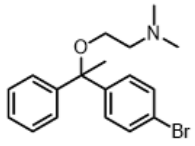
Medrylamine

2-((4-methoxyphenyl)(phenyl) methoxy)-*N*,*N*-dimethylethan-1-amine



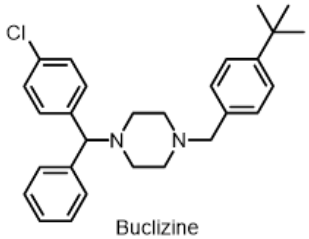
Bromazine

2-((4-bromophenyl)(phenyl)methoxy)-*N*,*N*-dimethylethan-1-amine



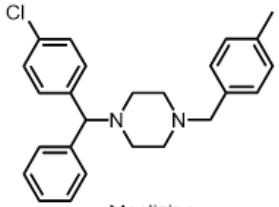
Embramine

2-(1-(4-bromophenyl)-1-phenylethoxy)-*N*,*N*-dimethylethan-1-amine



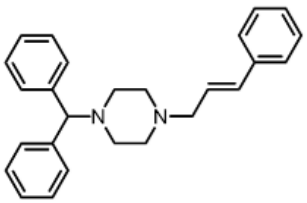
Buclizine

1-(4-(*tert*-butyl)benzyl)-4-((4-chlorophenyl)(phenyl)methyl) piperazine



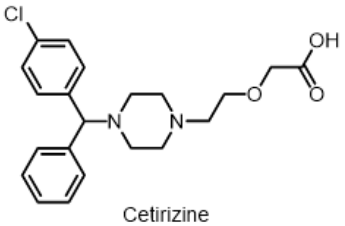
Meclizine

1-((4-chlorophenyl)(phenyl)methyl)-4-(4-methylbenzyl)piperazine



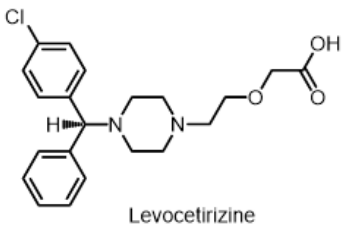
Cinnarizine

1-benzhydryl-4-cinnamylpiperazine



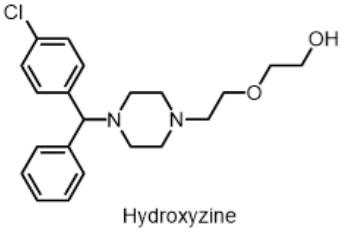
Cetirizine

2-(2-(4-((4-chlorophenyl)(phenyl)methyl) piperazin-1-yl)ethoxy)acetic acid



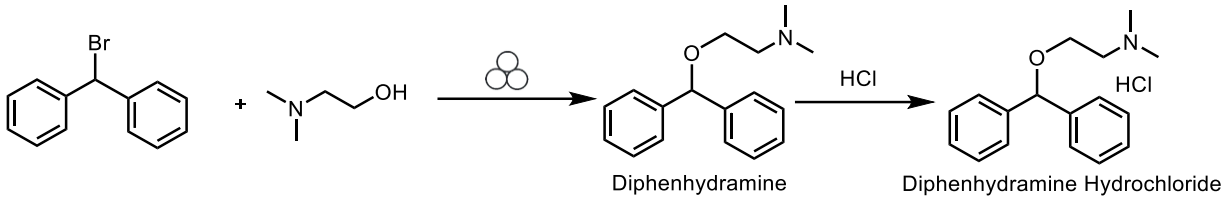
Levocetirizine

(*S*)-2-(2-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)ethoxy)acetic acid



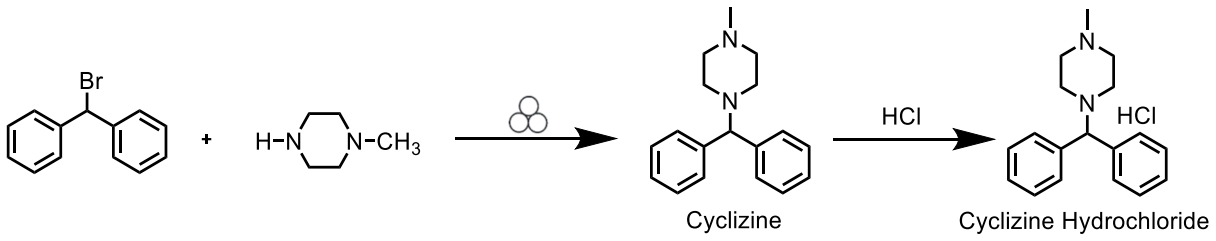
Hydroxyzine

2-(2-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)ethoxy)ethan-1-ol



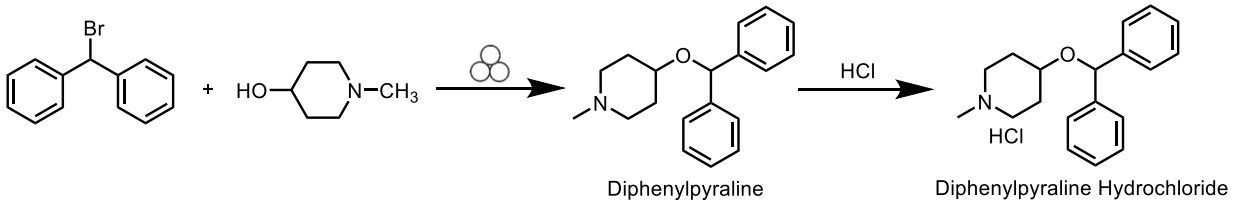
Equation A. Mechanochemical synthetic route of Diphenhydramine hydrochloride.

Diphenhydramine hydrochloride is successfully synthesized according to Equation A with high yields and characterized by ^{1}H NMR, ^{13}C NMR and HRMS. HCl salt formation can be achieved easily by treating the DPH in methanol with 2-3 drops of concentrated HCl until pH becomes 4-5. Product can be heated and stirred until fully dissolved. The mixture can be cooled slowly to room temperature to crystallize diphenhydramine hydrochloride (DPH HCl).



Equation B. Mechanochemical synthetic route of Cyclizine hydrochloride.

Cyclizine hydrochloride is successfully synthesized with sufficient yields according to Equation B and characterized by ^{1}H NMR, ^{13}C NMR and HRMS. The transformation to cyclizine hydrochloride can be performed by following the procedure explained for DPH HCl.



Equation C. Mechanochemical synthetic route of Diphenlpyraline hydrochloride.

To start mechanochemical synthetic investigation on the selected antihistamine APIs, bromodiphenylmethane and N,N-dimethylethanolamine (DMAE) were initially selected as representative substrates for synthesizing DPH. All DPH derivatives were prepared using several ball-milling parameters (type of ball-mill apparatus, nature of the jars, time) and tested (Table 1). As was mentioned above, the synthesis of DPH takes hours to complete if conventional synthesis is followed. Therefore, the time dependence of mechanochemical synthesis of DPH was first explored. DPH was obtained with a high yield (76%) when the reactants were milled with a zirconium dioxide jar and balls for 1 hr at room temperature (Table 1, entry 5). At this stage, having high yields in one hour with mechanochemical synthesis can be said promising, as the conventional synthetic alternatives can provide yields around 70% mostly in 6 hours by heating the reaction mixture at 125-150 ^{o}C. In the latter experiments, the milling time was reduced (e.g. 1 to 20 min), even better results in terms of yield were obtained (80-90%) in comparison to longer reaction processes (Table 1, entry 1-4). Therefore, we can conclude that mechanical force to drive chemical transformations is highly sufficient for the conversion of starting materials to DPH by conducting the milling only for minutes. Performing the syntheses identically under both temperature conditions (room temperatures and cryo conditions), it was observed that this difference in temperature does not significantly change the obtained DPH yield. (Table 1). Grinding via ball mill in cryo conditions can offer a pathway to proceed solid state reactions, however, one of the starting materials N,N-dimethylethanolamine (DMAE) is liquid in room temperature and can freeze at -70 ^{o}C. It can be said that DMAE cannot freeze immediately before it reacts and the reaction media does not completely contain solid state reactions. This is why the cryo conditions does not possess a huge impact on the change of isolated yields of DPH. In mechanochemical approaches, milling materials can be various (e.g. zirconium dioxide, tungsten carbide, stainless-steel, agate, PMMA, glass) depending on the targeted chemical reactions. For this reason, next, the effect of the milling material was tried to be verified by changing the milling medium to steel using stainless steel (SS) (Table 1, entries 10, 11) jar and balls at both room temperature and at -196 ^{o}C. No exact yields were recorded since stainless-steel (SS)

vessels have loosened up at each trial, however, the formation of DPH was confirmed and verified by 1H and 13C NMR. We concluded that both milling materials are applicable to the mechanosynthesis of DPH. Finally, DPH grinded with pestle and mortar were demonstrated for a comparison. Grinding with pestle and mortar led to a moderate yield of 45% (Table 1, entry 12) and it expected to have lower yields for manual grinding since the mechanical activation cannot be achieved as efficiently as ball milling at high frequencies.

Table 1. Examination of Reaction Conditions for the Synthesis of DPH (SS: Stainless steel).

Diphenhydramine (DPH)					
Entry	**Jar/ Ball material**	**Milling frequency (Hz)**	**Time (min)**	**Temperature (ºC)**	**Yield (%)[b]**
1	ZrO_2	30 Hz	1 min	25 ºC	77
2	ZrO_2	30 Hz	5 min	25 ºC	88
3	ZrO_2	30 Hz	10 min	25 ºC	88
4	ZrO_2	30 Hz	20 min	25 ºC	81
5	ZrO_2	30 Hz	60 min	25 ºC	76
6	ZrO_2	30 Hz	5 min	-196 ºC	77
7	ZrO_2	30 Hz	10 min	-196 ºC	91
8	ZrO_2	30 Hz	20 min	-196 ºC	85
9	ZrO_2	30 Hz	60 min	-196 ºC	70
10	SS	30 Hz	5 min	-196 ºC	N/A
11	SS	30 Hz	5 min	25 ºC	N/A
12	Pestle & mortar	-	5 min	25 ºC	45

[a]Reaction conditions: Bromodiphenylmethane (2.03 mmol, 1.0 equiv) and N,N-dimethylethanolamine (DMAE) (2.00 mmol, 1.0 equiv) were ball-milled in a 25 mL zirconia milling jar with 6 zirconia milling balls (10.06 mm diameter) or in a 25 mL stainless-steel milling (SS) jar with 6 stainless-steel (SS) milling balls (10.06 mm

diameter) or grinded by pestle and mortar for the specified time and temperature. [b]Isolated yield.

In the next set of reactions, an evaluation of the applicability of the mechanochemical approach to cyclizine was targeted due to structural resemblance to the previously studied DPH and the use of the same starting material, bromodiphenylmethane. The ball mill and manual grinding techniques, for which the results are summarized in Table 2. Milling experiments were performed in zirconia and stainless-steel milling vessels (25 mL volumetric capacity) with complementary ball materials (six milling balls, 10.06 mm in diameter). Firstly, different reaction times was probed. After the trial with one hour at 25 ^{o}C, cyclizine was obtained in 57% yield (Table 2, entry 4). The yields improved slightly when the reaction was performed for 20 minutes as 63% yield (Table 2, entry 3). Further investigations on mechanochemical reactions of CYC were carried out under cryo conditions. The results demonstrated that lower temperatures showed outstanding improvement with around 75-80% yields (Table 2, entry 5-9) with well-defined ^{1}H NMR spectra in the figures. The starting materials were fully converted to the product. Grinding via ball mill in cryo conditions offered a way to proceed solid state reactions for the synthesis of cyclizine since the starting materials; bromodiphenylmethane (MP: 35-39 ^{o}C) and N-methyl piperazine (MP: -5.57 ^{o}C) have low melting points. So, they freeze before the reaction starts which creates liquid-free reaction media and increases the yields of the reaction. Milling was also performed using stainless steel jar at 25 ^{o}C and -196 ^{o}C for 5 minutes (Table 2, entries 9 and 10), with yields higher than those obtained by milling in zirconia media or grinding with pestle and mortar for 5 minutes. Manual grinding led to lower yields as expected since the mechanical activation cannot be highly achieved as in the case of DPH. To summarize, the experimental results of the invention suggest that the secondary halide exhibits good mechanochemical reactivity with methyl piperazine and provided the expected benzhydryl piperazine in 45−84 % yields.

Table 2. Examination of Reaction Conditions[a] for the Synthesis of CYC.

Cyclizine (CYC)					
Entry	**Jar/ ball material**	**Milling frequency (Hz)**	**Time (min)**	**Temperature (^{o}C)**	**Yield (%)[b]**

1	ZrO_2	30 Hz	5 min	25 °C	41
2	ZrO_2	30 Hz	10 min	25 °C	55
3	ZrO_2	30 Hz	20 min	25 °C	63
4	ZrO_2	30 Hz	60 min	25 °C	57
5	ZrO_2	30 Hz	5 min	-196 °C	75
6	ZrO_2	30 Hz	10 min	-196 °C	78
7	ZrO_2	30 Hz	20 min	-196 °C	73
8	ZrO_2	30 Hz	60 min	-196 °C	84
9	SS	30 Hz	5 min	-196 °C	68
10	SS	30 Hz	5 min	25 °C	64
11	Pestle & mortar	-	5 min	25 °C	35

[a]Reaction conditions: Bromodiphenylmethane (0.81 mmol, 1.0 equiv) and N- Methyl piperazine (0.81 mmol, 1.0 equiv) were ball-milled in a 25 mL zirconia milling jar with 6 zirconia milling balls (10.06 mm diameter) or in a 25 mL stainless-steel milling (SS) jar with 6 stainless-steel (SS) milling balls (10.06 mm diameter) or grinded by pestle and mortar for the specified time and temperature. [b] Isolated yield

Another antihistamine derivative - DPP was succsefully synthesized by mean of milling bromodiphenylmethane and N-methyl 4-piperidinol with the application of different milling conditions (Table 3). Briefly, experiments were performed in zirconia milling vessels (25 mL volumetric capacity) with complementary six balls (10.06 mm in diameter) probing different reaction times at room temperature. Products were isolated with satisfactory yields however, the highest yield was obtained when the reaction mixture was ball milled for 10 minutes (Table 3, entry 2). To study the effect of lower temperature on the product formation, reactions were also performed in cryo conditions. Suprisingly, the products were obtained in low yields (Table 3, entry 5-9), showing that the formation of diphenylpyraline is favored at higher temperatures. DPP was synthesized with good yield by manual grinding using pestle and mortar (Table 3, entry 11). To sum up, mechanochemistry can be succesfully applied in the synthesis of (4-(benzhydryloxy)-1-methylpiperidine by the usage of ball mill at room temperature and the expected yields range between 66-84%.

Table 3. Examination of Reaction Conditions[a] for the Synthesis of DPP.

Diphenylpyraline (DPP) [a]					
Entry	**Jar/ ball material**	**Milling frequency (Hz)**	**Time (min)**	**Temperature (°C)**	**Yield (%)[b]**
1	ZrO_2	30 Hz	5 min	25 °C	71
2	ZrO_2	30 Hz	10 min	25 °C	84
3	ZrO_2	30 Hz	20 min	25 °C	67
4	ZrO_2	30 Hz	60 min	25 °C	66
5	ZrO_2	30 Hz	5 min	-196 °C	N/A
6	ZrO_2	30 Hz	10 min	-196 °C	5
7	ZrO_2	30 Hz	20 min	-196 °C	23
8	ZrO_2	30 Hz	60 min	-196 °C	29
9	SS	30 Hz	5 min	-196 °C	N/A
10	SS	30 Hz	5 min	25 °C	N/A
11	Pestle & mortar	-	5 min	25 °C	67

[a]Reaction conditions: Bromodiphenylmethane (1.85 mmol, 1.0 equiv) and N-Methyl 4-piperidinol (1.85 mmol, 1.0 equiv) were ball-milled in a 25 mL zirconia milling jar with 6 zirconia milling balls (10.06 mm diameter) or grinded by pestle and mortar for the specified time and temperature. [b] Isolated yield

Mechanochemical synthesis method of hydrochloride salts of histamine antagonist active pharmaceutical ingredients (APIs) comprises the following process steps:

i) ball-milling of starting materials in 1:1 equivalency in a 25 mL milling jar with 6 complementary milling balls made from zirconia (ZrO_2) or stainless-steel (SS) with a 10.06 mm diameter for 5-60 min at 25 °C or -196 °C at 30 Hz, or grinding with a pestle and a mortar at 25 °C for 5 min,

ii) scratching the reaction mixture from the ball milling vessels or pestle and mortar and transferring into a flask,

iii) purifying the reaction mixture,

iv) treating purified active pharmaceutical ingredients (APIs) in 5-10 mL of methanol with 2-3 drops of concentrated HCl until pH becomes 4-5,

v) heating and stirring the treated products until being fully dissolved,

vi) cooling the mixture slowly to room temperature first, and then cooling the mixture in ice bath to crystallize hydrochloride salts.

In the mechanochemical synthesis method of the present invention; the starting materials are chosen according to histamine antagonist to be sythesized. Bromodiphenylmethane and N,N-dimethylethanolamine (DMAE) are used as starting materials for the mechanosynthesis of DPH in step (i) of the method. Bromodiphenylmethane and N-methyl piperazine are used as starting materials for the mechanosynthesis of CYC in step (i) of the method. Bromodiphenylmethane and 4-hydroxy-1-methylpiperidine are utilized as starting materials for the mechanosynthesis of DPP in step (i) of the method.

The purification processes applied in step (iii) of the mechanochemical synthesis method of the present invention also changes due to which histamine antagonist is sythesized.

In the purification process applied in step (iii) of the mechanochemical synthesis method of the present invention for Diphenhydramine (2-(benzhydryloxy)-N,N-dimethylethan-1-amine) (DPH); the reaction mixture is washed with 5 mL of dichloromethane three times, DPH is collected and the collected DPH is dried in vacuum.

In the purification process applied in step (iii) of the mechanochemical synthesis method of the present invention for Cyclizine (1-benzhydryl-4-methylpiperazine) (CYC), following steps are applied:

i. collected reaction mixture is dissolved with 10 mL of ethyl acetate and 10 mL of distilled water,
ii. saturated HCl is added to the solution until pH is 3,
iii. the creamy white aqueous phase is extracted with ethyl acetate (3 x 15 mL),
iv. the aqueous phase is treated with 2.5 M NaOH solution until the pH is 10,

v. the final solution is extracted with ethyl acetate (3 x 15 mL), dried over sodium sulfate, and ethyl acetate is removed under reduced pressure.

In the purification process applied in step (iii) of the mechanochemical synthesis method of the present invention for Diphenylpyraline (4-(benzhydryloxy)-1-methylpiperidine) (DPP), following steps are applied:

i. crude material is purified by column chromatography (eluent: methanol/diethyl ether 1:1),
ii. solvent is removed under reduced pressure and product is dried in vacum.

In one embodiment of the invention; chlorodiphenylmethane, diphenylmethanol, or 1,1'-(diazomethanediyl)dibenzene can be used as starting material instead of bromodiphenylmethane. If diphenylmethanol is used, dimethylaminoethanol should be changed with 2-Chloro-N,N-dimethylethylamine to obtain diphenhydramine (DPH).

In one embodiment of the invention, for cyclizine synthesis, aminodiphenylmethane or chlorodiphenylmethane can be preferred as starting material instead of bromodiphenylmethane. Moreover, N-methyldiethanolamine should be used in exchange for N-methyl piperazine when aminodiphenylmethane is chosen as the other reactant.

In one embodiment of the invention, DPP can also be obtained by similar starting materials as chlorodiphenylmethane, diphenylmethanol, or 1,1'-(diazomethanediyl)dibenzene reacting with 4-hydroxy-1-methylpiperidine.

In the synthesis method of the invention, reactions are performed without any solvents; however, products mostly stick to the surface of vessels after the reactions end if the amount of the starting materials is low. When the products cannot be scratched out from the surface of the vessels, sufficient amount of solvents that can dissolve the APIs are utilized to remove them from the vessels (around 5-10 mL of solvent for 250 mg of product). If the amount of starting materials is increased, more products are formed and they can be scratched more easily from the vessel which ends up with less to no solvent use. This situation can be counted as an advantage for mass production of APIs). In the present invention, appropriate solvent for filtration, extraction, or

crystallization parts if necessary and less toxic solvents (i.e. water, methanol) compared to chloroform, hexane, etc are chosen.

In the present invention, reaction progresses were monitored by thin layer chromatography (TLC) using aluminum-backed plates pre-coated with silica gel and visualized under a UV lamp with λ at 254 nm and 365 nm and/or by immersion in an aqueous solution of potassium permanganate ($KMnO_4$) and heating of the stained plates with a heat-gun at 200 °C until dryness. All organic solutions after extraction or filtration were dried over anhydrous Na_2SO_4 and concentrated using a rotary evaporator, and yields were obtained after drying the products overnight. APIs were characterized by ^1H NMR, ^{13}C NMR and HRMS as it was mentioned earlier. ^1H and ^{13}C NMR spectra were recorded on spectrometer operating at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR, using deuterated solvents ($CDCl_3$-d, methanol-d_4) with tetramethyl silane (TMS) as internal standard and chemical shifts are reported in ppm values. Chemical shifts (δ) are given in parts per million (ppm) relative to the residual solvent peaks (^1H NMR δ = 7.26 ppm; ^{13}C NMR δ = 77.16 ppm for $CDCl_3$; ^1H NMR δ = 3.31 ppm; ^{13}C NMR δ = 49.00 ppm for methanol-d_4). Spin multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), m (multiplet), bs (broad signal).

DPH: 2-(benzhydryloxy)-N,N-dimethylethan-1-amine

Chemical Formula: $C_{17}H_{21}NO$

Exact Mass: 255.16

Molecular Weight: 255.36

m/z: 255.16 (100.0%), 256.17 (18.4%), 257.17 (1.6%)

Elemental Analysis: C, 79.96; H, 8.29; N, 5.49; O, 6.27

MS (TOF- ESI): m/z Calcd for C17H21NO [M+H]+: 256.16959, Found for [M+H]+: 256.16889, 256.16978, 256.17059, 256.16974, 256,16818, respectively for Figures 1-5.

^1H NMR (400 MHz, $CDCl_3$): δ_H 7.86-7.80 (m, 5H) 7.42-7.38 (m, 5H), 6.30 (s, 1H), 3.95 (t, 2H), 3.56 (t, 2H), 3.25 (s, 6H) (Figures 7-9, 11)

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 135.9, 135.3, 134.4, 133.5, 86.6, 68.4, 60.0, 53.3 (Figures 10, 12)

DPH HCl: 2-(benzhydryloxy)-N,N-dimethylethan-1-amine hydrochloride

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.83-7.81 (m, 4H) 7.42-7.37 (m, 6H), 6.30 (s, 1H), 3.97 (t, 2H), 3.57 (t, 2H), 3.24 (s, 6H) (Figure 6).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 135.9, 135.3, 134.4, 133.5, 86.6, 68.4, 60.0, 53.3 (Figure 10).

HRMS data of DPH HCl had the same m/z ratio with DPH where m/z Calcd for $C_{17}H_{21}NO$ [M+H]+ is 256.16959, found for [M+H]+ as 256.16781 and 256.16974, respectively (Figure 13). Since DPH HCl possesses a proton when it ionizes into [DPH+H]+ and chloride ions, the m/z ratio for [DPH+H]+ is similar to DPH, which takes a proton from methanol.

The ^{1}H NMR spectra of the DPHs have well-resolved characteristic signals where specific proton peak of bromodiphenylmethane at δ = 5.3 ppm disappears and the aliphatic protons of dimethylaminoethanol are shifted downfield. The singlet at δ = 6.3 ppm is attributable to a proton on the -CH and it is an indicator of DPH formation.

The ^{13}C NMR spectrum of DPH also proves the complete conversion by showing eight carbon peaks in total. Due to the symmetry of DPH, four aromatic carbon signals around 134 ppm can be observed while the peak at δ = 86.6 ppm comes from the carbon attached oxygen and aromatic rings. The signals at δ = 68.4 ppm and δ = 60.0 ppm are attributable to the carbons on the -CH_2's.

Cyclizine (CYC): 1-benzhydryl-4-methylpiperazine

Chemical Formula: $C_{18}H_{22}N_2$

Exact Mass: 266.18

Molecular Weight: 266.39

m/z: 266.18 (100.0%), 267.18 (19.5%), 268.19 (1.8%)

Elemental Analysis: C, 81.16; H, 8.32; N, 10.52

MS (TOF- ESI): m/z Calcd for $C_{17}H_{21}N_2$ [M+H]+: 267.18558, Found for [M+H]+: 267.19054, 267.18351, 267.18507, 267.18558, 267.18483, 267.18381, 267.18394, 267.18462, 267.18454, 267.18498 respectively for Figures 14-23.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.45 (m, 4H) 7.25 (m, 4H), 7.18 (m, 2H), 4.26 (s, 1H), 2.5 (s, broad, 8H), 2.3 (s, 3H) (Figures S24-27).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 142.6, 128.5, 127.9, 126.9, 76.3, 55.2, 51.6, 45.7 (Figure S28).

<u>Cyclizine HCl: 1-benzhydryl-4-methylpiperazine hydrochloride</u>

MS (TOF- ESI): m/z Calcd for $C_{18}H_{22}N_2$ [M+H]+: 267.18558, Found for [M+H]+: 267.18508 (Figure S29)

^{1}H NMR (400 MHz, MeOD): δ_H 7.97-7.95 (m, 4H) 7.50-7.40 (6H, m) 4.84 (1H, bs) 3.90 (bs, 4H), 3.69 (bs, 4H) 3.07 (bs, 3H) (Figure S30)

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 142.6, 128.5, 127.9, 126.9, 76.3, 55.2, 51.5, 45.6 (Figure S31)

Cyclizine formation was characterized by HRMS data where CYC has 266.18 exact mass. The separated ions were measured where the m/z ratios were stored together along with their relative abundance. As H+ ions were present in a CYC sample, mass-to-charge (m/z) ratio was found for each product around the calculated [M+H]+: 267.18558 (Molecular weight of H= 1.0079 g/mol) (Figures S13-S22, S28).

The ^{1}H NMR spectra of the CYCs have well-resolved characteristic signals where specific proton peak of bromodiphenylmethane at δ = 5.3 ppm disappears. Aliphatic protons of N-Methyl piperazine are also not present in the spectra of CYC. The singlet at δ = 4.26 ppm is attributable to the -CH proton of the expected product CYC. Four -CH_2's attached to nitrogen atoms lead to the broad singlet at δ = 2.5 ppm.

The ^{13}C NMR spectra of CYCs also proves the full conversion by showing eight expected carbon signals. Due to the symmetry of CYC, there are three aromatic carbon

signals around 127 ppm and one around 142 ppm. The signal at δ = 76.3 ppm is from the carbon attached nitrogen and aromatic rings. The signals at δ = 55.2 ppm and δ = 51.6 ppm are attributable to the carbons on the -CH_2's connected directly to the nitrogens, and the signal at 45.7 ppm belongs to the carbon on the -CH_3.

DPP: 4-(benzhydryloxy)-1-methylpiperidine

Chemical Formula: $C_{19}H_{23}NO$

Exact Mass: 281.18

Molecular Weight: 281.40

m/z: 281.18 (100.0%), 282.18 (20.5%), 283.18 (2.0%)

Elemental Analysis: C, 81.10; H, 8.24; N, 4.98; O, 5.69

MS (TOF- ESI): m/z Calcd for $C_{19}H_{23}NO$ [M+H]+: 267.18558, Found for [M+H]+: 282.18452 (Figure S32).

^{1}H NMR (400 MHz, MeOD): δ_H 7.93-7.91 (m, 4H) 7.58-7.54 (m, 6H) 5.90-5.84 (m, 1H) 4.04-3.78 (m, 2H) 3.54-3.41 (m, 2H) 3.25 (bs, 3H) 3.21 (s, 1H) 2.24-2.14 (m, 2H) 1.93-1.83 (m, 2H) (Figure S33).

^{13}C NMR (100 MHz, MeOD): δ_C 132.2, 131.4, 131.3, 130.1, 130.0, 129.3, 129.2, 83.6, 59.5, 58.3, 54.0, 42.9, 28.4, 27.1 (Figure S34).

DPP HCl: 4-(benzhydryloxy)-1-methylpiperidine hydrochloride

MS (TOF- ESI): m/z Calcd for $C_{19}H_{23}NO$ [M+H]+: 267.18558, Found for [M+H]+: 282.18435 (Figure S35).

^{1}H NMR (400 MHz, MeOD): δ_H 8.02-7.98 (m, 4H) 7.50 (m, 6H) 6.19-6.06 (m, 1H) 4.01-3.63 (m, 4H) 3.28 (m, 3H) 3.19 (bs, 1H) 2.21-2.17 (m, 2H) 1.90-1.87 (m, 2H) (Figure S36)

^{13}C NMR (100 MHz, MeOD): δ_C 132.2, 131.4, 131.4, 130.1, 130.0, 129.3, 129.3, 83.7, 59.4, 58.3, 54.1, 42.8, 28.4, 27.1 (Figure S37)

The ^{1}H NMR spectra of the DPPs have well-resolved characteristic signals including multiplet at δ = 6.2-6.1 attributed to a -C<u>H</u> proton neighbouring with aromatic rings and confirming the formation of DPP. What is more, proton peak at δ = 5.3 ppm attributed to -C<u>H</u>Br of the starting material bromodiphenylmethane disappeared, indicating its consumption and generetion of the product.

In the ^{13}C NMR spectrum of DPPs four signals observed at δ = 27.1, 28.4, 58.3, and 59.5 ppm indicated the presence of two CH_2 groups. The methylene carbon atom of -N<u>C</u>H_3 group appeared as singlet at δ = 42.9 ppm. Carbon peak at δ = 54.0 ppm was assigned to -O<u>C</u>H group. Signal derived from Ar<u>C</u>HAr appeared as singlet at δ = 83.1 ppm. Aromatic carbon signals at δ = 132.2-129.2 ppm also confirmed the presence of four carbon atoms.

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CLAIMS

1. A mechanochemical synthesis method of hydrochloride salts of histamine antagonist active pharmaceutical ingredients, characterized by comprising following steps;

i) ball-milling of starting materials in 1:1 equivalency in a 25 mL milling jar with 6 complementary milling balls made from zirconia (ZrO_2) or stainless-steel (SS) with a 10.06 mm diameter for 5-60 min at 25 ^oC or -196 ^oC at 30 Hz, or grinding with a pestle and a mortar at 25 ^oC for 5 min,

ii) scratching the reaction mixture from the ball milling vessels or pestle and mortar and transferring into a flask,

iii) purifying the reaction mixture,

iv) treating purified active pharmaceutical ingredients (APIs) in 5-10 mL of methanol with 2-3 drops of concentrated HCl until pH becomes 4-5,

v) heating and stirring the treated products until being fully dissolved,

vi) cooling the mixture slowly to room temperature first, and then cooling the mixture in ice bath to crystallize hydrochloride salts.

2. A method according to Claim 1, characterized in that said histamine antagonist is diphenhydramine (2-(benzhydryloxy)-N,N-dimethylethan-1-amine ; DPH) or cyclizine (1-benzhydryl-4-methylpiperazine ; CYC) or diphenylpyraline (4-(benzhydryloxy)-1-methylpiperidine ; DPP).

3. A method according to Claim 2, characterized in that starting materials are bromodiphenylmethane and N,N-dimethylethanolamine (DMAE) for mechanosynthesis of hydrochloride salts of DPH.

4. A method according to Claim 2, characterized in that starting materials are chlorodiphenylmethane and N,N-dimethylethanolamine (DMAE) for mechanosynthesis of hydrochloride salts of DPH.

5. A method according to Claim 2, characterized in that starting materials are 1,1'-(diazomethanediyl)dibenzene and N,N-dimethylethanolamine (DMAE) for mechanosynthesis of hydrochloride salts of DPH.

6. A method according to Claim 2, characterized in that starting materials are diphenylmethanol and 2-Chloro-N,N-dimethylethylamine for mechanosynthesis of hydrochloride salts of DPH.

7. A method according to Claim 2, characterized in that starting materials are bromodiphenylmethane and N-methyl piperazine for mechanosynthesis of hydrochloride salts of CYC.

8. A method according to Claim 2, characterized in that starting materials are chlorodiphenylmethane and N-methyl piperazine for mechanosynthesis of hydrochloride salts of CYC.

9. A method according to Claim 2, characterized in that starting materials are aminodiphenylmethane and N-methyldiethanolamin for mechanosynthesis of hydrochloride salts of CYC.

10. A method according to Claim 2, characterized in that starting materials are bromodiphenylmethane and 4-hydroxy-1-methylpiperidine for mechanosynthesis of hydrochloride salts of DPP.

11. A method according to Claim 2, characterized in that starting materials are one of chlorodiphenylmethane, diphenylmethanol, or 1,1'-(diazomethanediyl)dibenzene and 4-hydroxy-1-methylpiperidine for mechanosynthesis of hydrochloride salts of DPP.

12. A method according to Claim 2, characterized in that the purifying process of the reaction mixture for mechanosynthesis of hydrochloride salts of diphenhydramine (DPH) comprises following steps;

i) the reaction mixture is washed with 5 mL of dichloromethane three times,
ii) DPH is collected, and
iii) the collected DPH is dried in vacuum.

13. A method according to Claim 2, characterized in that the purifying process of the reaction mixture for mechanosynthesis of hydrochloride salts of cyclizine (CYC) comprises following steps;

i) collected reaction mixture is dissolved with 10 mL of ethyl acetate and 10 mL of distilled water,

ii) saturated HCl is added to the solution until pH is 3,

iii) the creamy white aqueous phase is extracted with ethyl acetate (3 x 15 mL),

iv) the aqueous phase is treated with 2.5 M NaOH solution until the pH is 10,

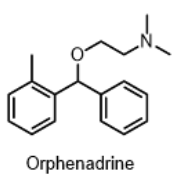
v) the final solution is extracted with ethyl acetate (3 x 15 mL), dried over sodium sulfate, and ethyl acetate is removed under reduced pressure.

14. A method according to Claim 2, characterized in that the purifying process of the reaction mixture for mechanosynthesis of hydrochloride salts of diphenylpyraline (DPP) comprises following steps;

i) crude material is purified by column chromatography (eluent: methanol/diethyl ether 1:1),

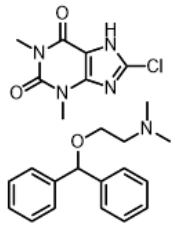
ii) solvent is removed under reduced pressure and product is dried in vacum.

15. A method according to Claim 1, characterized in that said histamine antagonist is one of the following compounds



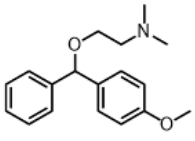
Orphenadrine

N,*N*-dimethyl-2-(phenyl(*o*-tolyl)methoxy)ethan-1-amine



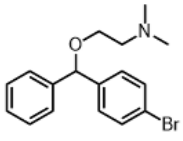
Dimenhydrinate

(Combination drug of diphenhydramine & 8-Chlorotheophylline)



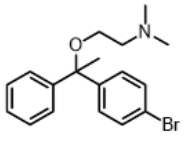
Medrylamine

2-((4-methoxyphenyl)(phenyl) methoxy)-*N*,*N*-dimethylethan-1-amine



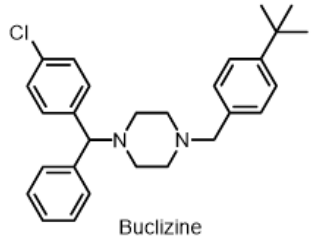
Bromazine

2-((4-bromophenyl)(phenyl)methoxy)-*N*,*N*-dimethylethan-1-amine



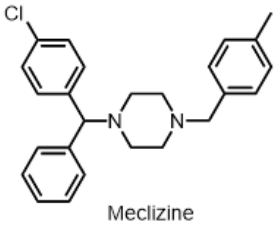
Embramine

2-(1-(4-bromophenyl)-1-phenylethoxy)-*N*,*N*-dimethylethan-1-amine



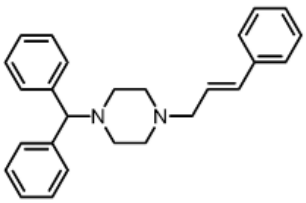
Buclizine

1-(4-(*tert*-butyl)benzyl)-4-((4-chlorophenyl)(phenyl)methyl) piperazine



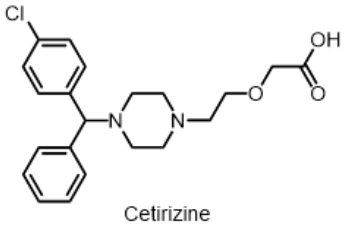
Meclizine

1-((4-chlorophenyl)(phenyl)methyl)-4-(4-methylbenzyl)piperazine



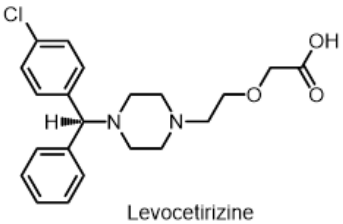
Cinnarizine

1-benzhydryl-4-cinnamylpiperazine



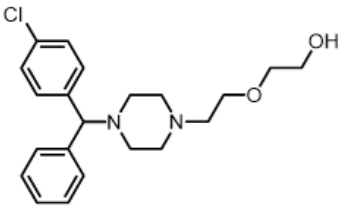
Cetirizine

2-(2-(4-((4-chlorophenyl)(phenyl)methyl) piperazin-1-yl)ethoxy)acetic acid



Levocetirizine

(*S*)-2-(2-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)ethoxy)acetic acid



Hydroxyzine

2-(2-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)ethoxy)ethan-1-ol

ABSTRACT

MECHANOCHEMICAL SYNTHESIS OF HISTAMINE H1-RECEPTOR ANTAGONISTS

The present invention relates to mechanochemical synthesis of histamine antagonists which are benzhydryl ethers and unsymmetrically disubstitutes piperazines and salts thereof. Said antihistamine active pharmaceutical ingredients can be diphenhydramine hydrochloride, cyclizine hydrochloride and diphenylpyraline hydrochloride. These antihistamines are used in the treatment of allergies, hives, hay fever (allergic rhinitis), conjunctivitis, reactions to insect bites and sings, nausea, motion sickness, insomnia.

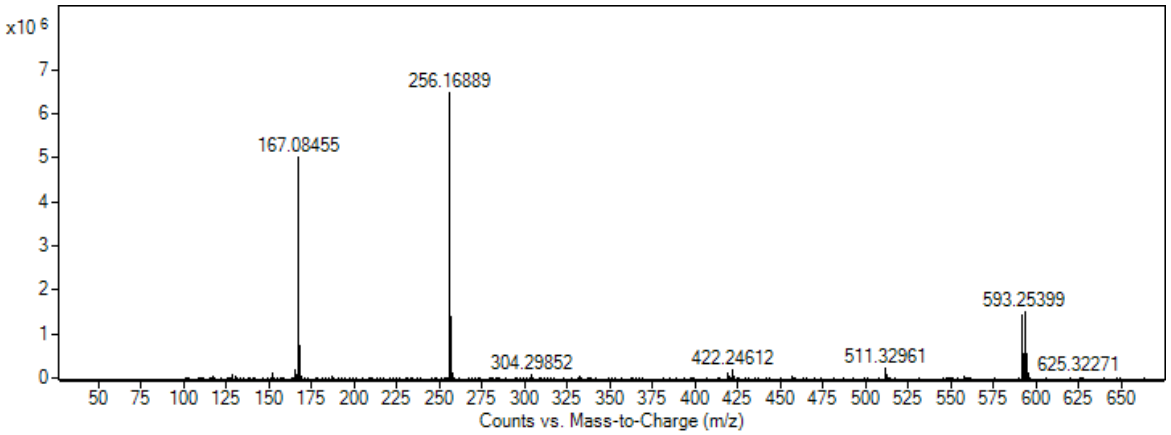


Figure 1

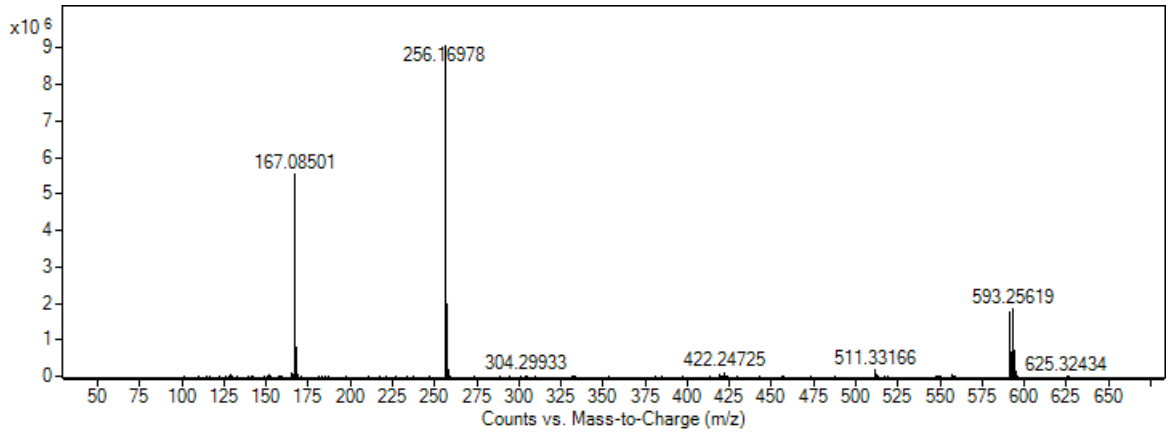


Figure 2

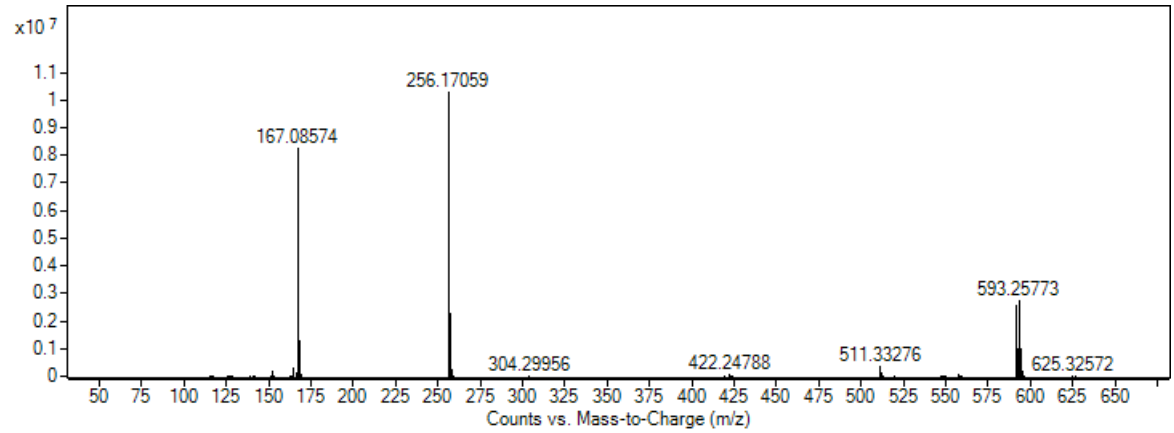


Figure 3

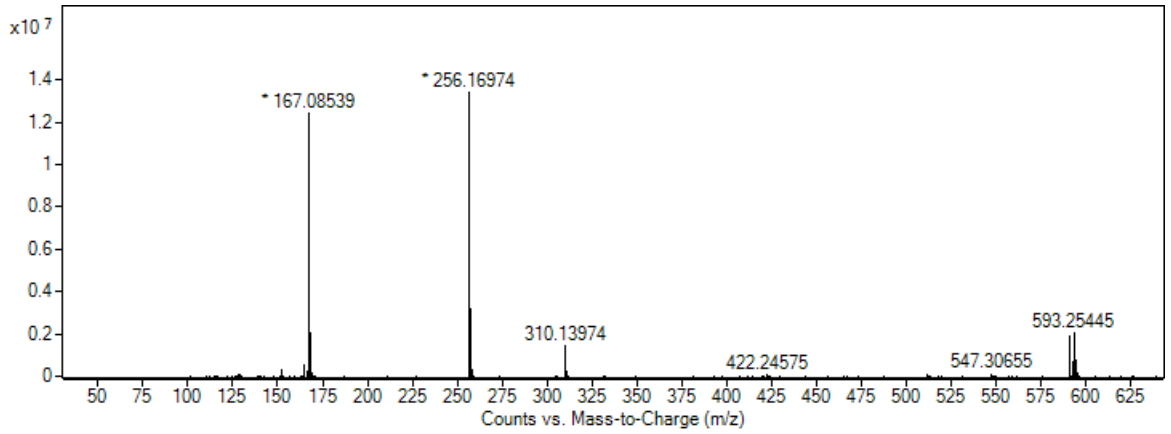


Figure 4

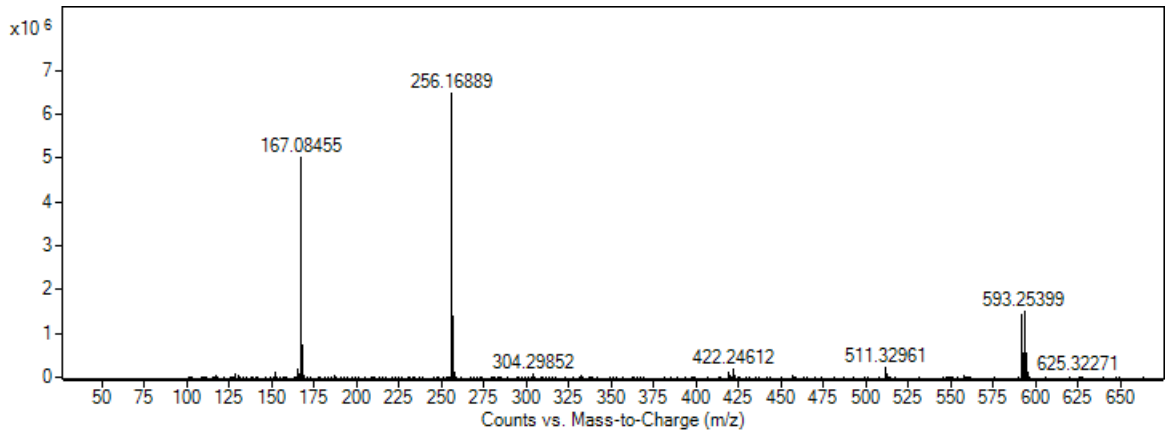


Figure 5

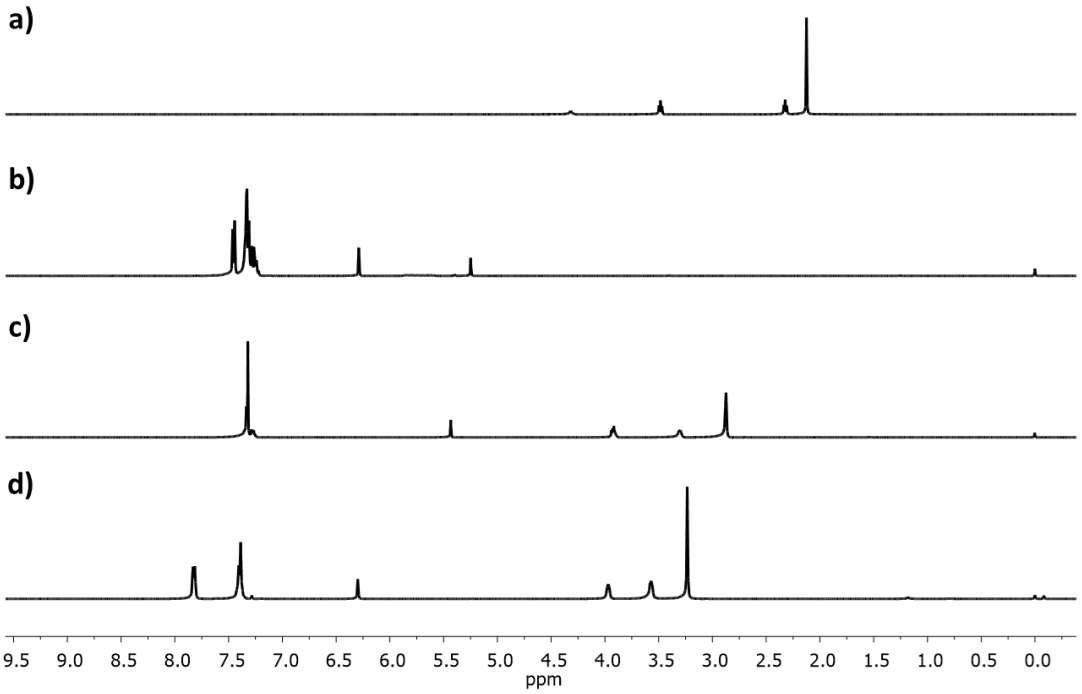
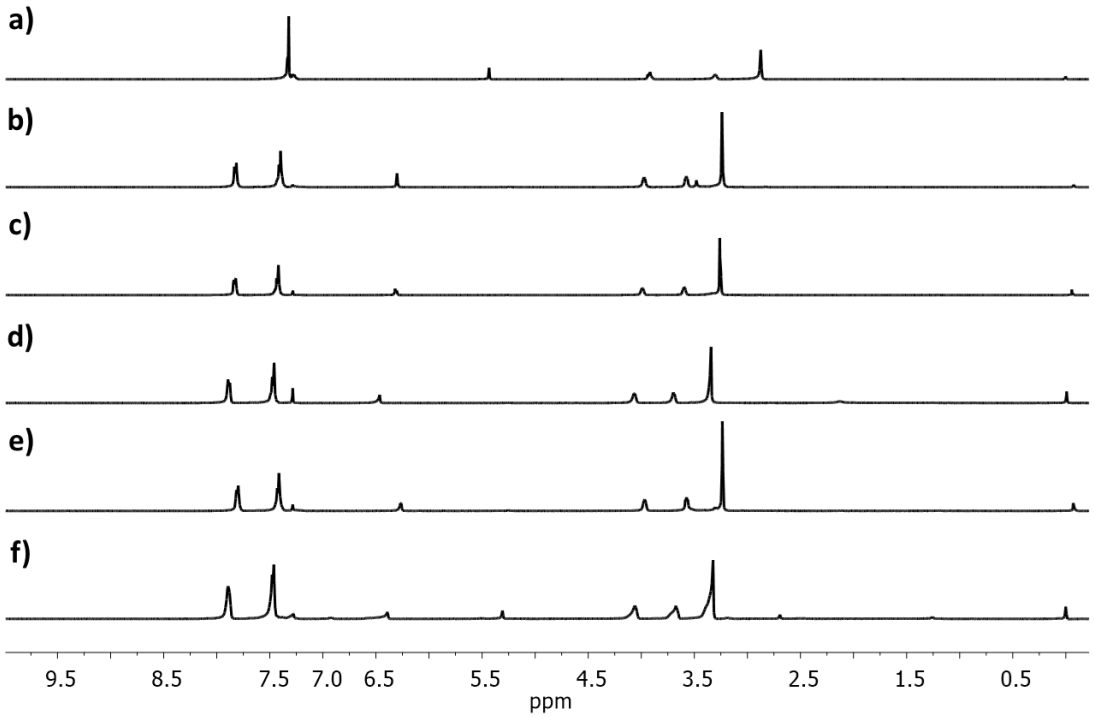


Figure 6



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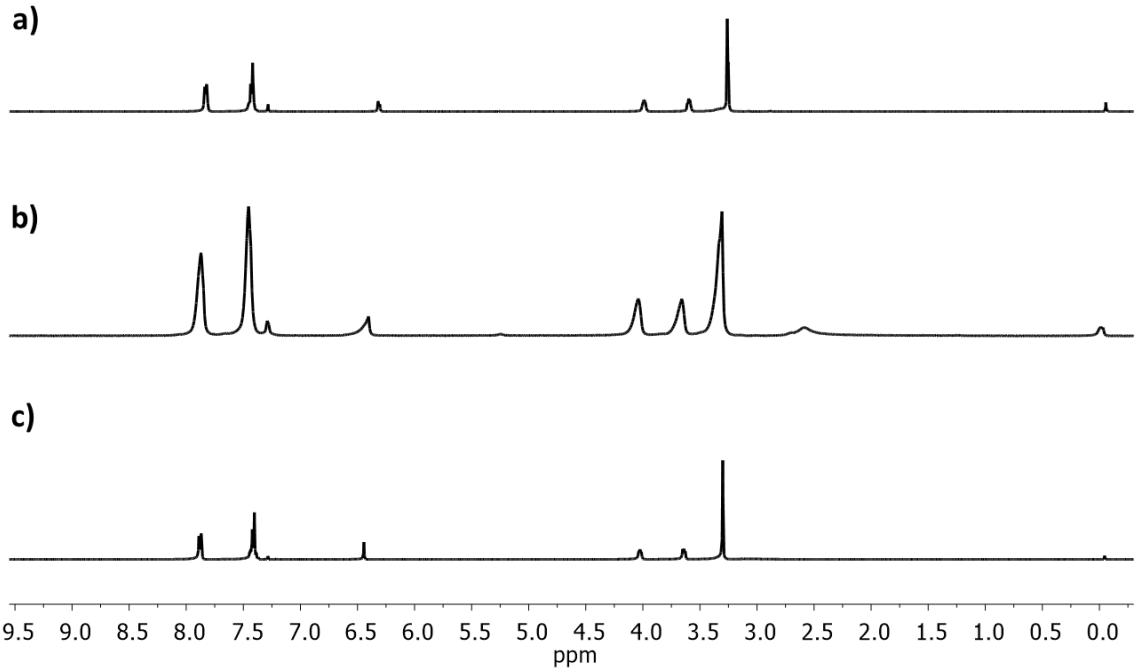

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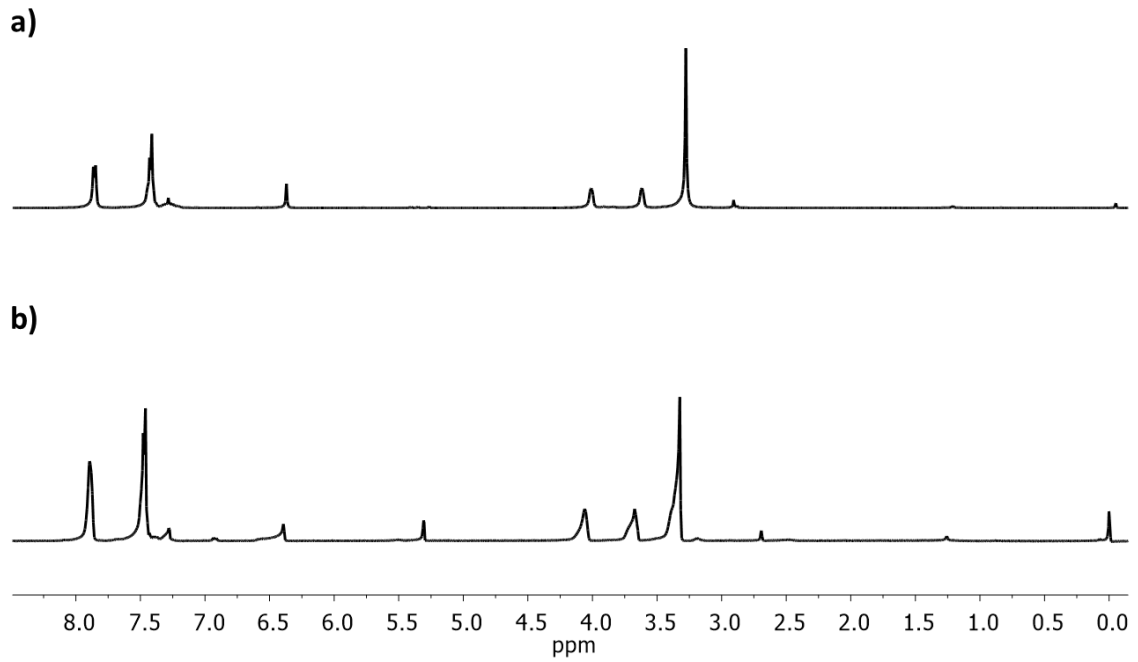

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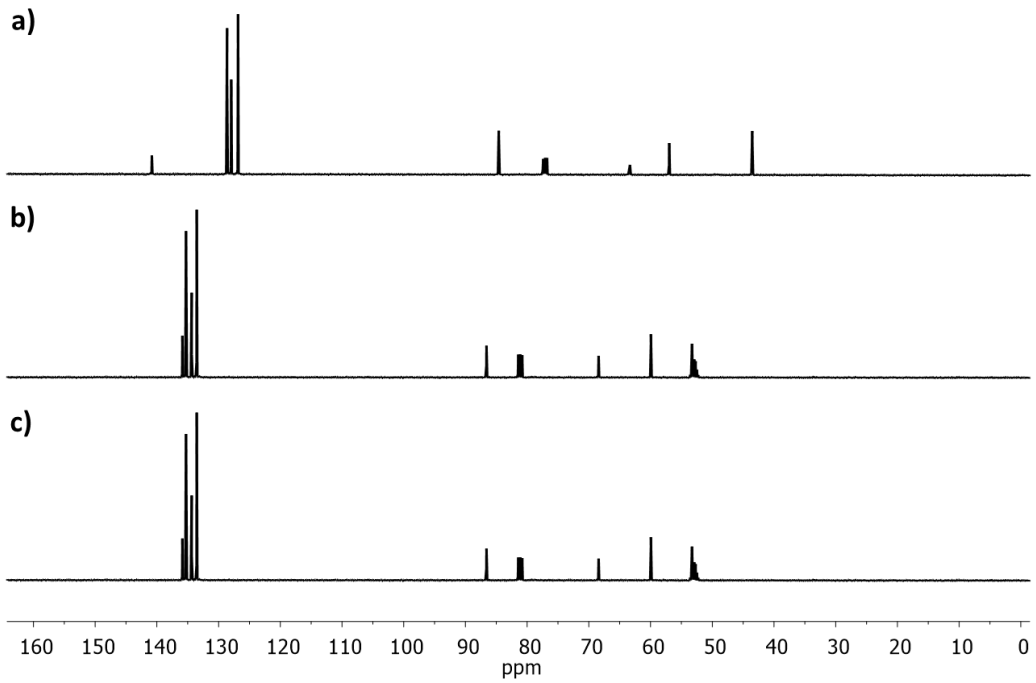

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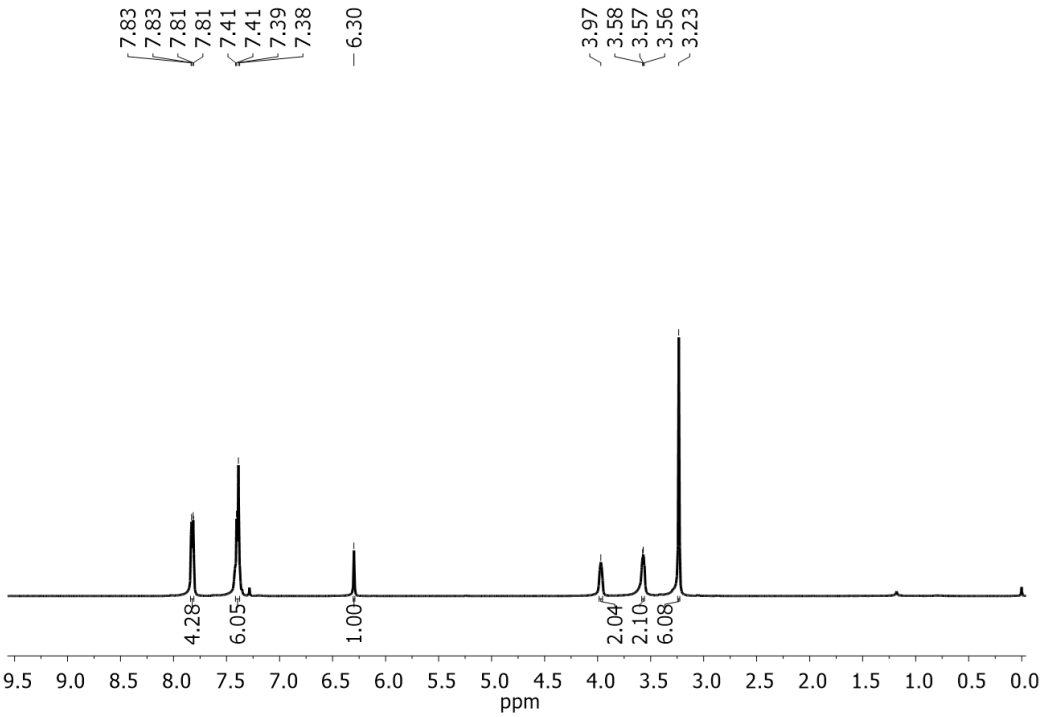

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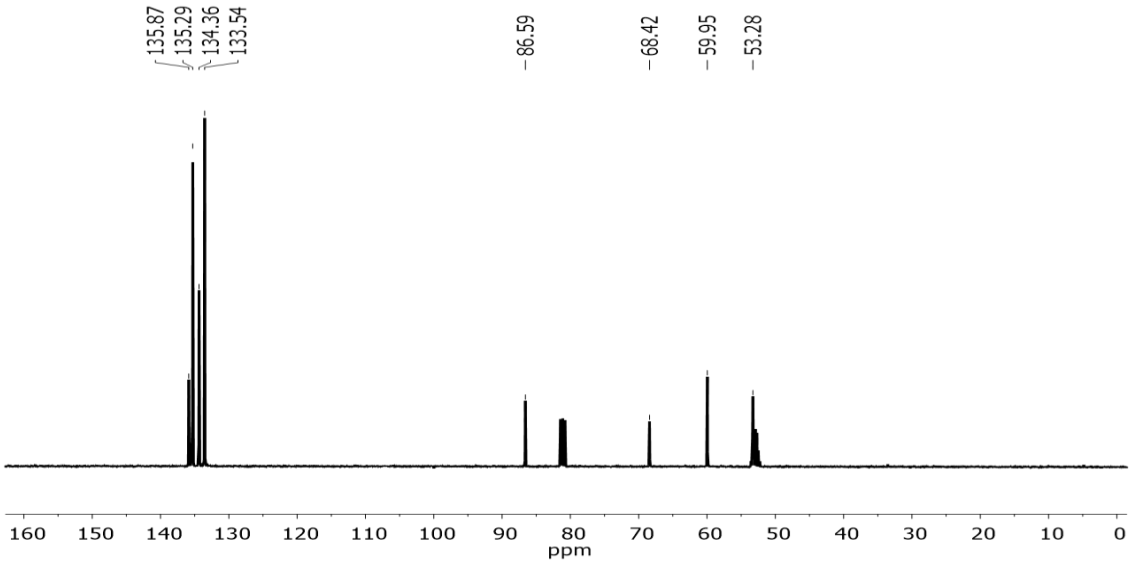

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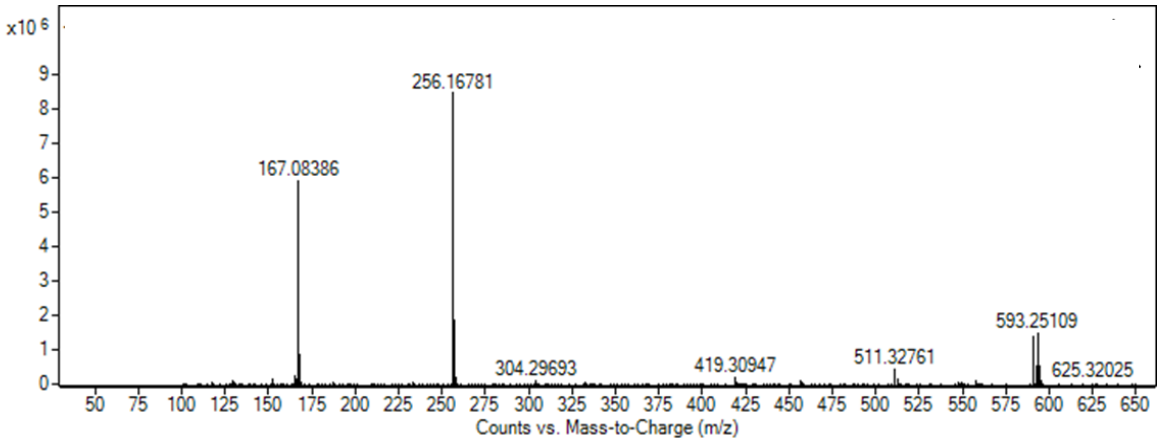

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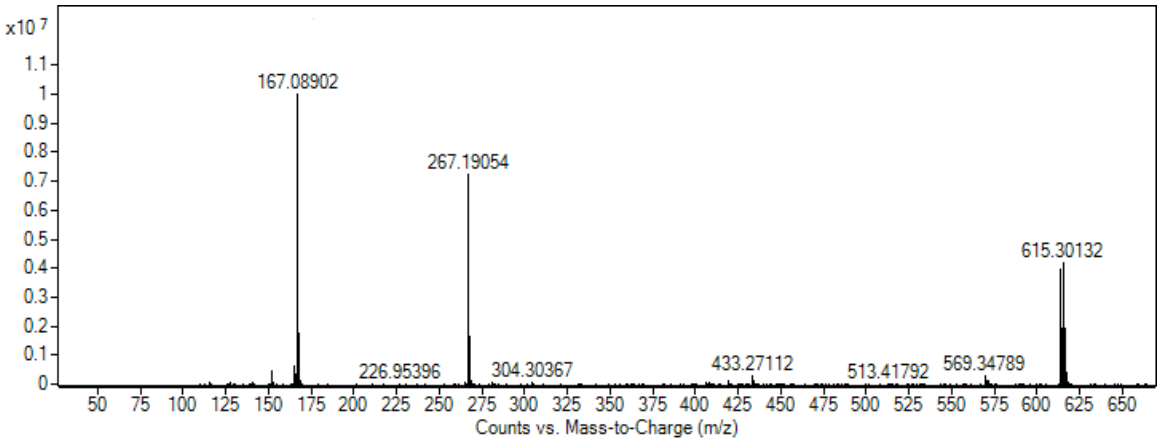

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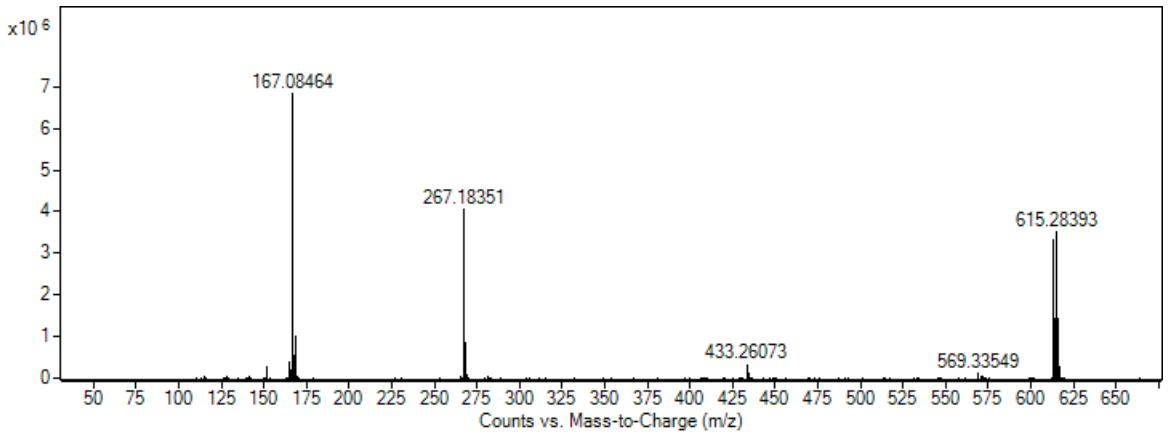

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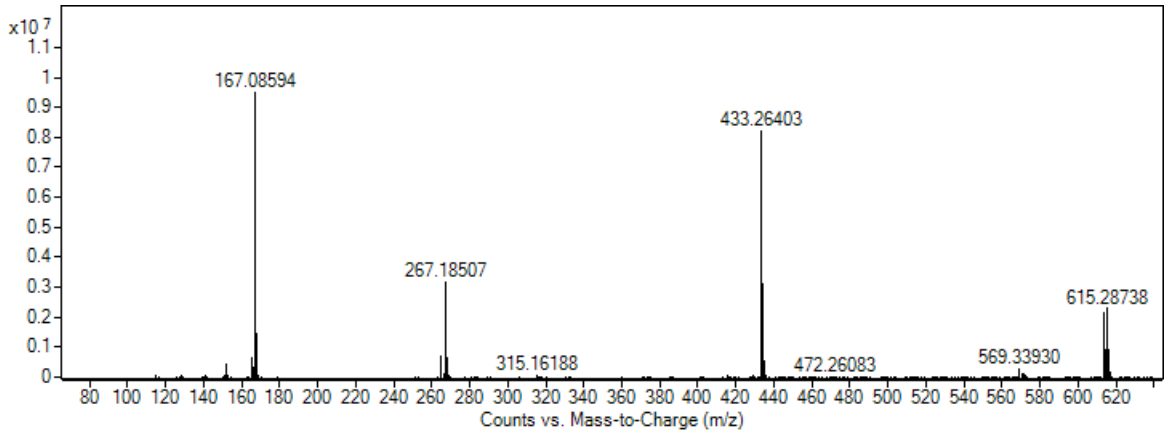

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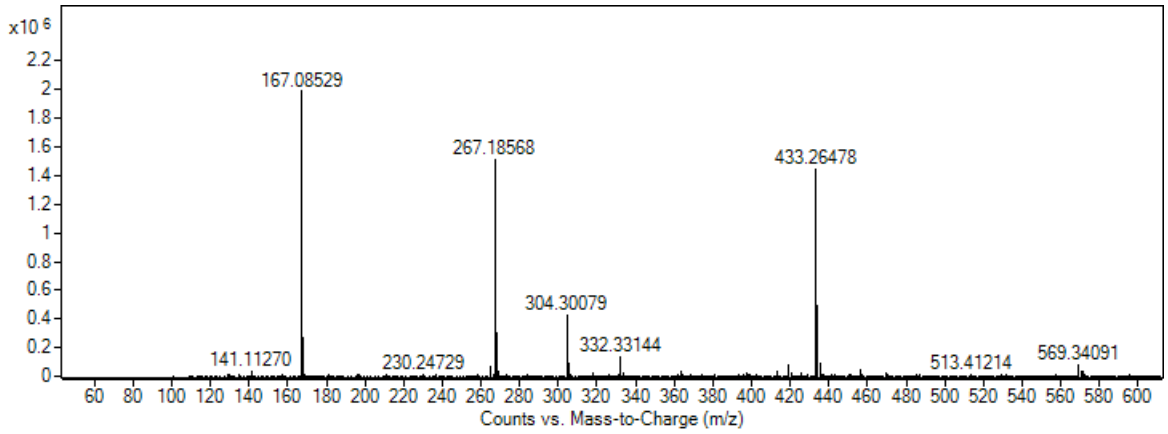

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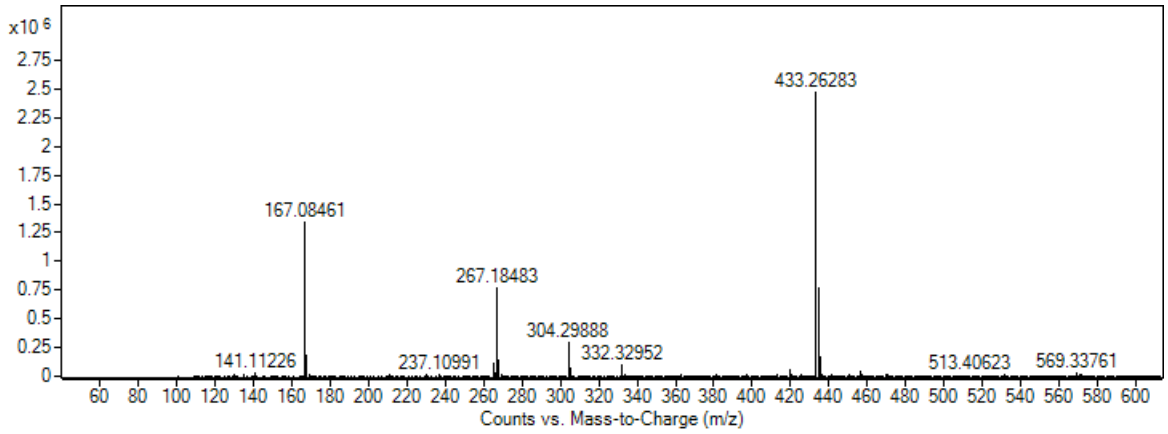

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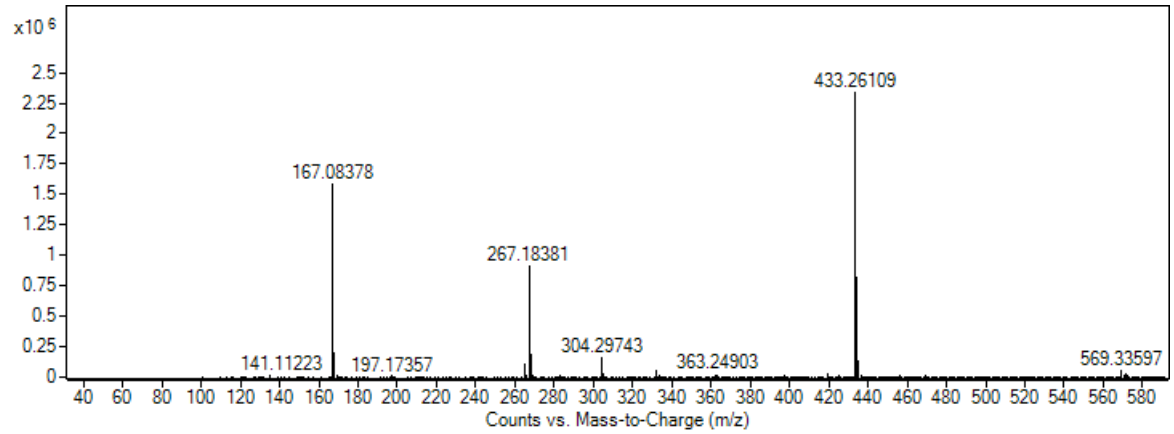

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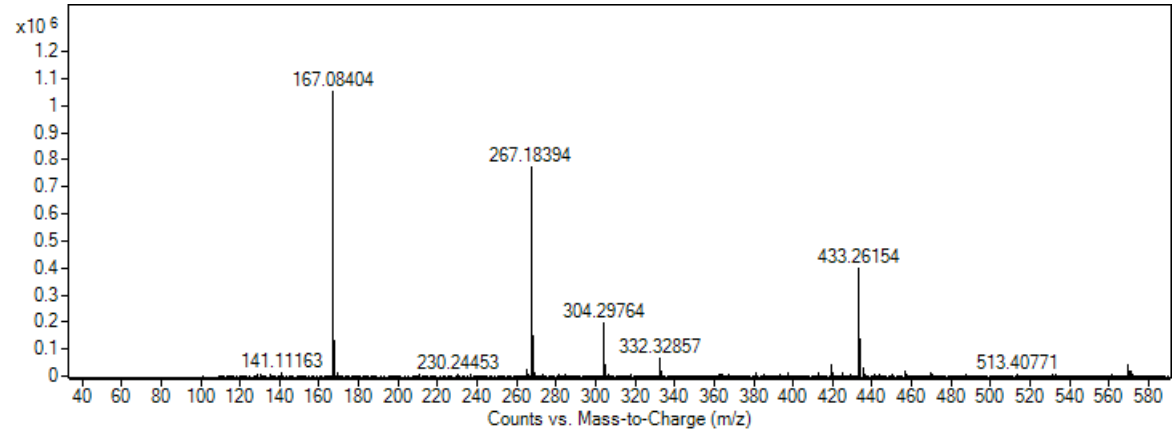

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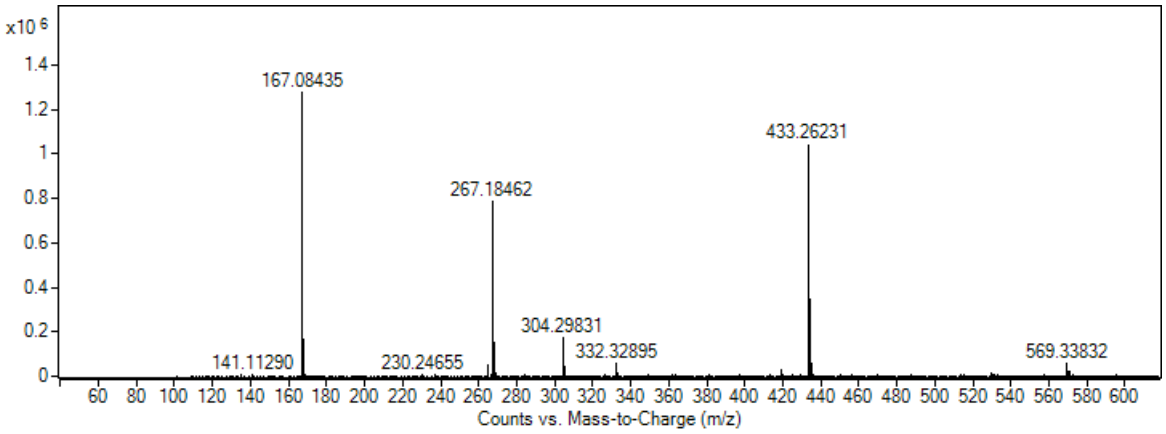

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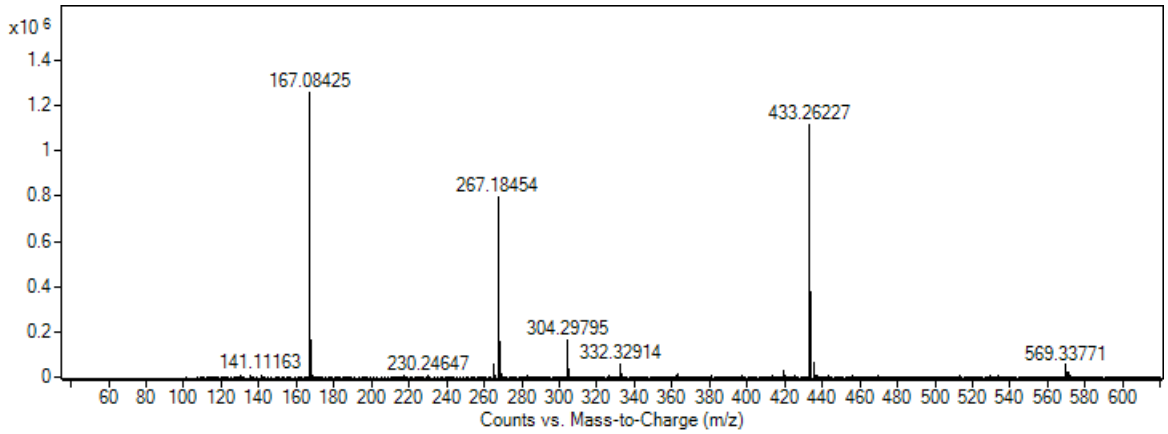

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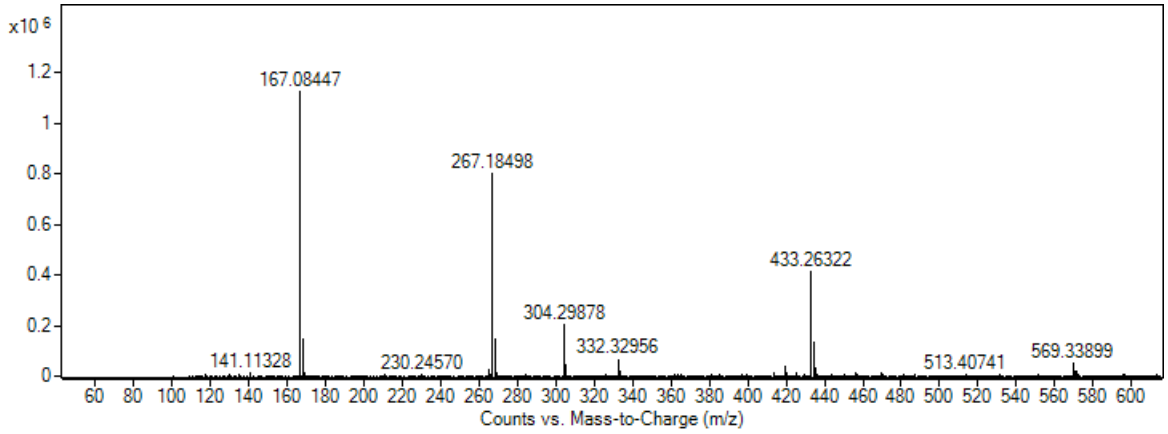

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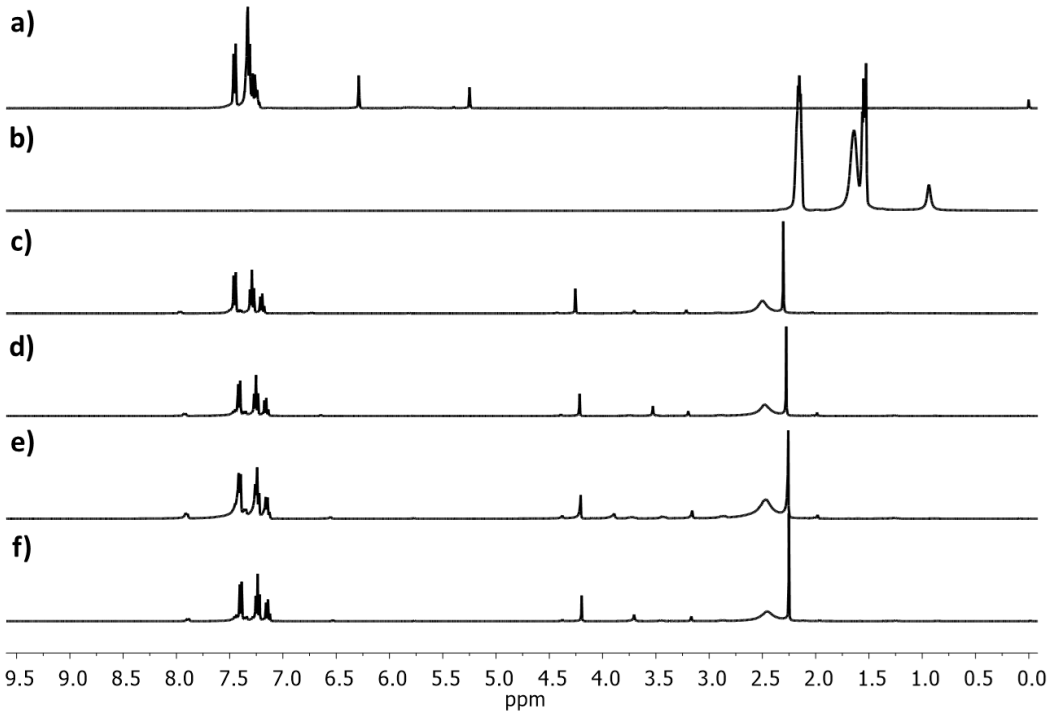

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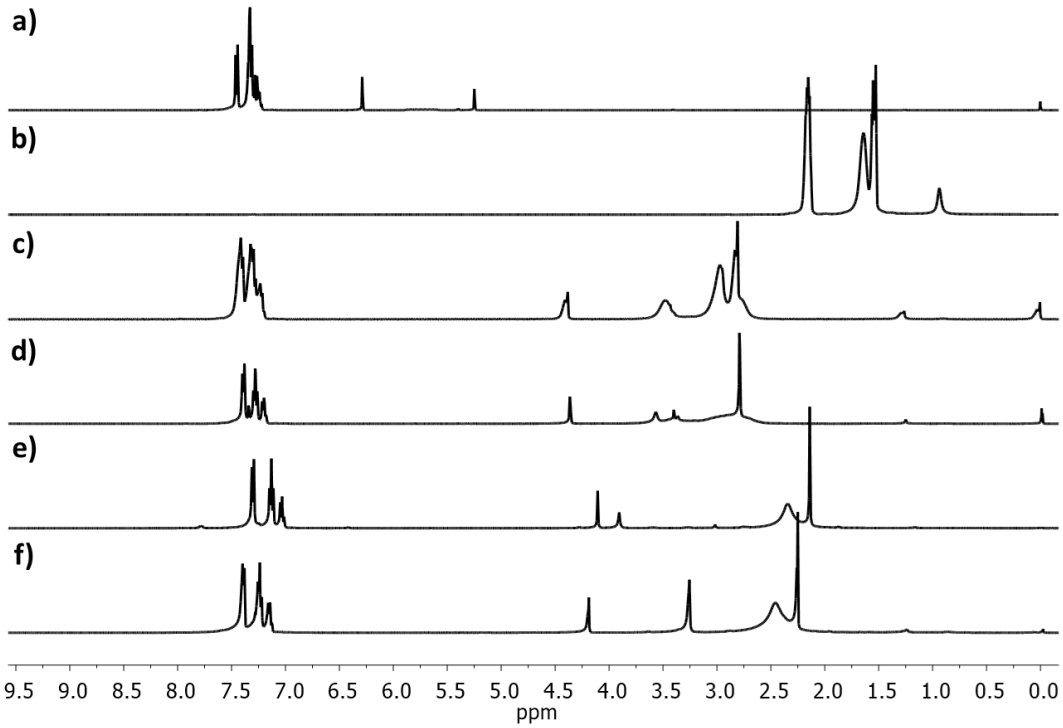

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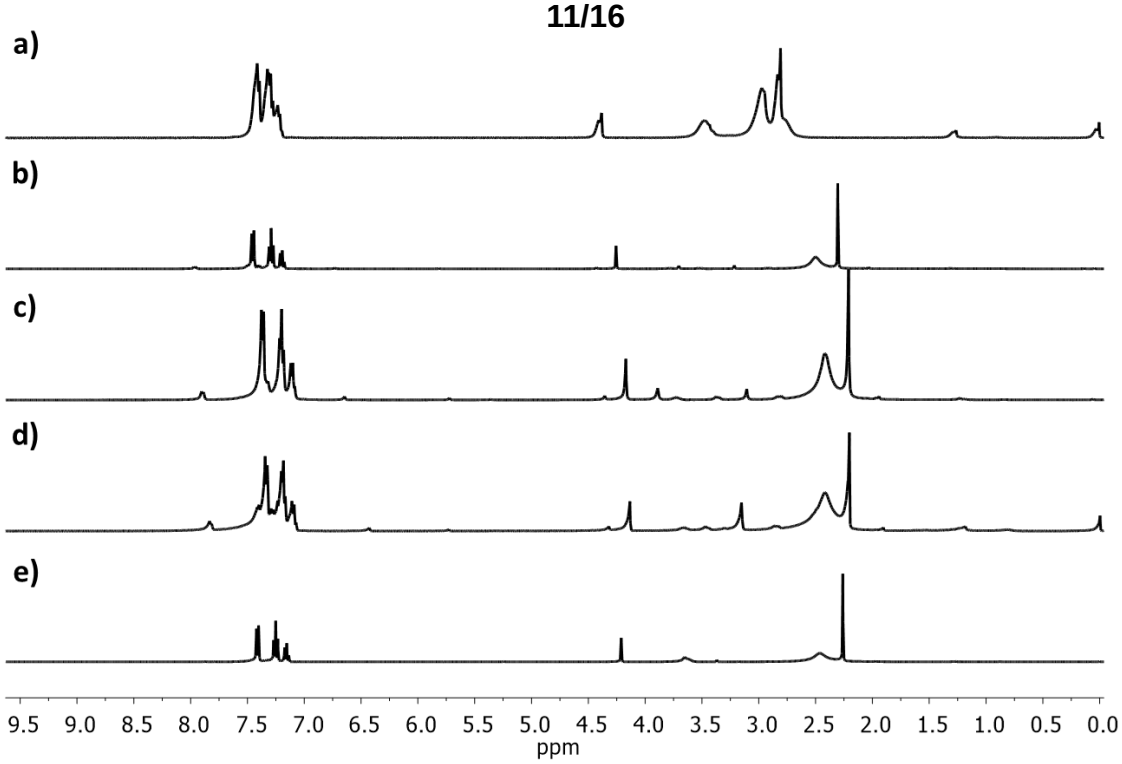

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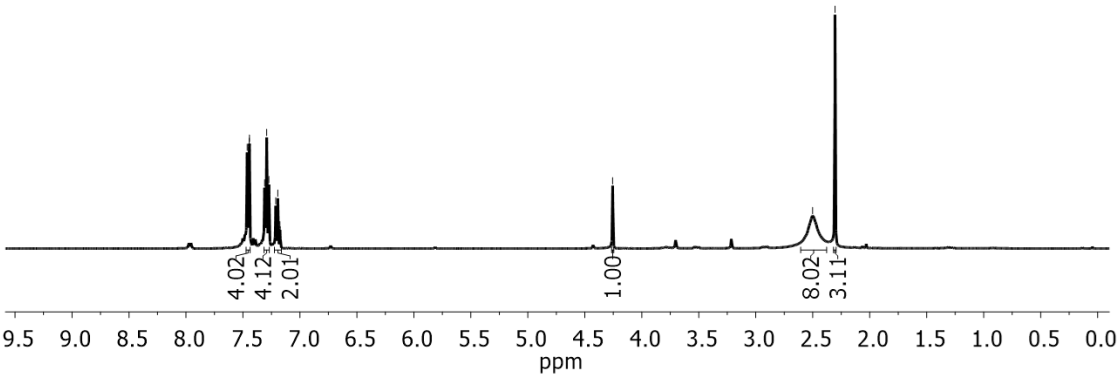

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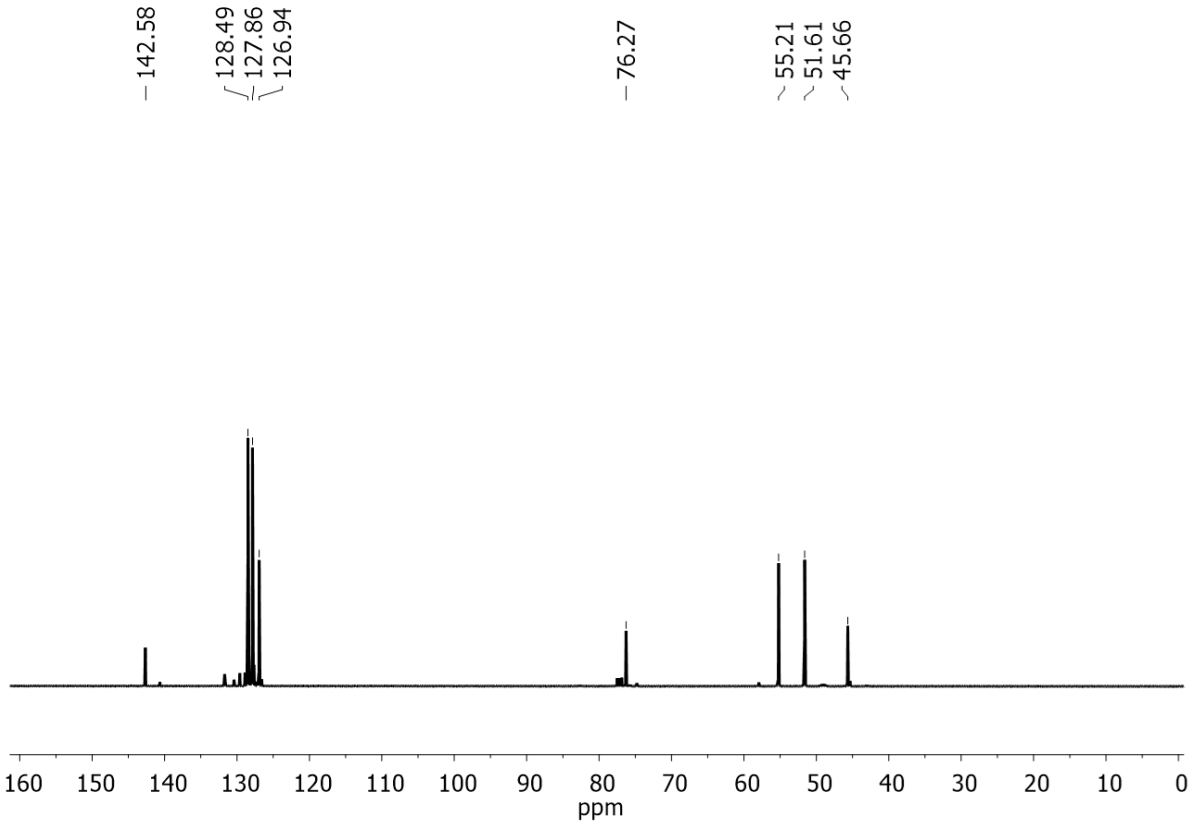

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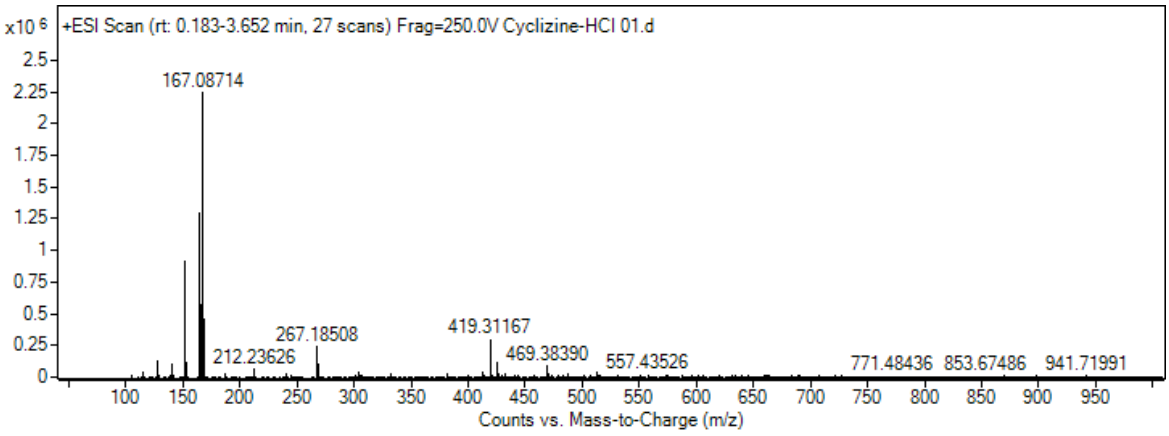

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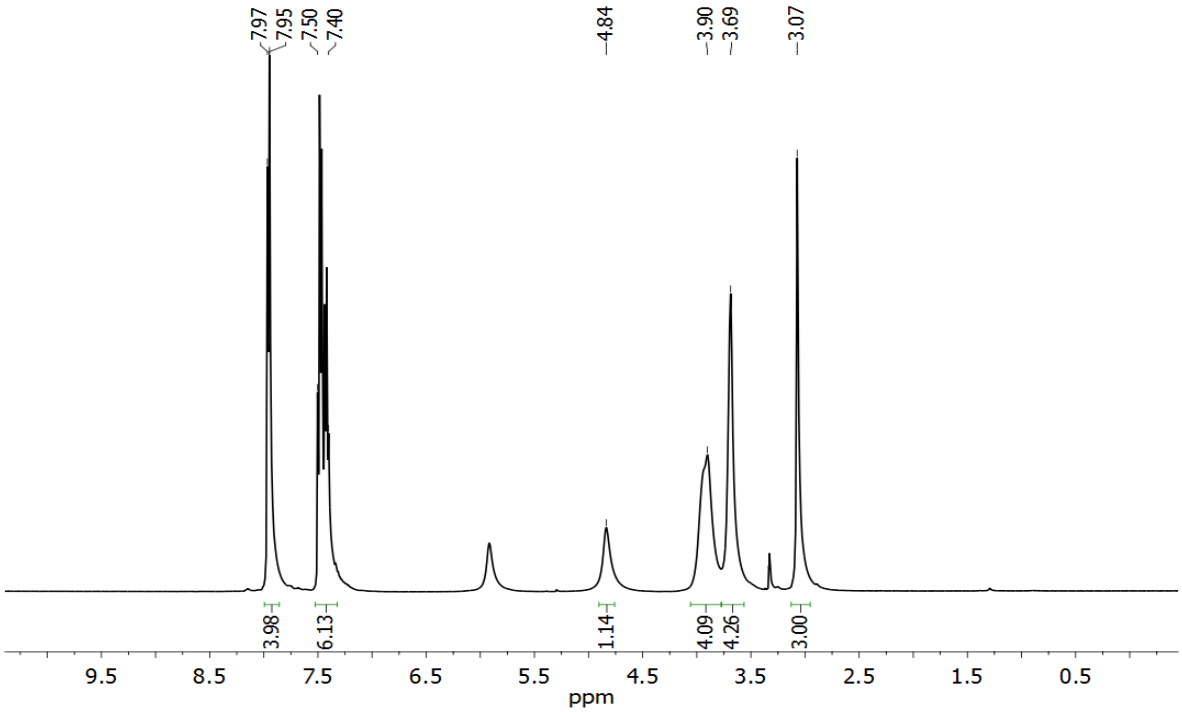

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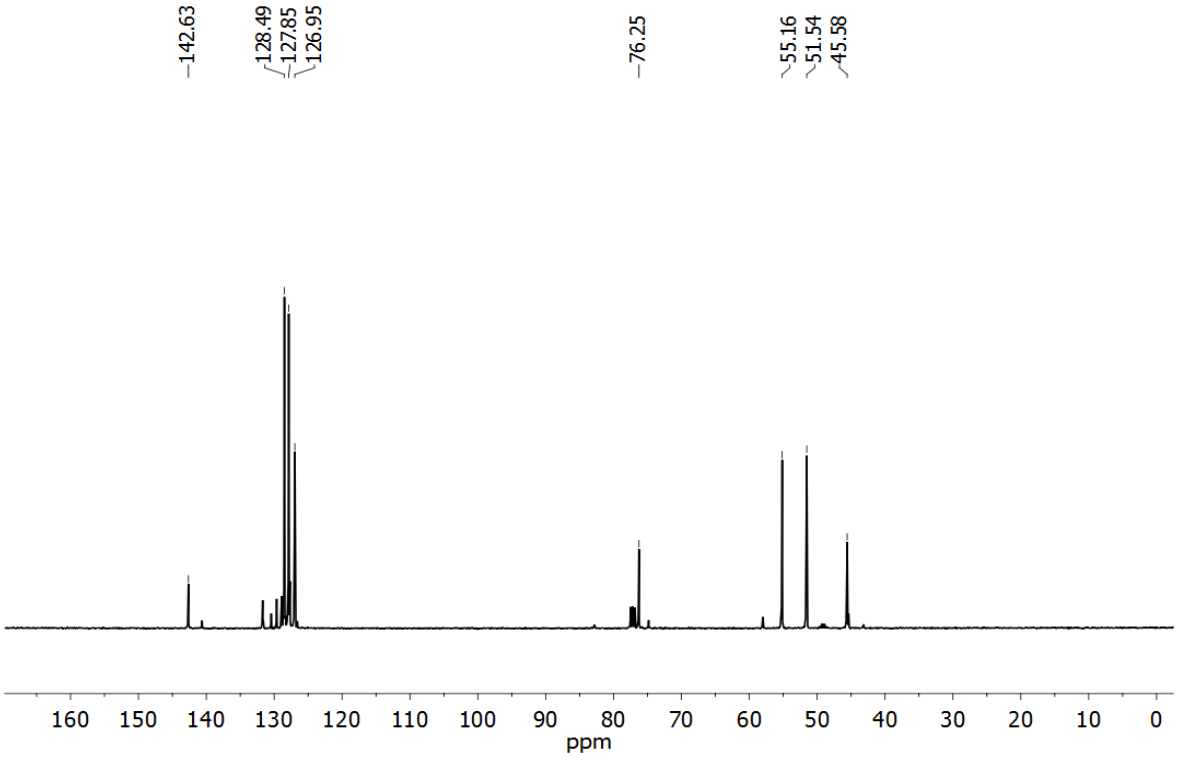

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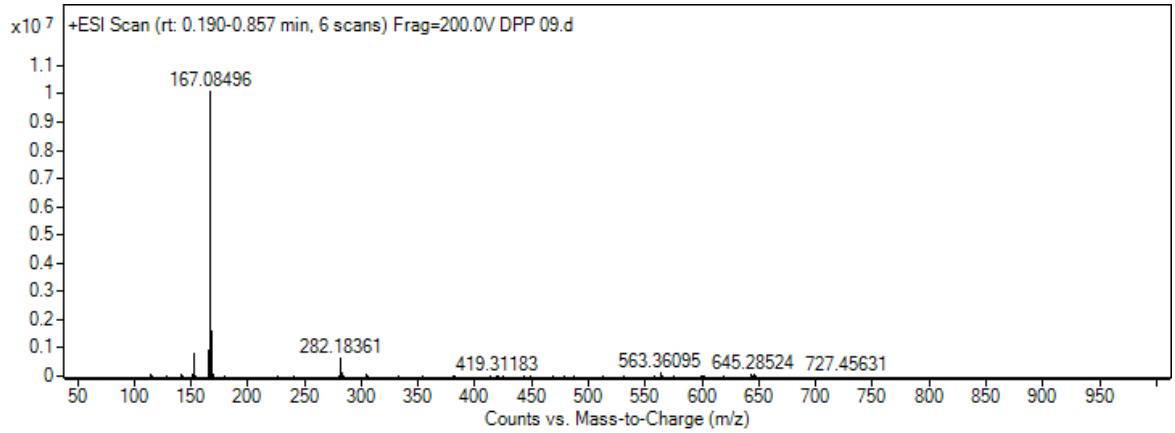

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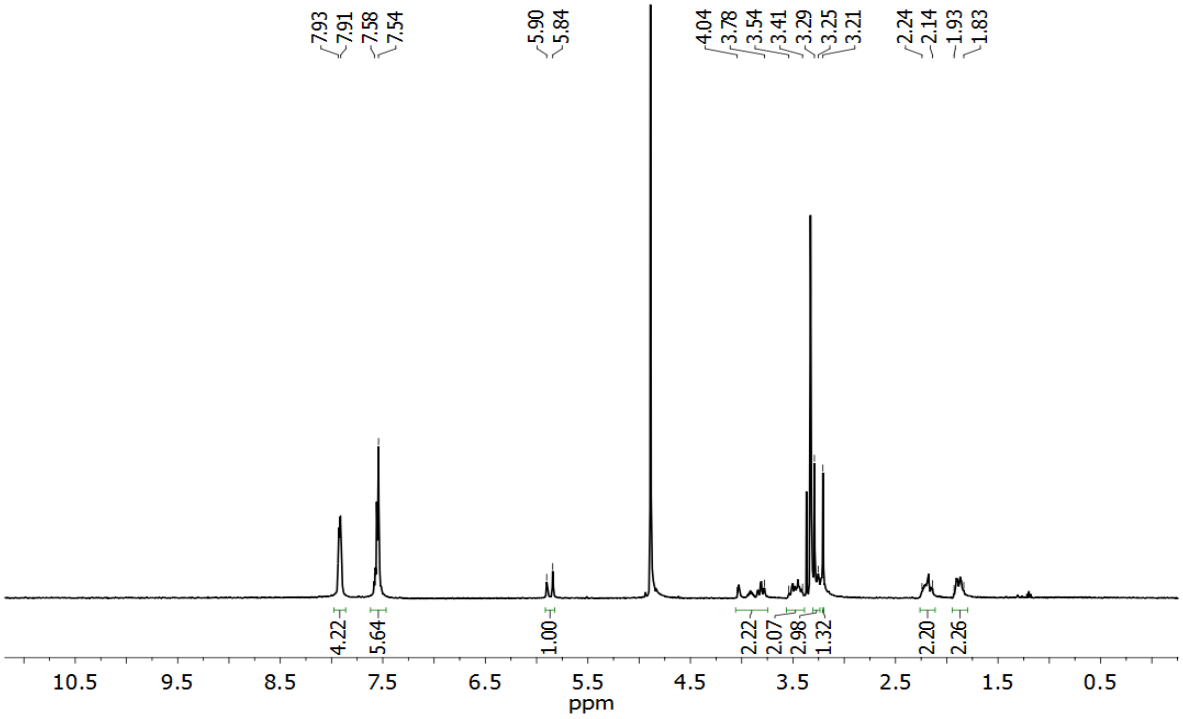

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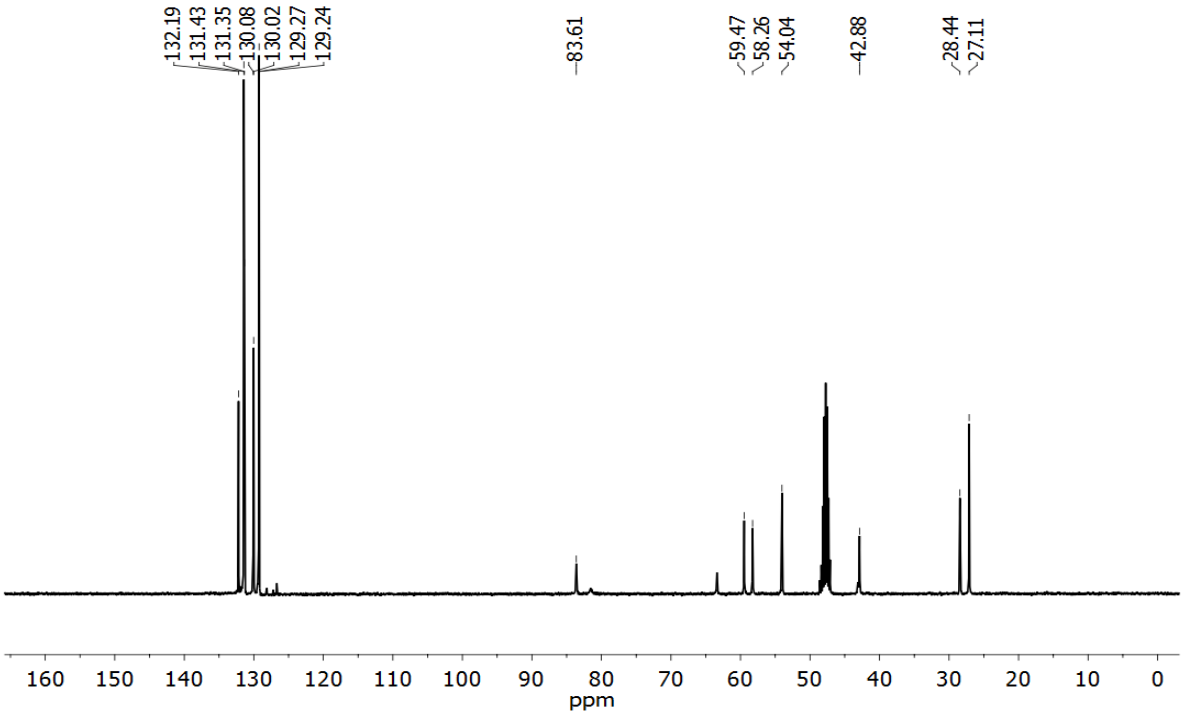

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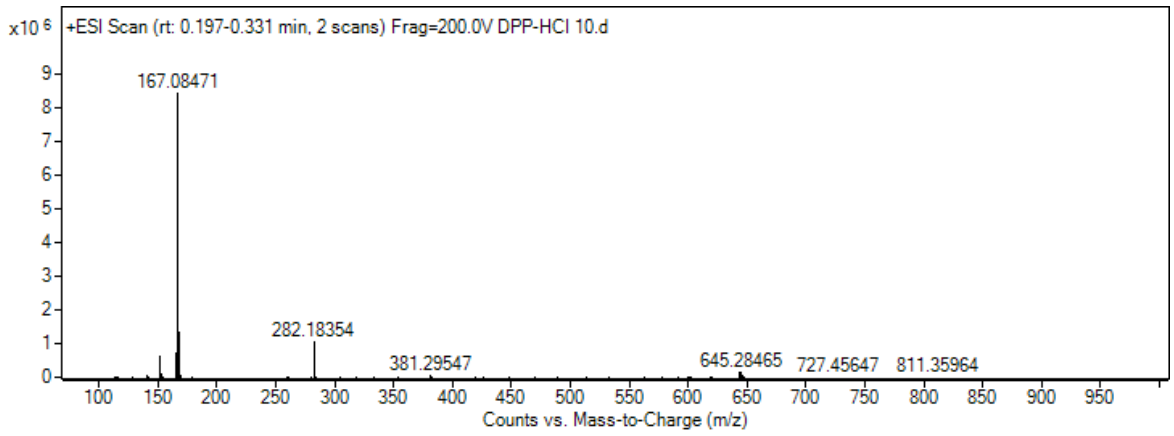

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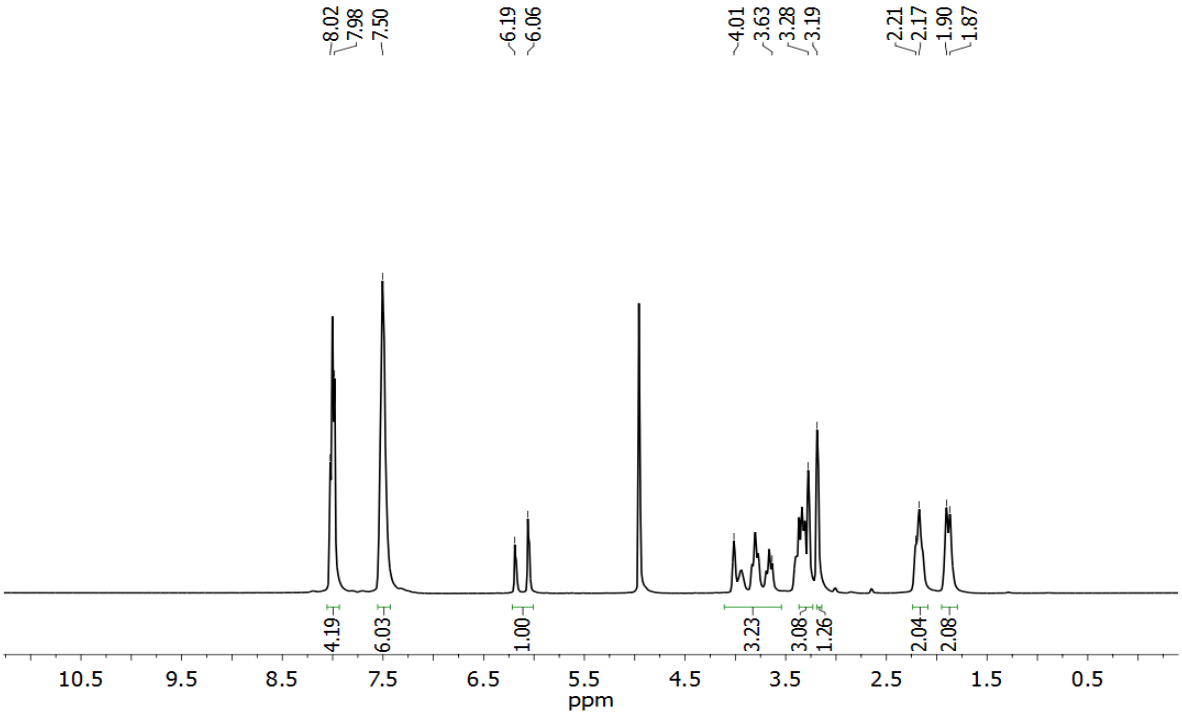

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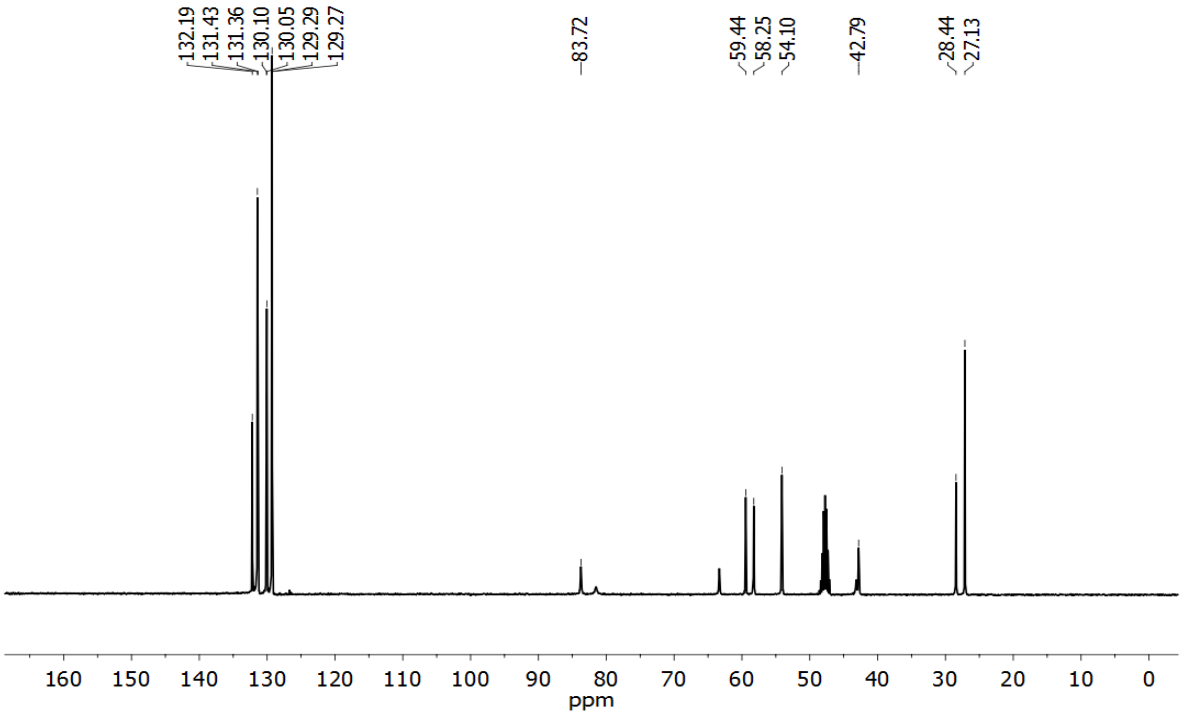

Figure 37