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One-Pot Three-Component Synthesis of 2-Amino-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile Derivatives Catalyzed by Cobalt Doped Iron (III) Tartrate Complex

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Abstract: An environmentally friendly one-pot three-component strategy synthesizing a series of 2-Amino-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives has been successfully performed in water. The products were obtained through conventional and microwave irradiation, which involving aldehyde, malononitrile, and 4-hydroxy coumarin, resulting in a green synthetic protocol with a high atom economy. The reaction was catalyzed by a water-soluble and reusable catalyst, i.e., cobalt doped iron (III) tartrate complex. The catalyst was recovered and efficiently reused.

Keywords: chromene-3-carbonitrile; cobalt doped iron (III) tartrate; reusable catalyst.

1. Introduction

2-Amino-4H-chromenes and their analogs have been studied widely, and they possess a wide range of biological activities such as spasmolytic, diuretic, anticoagulant, anticancer, and anti anaphylactic activity [1]. Also, they can be used as cognitive enhancers to treat neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, AIDS-associated dementia, and Down's syndrome for the treatment of schizophrenia and myoclonus [2]. The aqueous medium for the organic reaction is the latest challenge for modern organic chemists. During the past two decades, many reactions that were conventionally believed to occur in organic solvents have been developed to run in water [3].

Another window of green chemistry to consider in developing the one-pot multicomponent reactions (MCRs), which are one of the best tools in synthesizing organic compounds [4].

Recently, MCRs have emerged as a highly valuable synthetic tool in the context of modern drug discovery. The atom economy and convergent character, the simplicity of a one-pot procedure, the possible structural variations, the accessible complexity of the molecules, and the very large number of accessible compounds are among the described advantages of MCRs [5]. Thus, they are perfectly amenable to automation for combinatorial synthesis [6].

The concepts are at the center of the chemical activity, and the research on high selectivity is the driving force for the conception of all new catalytic processes.

Now it’s well known heterogeneous catalysts have three characteristics; stability, selectivity, and high activity. The scientific interests and economic are great. There is no doubt that the community of catalysis closely follows the development of nanotechnology. Attempts to exploit the breakthroughs already exist, especially to achieve the optimum activity, selectivity, and stability in catalytic reactions. Some progress has been accomplished, particularly in the conception of active sites and the control of the surrounding of these sites, but many challenges that deal with the control of the localization of active sites and the environment in the atomic scale still exist [7].

We have efficiently developed series of scaffold 2-amino-chromenes in water using Manganese Fe(III) tartrate as a water-soluble and reusable catalyst. Various methods with various conditions have been reported. The compounds have been already prepared in the presence of piperidine [8], diammonium hydrogen phosphate (DAHP) [9], K_2CO_3 under microwave irradiation [10], MgO [11], tetra-butylammonium bromide (TBAB) [12], DBU [13] and 3- hydroxypropanaminium acetate (HPAA) [14].

2. Materials and Methods

2.1. Experimental.

2.1.1. General procedure for the synthesis of 2-amino-chromenes by the conventional method.

A mixture of the aldehyde (1 mmol, 106 mg), malononitrile (1 mmol, 66 mg), 4-hydroxy coumarin (1 mmol, 162 mg) and $CoFe_2(C_4H_4O_6)3.6H_2O$ catalyst (10 mg) was refluxed in 10 cm3 water. The completion of the reaction was decided and monitored by TLC. After the reaction was completed, the mixture was filtered, and the residue was washed by water; as the reaction was carried out in the water, recrystallization did not require, and the product leads to an analog 2-amino-chromene. The catalyst was recovered by evaporation of water from the filtrate.

2.1.2. General procedure for the synthesis of 2-amino-chromenes by microwave method.

A mixture of the aldehyde (1 mmol, 106 mg), malononitrile (1 mmol, 66 mg), 4-hydroxy coumarine (1 mmol, 162 mg) and $CoFe_2(C_4H_4O_6)_3.6H_2O$ catalyst (10 mg) was irradiated with microwave radiations in 10 cm3 water for 120 seconds. The completion of the reaction was decided and monitored by TLC. After the reaction was completed, the mixture was filtered, and the residue was washed by water as the reaction was carried out in water recrystallization did not require, and the product leads to an analog 2-amino-chromene. The catalyst was recovered by evaporation of water from the filtrate.

2.1.3. Analytical data of selected compound.

2-Amino-3-cyano-4-phenyl-4H-benzo[h]chromene (4a): Yellow solid, mp = 256-258°C. FTIR (KBr) cm-1: 3436 (CH), 3317 (NH2), 2183 (CN), 1655 (NH2). 1H NMR (CDCl3, 300 MHz) ppm: 4.79 (2H, s, NH2), 4.86 (1H, s), 7.02 (1H, d), 7.12 -7.38 (5H, m), 7.44 -7.6 (3H, m), 7.80 (1H, d), 8.17 (1H, d).

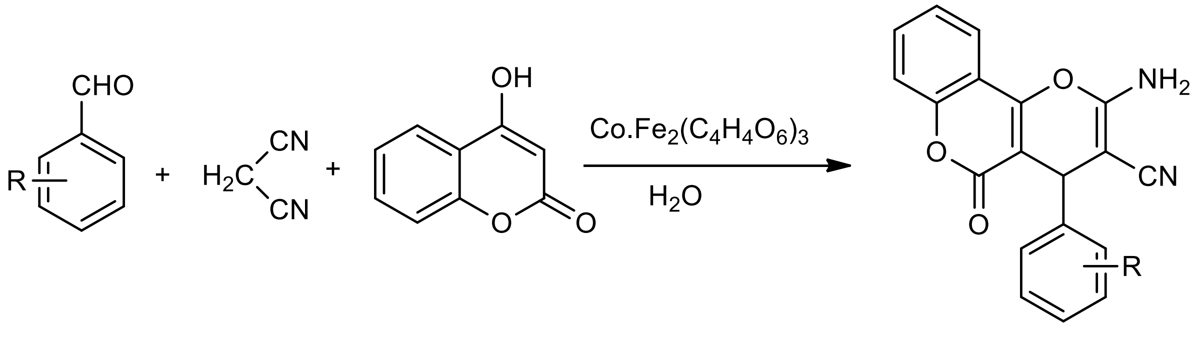
2-Amino-3-cyano-4-(4-nitrophenyl)-4H-benzo[h]chromene (4f): Yellow solid, mp= 258-260 °C. FTIR (KBr) cm-1: 3454 (CH), 3330 (NH2), 2182 (CN), 1614 (NH2). 1H NMR (CDCl3, 300 MHz): 4.96 (2H, s), 5.00 (1H, s), 6.95 (1H, d), 7.40 (2H, d), 7.52 -7.62 (3H, m), 7.81 (1H, d), 8.17 (2H,d), 8.28 (1H, d). The figure S1-S3 are shown in Supplementary files.

3. Results and Discussion

To determine the appropriate weight of the catalyst, the synthesis of 1a was carried out in different amounts of catalysts in water. There was a notable increase in yield according to the increase in the number of catalysts. We have been limited to 10 mg of the catalyst by minimizing the quantity for further study. To comprehend the effect of water on the three-component reaction catalyzed by cobalt doped iron (III) tartrate complex ($CoFe_2(C_4H_4O_6)_3.6H_2O$), different volumes of water were added to the reaction mixture. In the presence of 1 to 5 cm^3 of water, the desired product was only about 50% in 1 hrs reaction. The observed yield has a significant increase by adding various volumes of water. Thus, in the presence of 10 cm^3 water, the yield reached 90% in 1a. Beyond this quantity, a notable decrease in yield was observed.

A heterogeneous catalyst is more interesting when it can be easily recovered and reused. For this purpose, the synthesis of 1a was carried out using fresh and recovered ($Co.Fe_2(C_4H_4O_6)_3.6H_2O$) catalyst for a 2-cycle run. After 45 minutes of reaction, product 1a was isolated and identified. The recovered catalyst was washed with acetone. The obtained yield after the 2-cycle run is almost stable and unchangeable, demonstrating that ($Co.Fe_2(C_4H_4O_6)_3.6H_2O$) can be easily recovered and reused without any loss of its activity. A large number of 2-amino-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives have been found to have interesting biological activities.

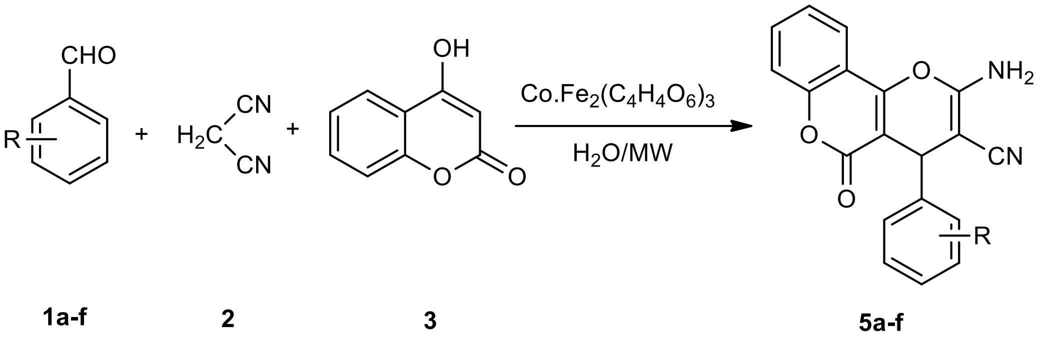
Our work of the multicomponent synthesis of aryl aldehydes, 4-hydro-xycoumarin, and malononitrile into 2-amino-5-oxo-4,5- dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives through a conventional method by the optimization of the reaction conditions. The synthetic pathway is shown in Scheme 1.



1a-f **2** **3** **4a-f**

Scheme 1. Synthesis of 2-amino-5-oxo-4-substituted phenyl-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile by conventional method.

We also carried out the same synthesis of aryl aldehydes, 4-hydro-xycoumarin and malononitrile into 2-amino-5-oxo-4,5- dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives through microwave irradiation shown in scheme 2.



Scheme 2. Synthesis of 2-amino-5-oxo-4-substituted phenyl-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile through microwave irradiation.

For the purpose of endorsing the developed method, we applied the optimum conditions as previously determined to a large variety of substrates. The three-component reactions of carbonyl compounds, malononitrile, and 4-hydroxy coumarin were carried out in the presence of ($Co.Fe_2(C_4H_4O_6)_3.6H_2O$) (10 mg) and refluxed in water to prepare multiple 2-amino-5-oxo-4,5- dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives (Scheme 1). The products were isolated and analyzed by melting points, ^{1}H NMR, and IR spectroscopy. As a reaction carried out in the water, recrystallization was not required. The results obtained with two schemes are summarized in Table 1. Thus, the scaffold of products was easily prepared in quantitative yields.

TEM images (Figure 1-5) show information about micro and nanomaterial's size, shape, dispersion, structure, and morphology. The bright-field TEM images of cobalt doped iron (II) tartrate, i.e. ($CoFe_2(C_4H_4O_6)_3.6H_2O$) are shown in Fig. 2.

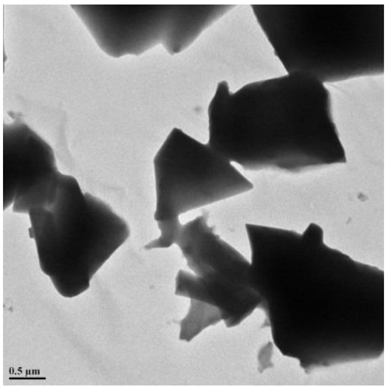


Figure 1. Size, shape, dispersion, structure, and morphology of micro and nanomaterial.

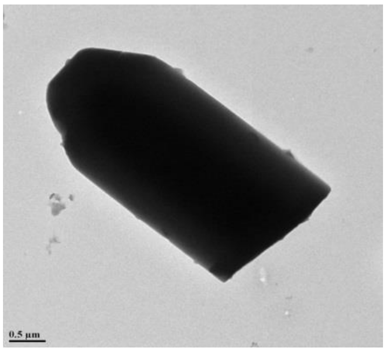


Figure 2. Size, shape, dispersion, structure, and morphology of micro and nanomaterial.

The majority of the particle sizes in the observed area fall within a range of 1.88 µm in diameter with the minimum particle size 4 µm and the maximum size of 4.5 µm in length. The overall observation suggests the spherical nature of most particles with a reasonably small range of diameter variation. The EDX spectrum of cobalt-doped Iron tartrate is shown in Figure 6.

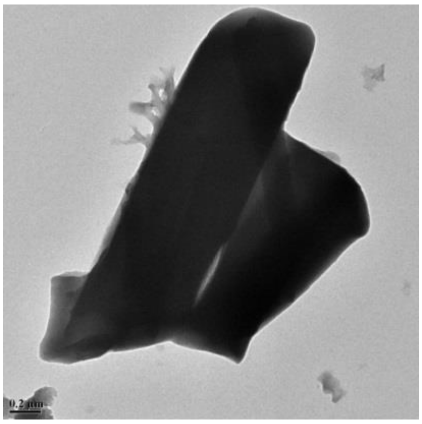


Figure 3. Size, shape, dispersion, structure, and morphology of micro and nanomaterial.

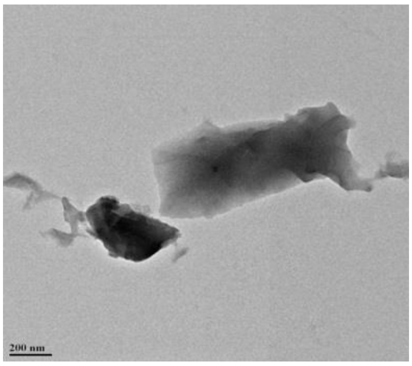


Figure 4. Size, shape, dispersion, structure, and morphology of micro and nanomaterial.

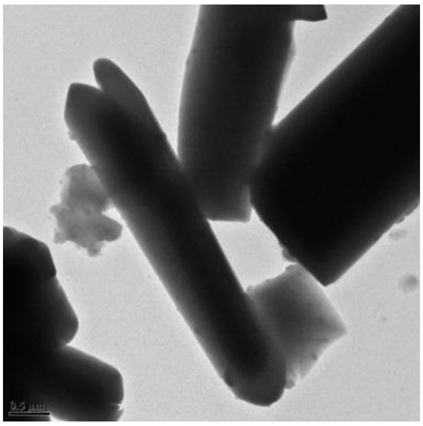


Figure 5. Size, shape, dispersion, structure, and morphology of micro and nanomaterial.

Table 1. Synthesis of 2-Amino-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives.

Entry	**Aldehyde**	**Product**	**Time (Min.)**	**Yield**	**MP(^{0}C)**	
					Obtained	**Reported**
1	$-C_6H_5$	**4a**	45	92	256-258	255-257[15]
2	$-C_6H_5$	**5a**	45	90	256-258	255-257[15]
3	$3-NO_2-C_6H_4$	**4b**	45	89	262-264	260-264[15]
4	$3-NO_2-C_6H_4$	**5b**	45	87	262-264	260-264 [15]
5	$4-OCH_3-C_6H_4$	**4c**	45	92	240-242	241-243[15]
6	$4-OCH_3-C_6H_4$	**5c**	45	93	240-242	241-243 [15]
7	$4-F-C_6H_4$	**4d**	45	90	278-282	277-284[15]
8	$4-F-C_6H_4$	**5d**	45	91	278-282	277-284 [15]
9	4-indole carbaldehyde	**4e**	45	90	264-268	Not reported
10	4-indole carbaldehyde	**5e**	45	89	264-268	Not reported

11	4-NO_2-C_6H_4	**4f**	45	90	258-260	257-262[15]
12	4-NO_2-C_6H_4	**5f**	45	91	258-260	257-262[15]

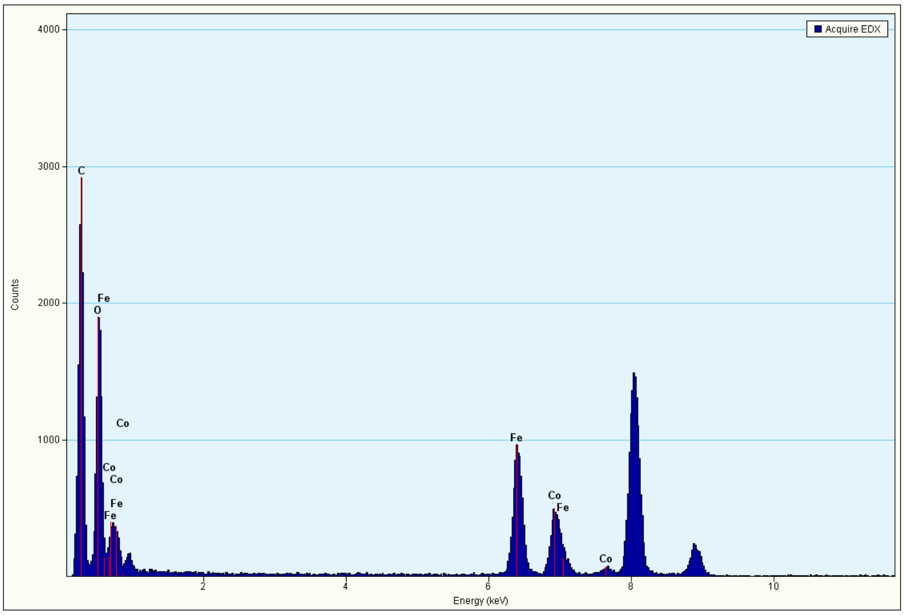


Figure 6. EDX spectrum of cobalt doped Iron tartrate.

Also, Figure S1 ^{1}H NMR of compound (4a), Figure S2. ^{1}H NMR of compound (4b) and Figure S3. ^{1}H NMR of compound (4c) are provided in the supplementary material for the confirmation of structure.

4. Conclusions

In conclusion, we described an efficient procedure for preparing 2-amino-chromene analogs through the one-pot three-component reactions of aromatic aldehydes, malononitrile, and 4-hydroxy coumarin using a catalytic amount of an efficiently reusable catalyst in water. The developed methodology is highly efficient and environmentally friendly by means of product recoveries, atom economy, and solvent usage. The success of this methodology would push us to use it for the synthesis of other biologically active molecules. Therefore, this research could be categorized within green chemistry.

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Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Supplementary materials

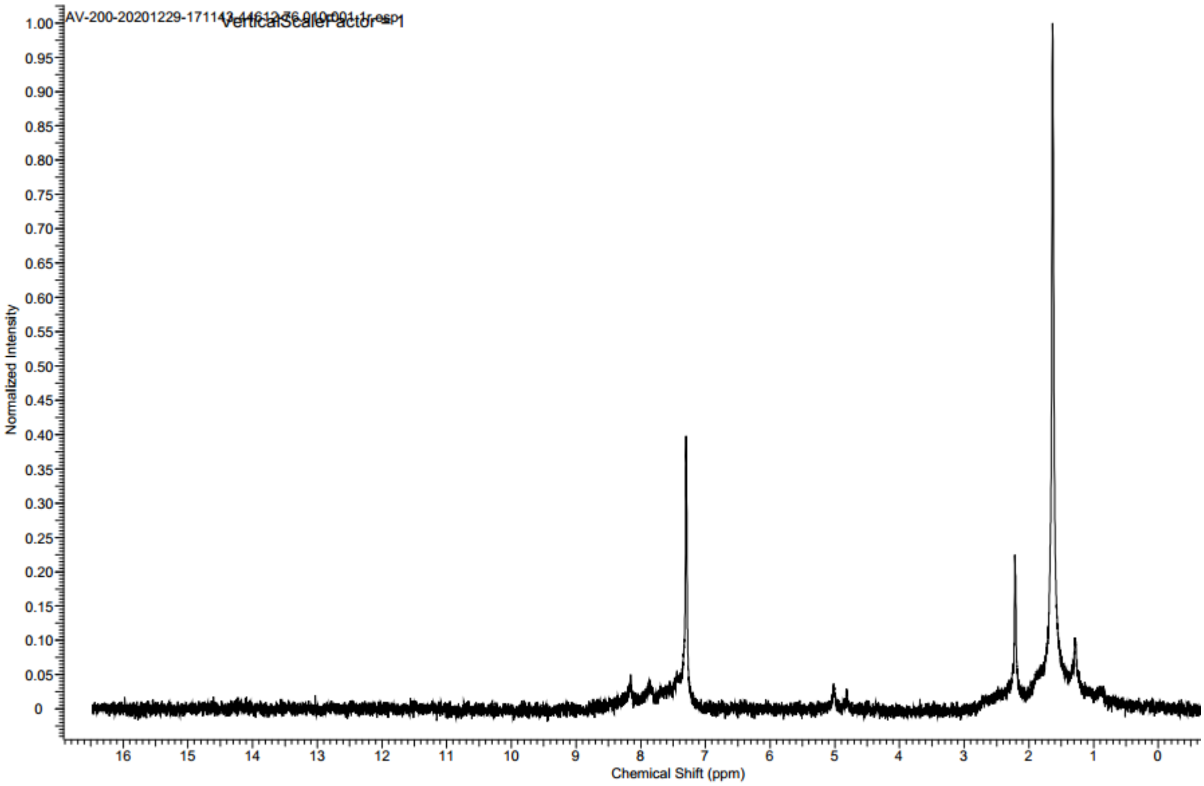

Figure S1. ^{1}H NMR of Compound 4a.

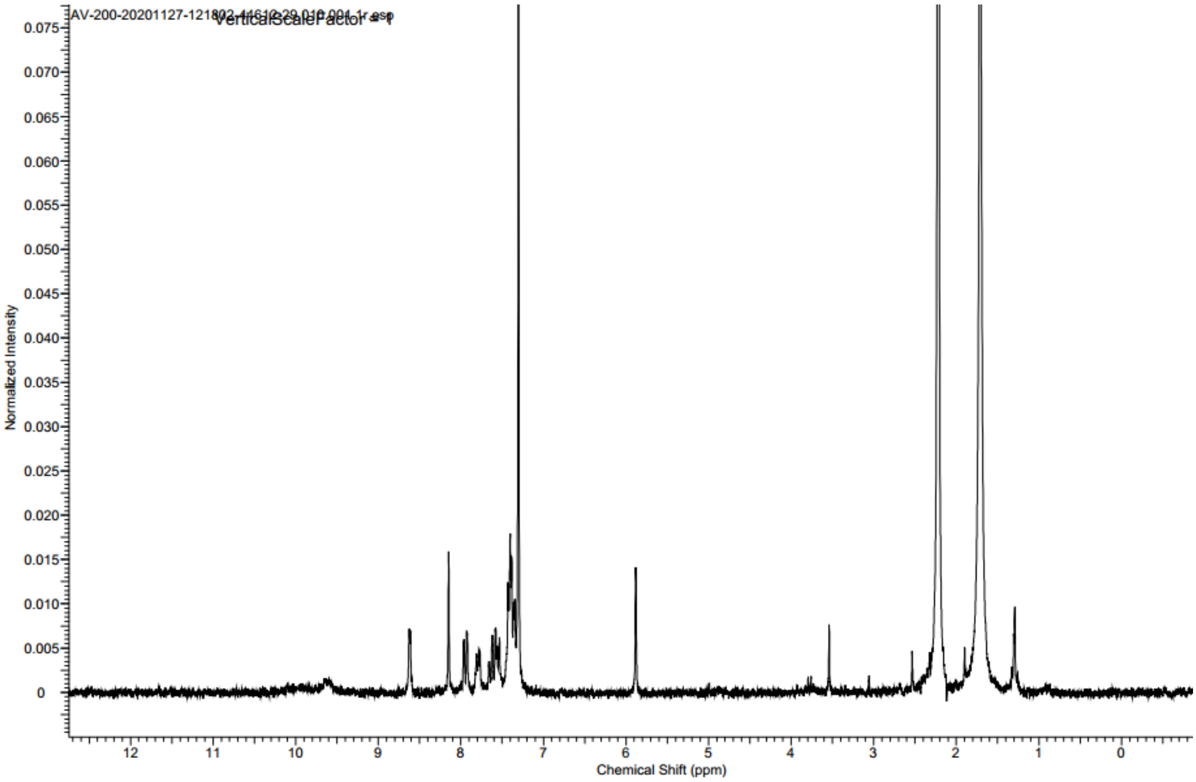

Figure S2. ^{1}H NMR spectra of Compound 4b.

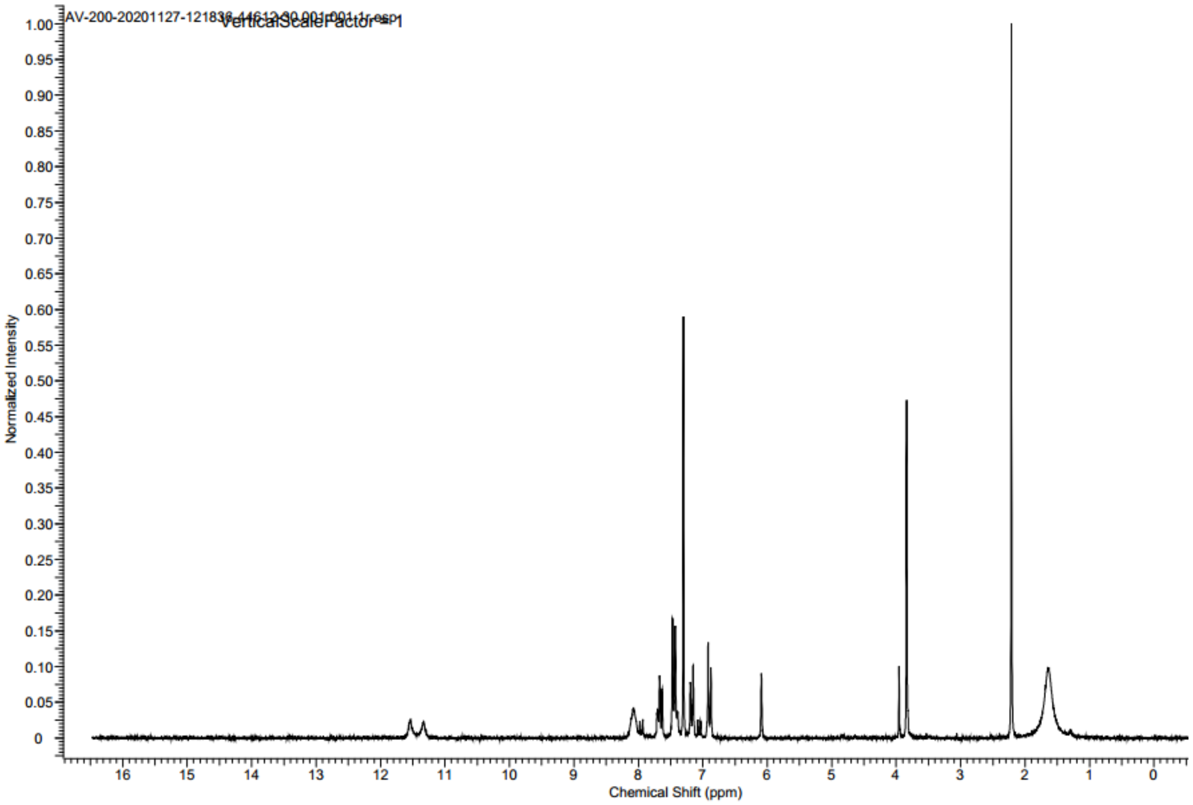

Figure S3. ^{1}H NMR spectra of Compound 4c.