chemistry proceedings

Proceeding Paper

Synthesis of a Symmetrical *tris*-tetrazole as Isostere of a Tricarboxylic Acid: Behind New Tridentate Ligands for MOFs †

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† Presented at the 25th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2021. Available online: https:// ecsoc-25.sciforum.net (accessed on).

Abstract: The synthesis and characterization of three tridentate ligands for new MOFs is described. A triple aminolysis of the 1,3,5-tribenzoyl chloride with *p*-aminobenzoic acid gave the tricarboxylic acid **3** in 90% yield. Moreover, the same reaction, also from the 1,3,5-tribenzoyl chloride, but using *p*-aminobenzonitrile gave the new *tris*-benzonitrile **5** in 85% yield. Finally, this later one was treated with sodium azide and a Lewis acid to synthesize the new *tris*-tetrazole-based ligand **7** in 72% yield through a [3+2] azide-nitrile cycloaddition. It is noteworthy that the isosterism between carboxylic acids and tetrazoles may be considered to design and fabricate new MOFs with similar properties.

Keywords: Metal-Organic Frameworks (MOFs); tridentate ligands; tricarboxylic acids; *tris*-benzonitriles; *tris*-tetrazoles; aminolysis

Citation: Flores-Reyes, J.C.; Islas-Jácome, P.; Gutiérrez-Carrillo, A.; Rincón-Guevara, M.A.; Suárez-Moreno, G.V.; Vázquez-Vera, Ó.; Lomas-Romero, L.; González-Zamora, E.; Islas-Jácome, A. Synthesis of a Symmetrical *tris*-tetrazole as Isostere of a Tricarboxylic Acid: Behind New Tridentate Ligands for MOFs. *Chem. Proc.* **2021**, 3, x. https://doi.org/10.3390/xxxxx

Academic Editor: Julio A. Seijas

Published: 15 November 2021

1. Introduction

Metal-organic frameworks (MOFs) also known as porous coordination polymers (PCPs), are formed by the union, through coordination bonds, of single metal cations (primary building unit, PBU) or metal clusters (secondary building unit, SBU) with organic ligands functionalized with donor groups, whose main characteristics are crystallinity, and permanent porosity [1]. These materials form ordered networks that spread in 1D, 2D and 3D architectures, and have found ample use in diverse applications, for example, in catalysis [2], biomedicine [3], sensing and luminescence [4], and as potential tools in environmental remediation as platforms for hazardous gas capture, for example, H_2S [5], SO_2 [6], and CO_2 [7], just to name a few.

While the choice of metal ion to construct MOFs is important, the variability in the material's structure and properties, for example pore size, will come from the ligand design. In this sense, the most used ligands for MOF synthesis are either neutral or anionic. Carboxylates are among the most common anionic coordinating groups and are often preferred due to the strong binding produced with metal ions through the formation of SBUs, which confer the network with great stability and promote its self-assembly. As for neutral ligands, the most used are pyrazine and 4,4′-bipyridine [8].

On the other hand, azoles, which are aromatic five-membered *N*-containing heterocycles, can be deprotonated to form the corresponding azolate, which allows them to bind metal ions in a similar way as pyridines [9]. Tetrazoles contain four *N*-atoms, and due to their electron-withdrawing effect, this heterocycle is turned slightly acidic, having pK_a values like those of carboxylic acids (pK_a = ~4.5–4.9) although tetrazoles are slightly larger. Due to these features, it is said that 5-substiuted tetrazoles are isosteres of carboxylic acids [10], and thus, they are also capable of coordinating to metal ions.

Carboxylates have various coordination modes [11] and can bind metal ions in a monodentate or a bidentate manner; furthermore, each oxygen donor can coordinate with up to three different metal ions [9]. However, bidentate binding produces the stronger interaction because it leads to the formation of SBUs [12]. 5-substituted tetrazoles, on the other hand, show up to ten different coordination modes, depending on whether they are in the neutral form or as a tetrazolates [13], making them very versatile ligands for MOF synthesis. Lastly, nitrile ligands generally exhibit a single linear coordination mode. However, they also show other less common side-on coordination to metal ions [14], Figure 1.

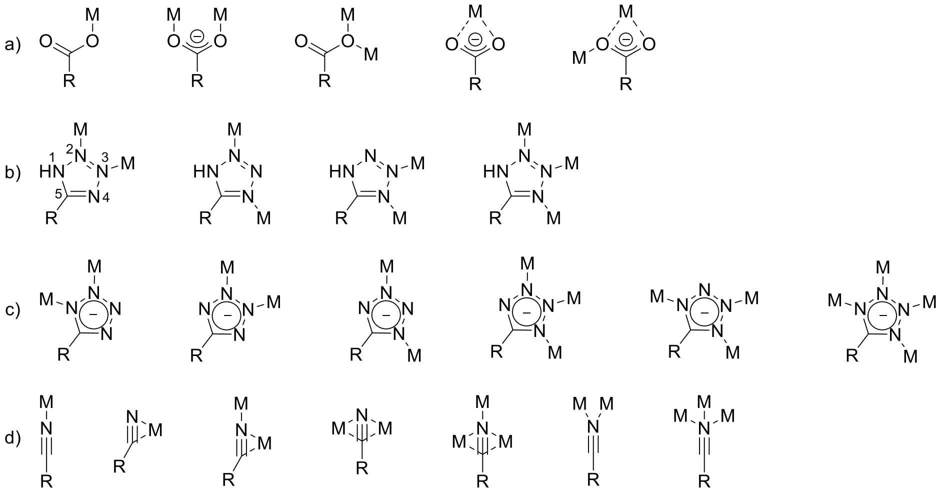


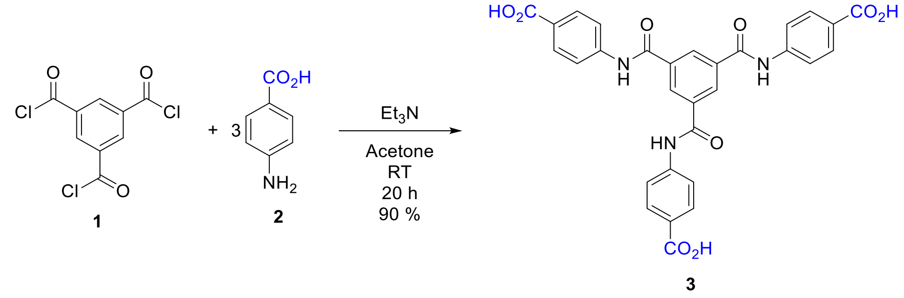
Figure 1. Most common coordination modes of (**a**) carboxylates, (**b**) 5-substituted tetrazoles, (**c**) 5-substituted tetrazolates, and (**d**) nitriles.

The classic method to synthesize 5-substituted tetrazoles consists of a Huisgen-type [3+2] dipolar cycloaddition between nitriles and a source of the azide anion, catalyzed by a Zn(II) salt. This methodology is operationally simple, minimizes the release of highly toxic hydrazoic acid, uses environmentally benign solvents, and often generates the desired compound in good yields, especially if the nitrile is bound to an electron deficient aromatic ring [15]. With this communication, we aim to provide the synthesis and characterization of two new tridentate ligands, and thus increase the number of available ligands that can be used in the synthesis of novel MOF-type materials. The *tris*-nitrile ligand was synthesized via a triple nucleophilic acyl substitution (triple aminolysis) and was later used to generate a *tris*-tetrazole-based ligand. We also present the synthesis of a previously reported *tris*-carboxylic acid, but in a higher yield. These syntheses were conducted in environmentally benign solvents, and the products were obtained in good yields after a simple aqueous workup.

2. Results and Discussion

2.1. Synthesis of 4,4′,4′′-((benzene-1,3,5-tricarbonyl)tris(azanediyl))tribenzoic Acid (3)

The tridentate ligand **3** was synthesized as reported by M. S. Lah and co-workers [16], with a slight modification. The process involves a triple nucleophilic acyl substitution by the reaction of 1,3,5-benzenetricarbonyl trichloride (**1**) with three equivalents of *p*-aminobenzoic acid (**2**), in the presence of triethylamine in acetone as solvent, Scheme 1. The target ligand was obtained in 90% yield, which is consistent with several reports in the literature [17–19].



Scheme 1. Synthesis of ligand 3.

The Figure 2 shows the NMR characterization of ligand **3**. The ^{1}H spectrum (Figure 2a) depicts a singlet at around 11.0 ppm, which can be attributed to the acidic protons of the carboxylic acid moieties. Next, there is another singlet at 8.80 ppm that accounts for the NH protons of the amide groups, and finally, a multiplet at 7.99 ppm integrating for the fifteen aromatic protons. The two small doublets at around 7.60 and 6.60 ppm are attributed to unreacted *p*-aminobenzoic acid that was leftover. As for the ^{13}C NMR spectrum shown in Figure 2b, it shows the expected eight signals, the key ones being those corresponding to the three carboxylic acid carbonyls at 167.2 ppm and the three amide carbonyls at 164.8 ppm, respectively.

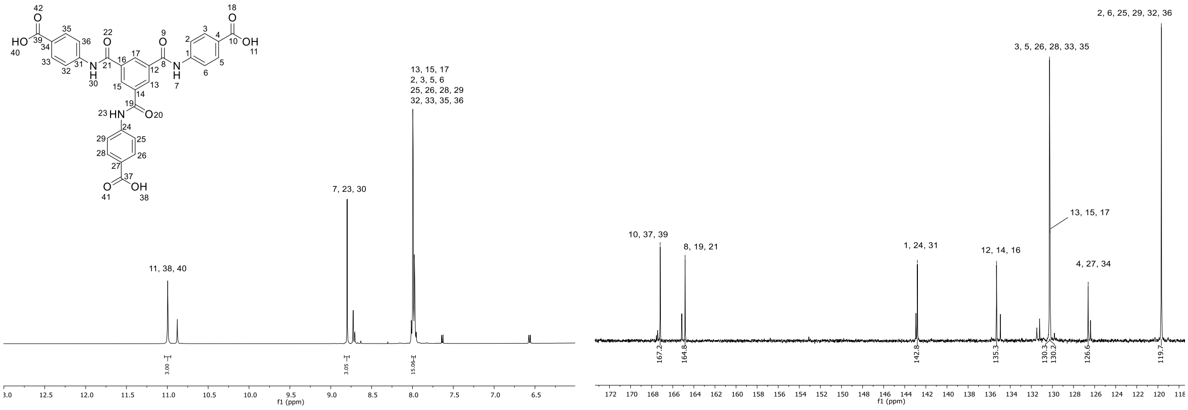
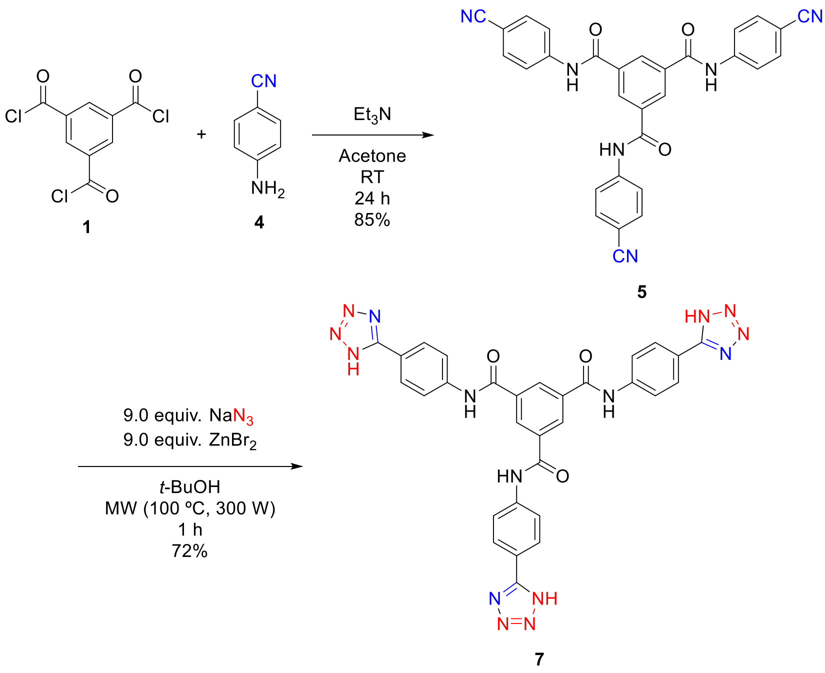


Figure 2. (**a**) ^{1}H NMR spectrum and (**b**) ^{13}C NMR spectrum of ligand **3**.

2.2. *Synthesis of N^1,N^3-bis(4-(1H-tetrazol-5-yl)phenyl)-N^5-(4-(2H-tetrazol-5-yl)phenyl)benzene-1,3,5-tricarboxamide (7)*

The ligand **7** was synthesized considering that 5-substituted tetrazoles are isosteres of carboxylic acids, meaning that these compounds have a similar electronic structure, as well as near steric and physicochemical properties [10]. This ligand was obtained via a two-step sequence consisting of a triple nucleophilic acyl substitution followed by a Zn-catalyzed azide-nitrile [3+2] intermolecular cycloaddition. Thus, for the first step of the sequence, 1,3,5-benzenetricarbonyl trichloride (**1**) was reacted with three equivalents of *p*-aminobenzonitrile (**4**) utilizing the conditions described for the previous ligand, affording the *tris*-nitrile **5** in 85% yield. This later compound is of high interest because it could potentially be used as a ligand for constructing new MOFs, also due to the presence of three cyanide groups. As was mentioned in the introduction, the cyanide group acts as a pseudohalide ligand, and when combined with transition metals is prone to form crystalline materials [12]. Nonetheless, the ligand **5** was taken as intermediate for the second step of the reaction scheme, and it was reacted with nine equivalents of sodium azide and Zn(II) bromide in *tert*-butanol with microwave heating, to afford the target *tris*-tetrazolic ligand **7** in 72% yield, Scheme 2.



Scheme 2. Reaction scheme for the synthesis of ligand **7**.

Nine equivalents of both sodium azide and Zn(II) bromide seem to be excessive to perform a [3+2] dipolar cycloaddition. However, they were the necessary amounts to synthesize the *tris*-tetrazole **7** in a reasonable yield (72%), which can be considered a good yield, especially because the synthesis of this ligand had never been reported, anywhere.

The ^{1}H NMR spectrum for compound **5** is shown in Figure 3a; it shows a singlet at 11.01 ppm corresponding to the NH protons, another singlet at 8.77 ppm which integrates for the three aromatic protons of the central phenyl ring, and finally a set of two doublets at 8.04 and 7.87 ppm, respectively, which integrate for six protons each and are attributed to the three *para*-substituted phenyl rings. The Figure 3b shows the ^{13}C NMR spectrum for compound **5**, which contains the expected signals for the eight magnetically different carbons. There is a key signal at 164.9 ppm which corresponds to the three amide carbonyls and another signal at 118.9 which belongs to the cyanide groups.

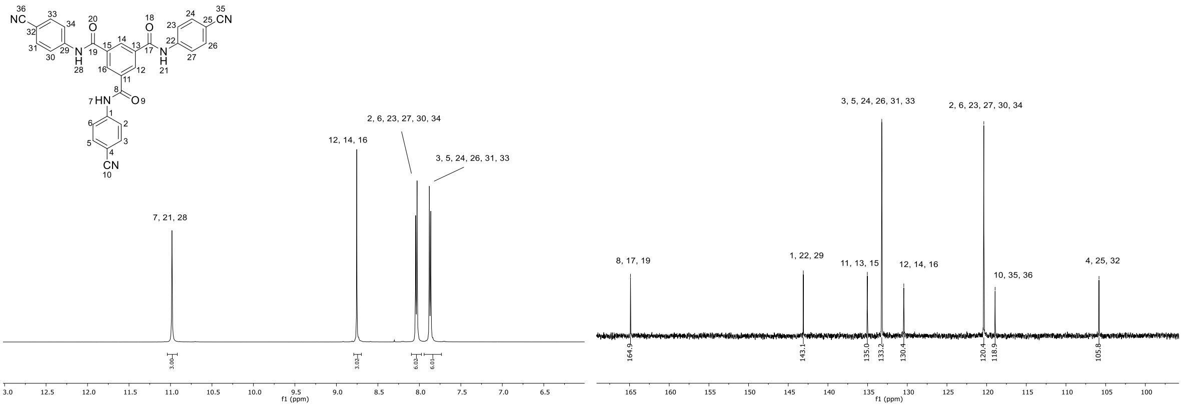


Figure 3. (**a**) ^{1}H NMR spectrum and (**b**) ^{13}C NMR spectrum of intermediate **5**.

The purification of compound **7** was difficult due to the tetrazole's reduced solubility in most organic solvents but some characteristic signals can be distinguished in the NMR spectra. The ^{1}H NMR spectrum shown in Figure 4a depicts a singlet at 11.19 ppm corresponding to the three NH protons, a multiplet at 8.87 ppm corresponding to the three aromatic protons of the center ring, and finally, two sets of signals at 8.14 and 7.89 ppm, respectively, which correspond to the twelve aromatic protons of the three *para*-substituted aromatic rings. On the ^{13}C NMR spectrum depicted in Figure 4b, the eight expected signals for the compound **7** are shown. The key signal for the amide carbonyls is found at 164.8 ppm and another key signal corresponding to the tetrazole carbons is located at 162.3 ppm. As can be seen in both spectrums, the impurity of the *tris*-tetrazole **7** corresponds just to its precursor **5** with a relationship near to 4:1.

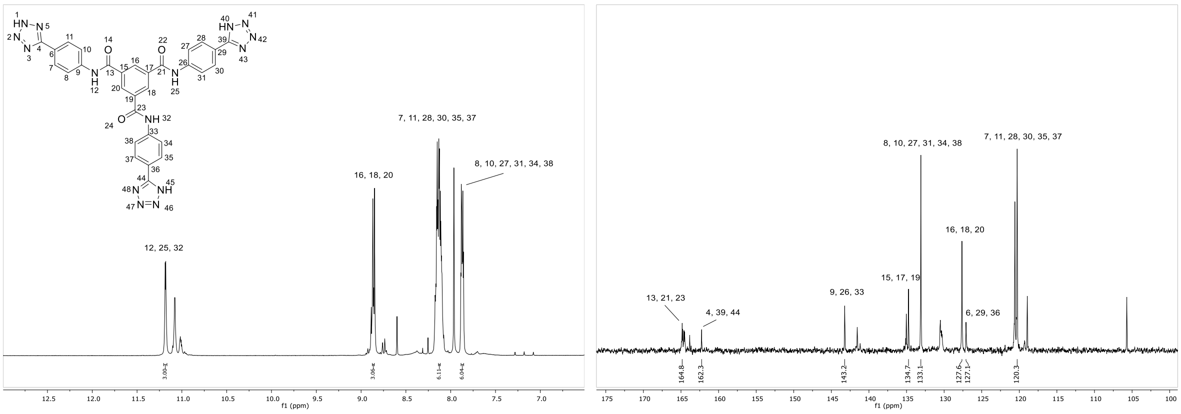


Figure 4. (**a**) ^{1}H NMR spectrum and (**b**) ^{13}C NMR spectrum of ligand **7**.

3. Conclusions

The tridentate ligand **3** was synthesized in an excellent 90% yield, which is consistent with literature reports. It has been extensively used with Zn salts for MOF synthesis, but there are reports of its use with several rare earth salts as well [20], which opens the possibility to try new combinations of metal salts with this ligand. The novel *tris*-nitrile **5** and *tris*-tetrazole **7** were obtained in 85% and 72% yields, respectively, although the latter one containing traces of its precursor **5**. These compounds could potentially be used with Cu(I) or Ag(I) salts for the construction of new MOFs. These experiments are underway.

4. Experimental Section

4.1. General Information, Instrumentation and Chemicals

^{1}H and ^{13}C NMR spectra were acquired on a Bruker Advance III (500 MHz) spectrometer. The solvent was deuterated dimethyl sulfoxide (d^6-DMSO). Chemical shifts are reported in parts per million (/ppm). The internal reference for NMR spectra is with respect to tetramethyl silane (TMS) at 0.0 ppm. Coupling constants are reported in Hertz (J/Hz). Multiplicities of the signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). NMR data were treated using MestReNova software (12.0.0–20080). The reaction progress was monitored by thin layer chromatography (TLC) on precoated kieselgel 60 F_{254} plates, and the spots were visualized under UV light (254 or 365 nm). Structural drawings were created using ChemDraw professional software (15.0.0.106). All starting materials were purchased from Sigma-Aldrich and were used without further purification or dehydration. The solvents were distilled and dried according to standard procedures.

4.2. Synthesis of 4,4′,4′′-((benzene-1,3,5-tricarbonyl)tris(azanediyl))tribenzoic Acid (3)

In a 1 L round-bottomed flask, a solution was prepared by dissolving 2.06 g (15.02 mmol, 5 equiv.) of 4-aminobenzoic acid in 80 mL of acetone and adding 1.34 mL of triethylamine (9.51 mmol, 3 equiv.). To this solution were added 0.55 mL (3.01 mmol, 1 equiv.) of 1,3,5-benzenetricarbonyl trichloride under inert atmosphere, and the resulting mixture was stirred for 24 h. After this time 500 mL of distilled water were added, the precipitate that formed was filtered and washed with diethyl ether affording 1.54 g of an off-white solid in 90% yield. ^{1}H NMR (500 MHz, d^6-DMSO): δ 10.99 (s, 3H, H-11, H-38, H-

40), 8.80 (s, 3H, H-7, H-23, H-30), 8.01–7.96 (m, 15H, H-13, H-15, H-17, H-2, H-3, H-5, H-6, H-25, H-26, H-28, H-29, H-32, H-33, H-35, H-36); ^{13}C NMR (126 MHz, *d*^{6}-DMSO): δ 167.2 (C-10, C-37, C-39), 164.8 (C-8, C-19, C-21), 142.8 (C-1, C-24, C-31), 135.3 (C-12, C-14, C-16), 130.3 (C-3, C-5, C-26, C-28, C-33, C-35), 130.2 (C-13, C-15, C-17), 126.6 (C-4, C-27, C-34), 119.7 (C-2, C-6, C-25, C-29, C-32, C-36).

4.3. Synthesis of N^1,N^3,N^5-tris(4-cyanophenyl)benzene-1,3,5-tricarboxamide (5)

In a 100 mL round-bottomed flask equipped with a magnetic stir bar, a solution was prepared by dissolving 0.28 g of 4-aminobenzonitrile (2.36 mmol, 3.3 equiv.) in 14 mL of acetone to which 0.32 mL of triethylamine (2.30 mmol, 3.3 equiv.) were added. To this solution were added 0.13 mL (0.74 mmol, 1 equiv.) of 1,3,5-benzenetricarbonyl trichloride under inert atmosphere, and the resulting mixture was stirred for 24 h. After this time 50 mL of distilled water were added, the precipitate that formed was filtered and washed with diethyl ether affording 0.32 g of an off-white solid in 85% yield. ^{1}H NMR (500 MHz, *d*^{6}-DMSO): δ 10.98 (s, 3H, H-7, H-21, H-28), 8.75 (s, 3H, H-12, H-14, H-16), 8.04 (d, *J* = 8.8 Hz, 6H, H-2, H-6, H-23, H-27, H-30, H-34), 7.87 (d, *J* = 8.8 Hz, 6H, H-3, H-5, H-24, H-26, H-31, H-33); ^{13}C NMR (126 MHz, *d*^{6}-DMSO): δ 164.9 (C-8, C-17, C-19), 143.1 (C-1, C-22, C-29), 135.0 (C-11, C-13, C-15), 133.2 (C-3, C-5, C-24, C-26, C-31, C-33), 130.5 (C-12, C-14, C-16), 120.3 (C-2, C-6, C-23, C-27, C-30, C-34), 118.9 (C-10, C-35, C-36), 105.8 (C-4, C-25, C-32).

4.4. Synthesis of N^1,N^3-bis(4-(1H-tetrazol-5-yl)phenyl)-N^5-(4-(2H-tetrazol-5-yl)phenyl)benzene-1,3,5-tricarboxamide (7)

In a microwave reactor 10 mL vial were added 0.079 g (0.16 mmol, 1.0 equiv.) of compound **5**, 0.091 g of sodium azide (1.40 mmol, 9.0 equiv.) and 0.32 g of $ZnBr_2$ (1.40 mmol, 9.0 equiv.) in 1 mL of *t*-BuOH. It was placed at the microwave reactor for 60 min at 100 ºC and a power of 300 W. After this time, the contents of the vial were poured into 10% HCl and the resulting solution was stirred for 20 min. The precipitate that was formed was filtered and washed with distilled water, ethanol and diethyl ether affording 73.6 mg of a light brown solid in 72% yield. ^{1}H NMR (500 MHz, *d*^{6}-DMSO): δ 11.19 (s, 3H, H-12, H-25, H-32), 8.87–8.85 (m, 3H, H-16, H-18, H-20), 8.14–8.12 (m, 6H, H-7, H-11, H-28, H-30, H-35, H-37), 7.89–7.86 (m, 6H, H-8 H-10, H-27, H-31, H-34, H-38). ^{13}C NMR (126 MHz, *d*^{6}-DMSO): δ 164.8 (C-13, C-21, C-23), 162.3 (C-4, C-39, C-44), 143.2 (C-9, C-26, C-33), 134.7 (C-15, C-17, C-19), 133.1 (C-8, C-10, C-27, C-31, C-34, C-38), 127.6 (C-16, C-18, C-20), 127.1 (C-6, C-29, C-36), 120.3 (C-7, C-11, C-28, C-30, C-35, C-37).

Author Contributions: All authors contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

Funding: A.I.-J. acknowledges "Proyecto Apoyado por el Fondo Sectorial de Investigación para la Educación CONACyT-SEP CB-2017-2018 (A1-S-32582)" and CBI-UAM-I Project (PAPDI2021_DQ 1) for financial support.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Acknowledgments: J.C.F.-R (886026) and P.I.-J. (1098528) thank CONACyT-México for their scholarships.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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