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PII: S0040-4020(15)00900-X

DOI: 10.1016/j.tet.2015.06.031

Reference: TET 26866

To appear in: *Tetrahedron*

Received Date: 23 May 2015

Revised Date: 4 June 2015

Accepted Date: 9 June 2015

Please cite this article as: Ershov OV, Maksimova VN, Lipin KV, Belikov MY, Ievlev MY, Tafeenko VA, Nasakin OE, Regiospecific synthesis of *gem*-dinitro derivatives of 2-halogenocycloalka[*b*]pyridine-3,4-dicarbonitriles, *Tetrahedron* (2015), doi: 10.1016/j.tet.2015.06.031.

## Graphical Abstract

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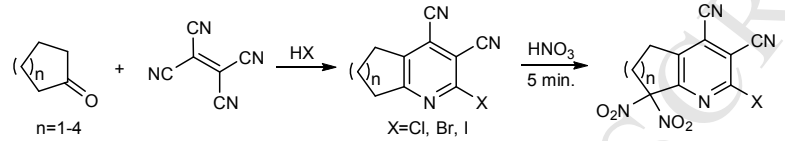

Tetrahedron
journal homepage: www.elsevier.com

# Regiospecific synthesis of *gem*-dinitro derivatives of 2-halogenocycloalka[***b***]pyridine-3,4-dicarbonitriles

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ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted
Available online

*Keywords:*
side-chain nitration
*gem*-dinitro derivatives
pyridine
tetracyanoethylene
2-alkylpyridines
nitric acid

ABSTRACT

A simple method for the synthesis of ~~the~~ inaccessible *gem*-dinitro derivatives of pyridine is described. A wide range of 2-halogencycloalka[*b*]pyridine-3,4-dicarbonitriles are produced by the three-component reaction (ketone, TCNE, hydrohalic acid), side-chain nitration of latter with 60% nitric acid in a solvent-free conditions leads to the formation of *gem*-dinitro derivatives with high selectivity and without disturbing of other reaction centers.



## 1. Introduction

Pyridine derivatives, highly developed by great contributions by *Alan Roy Katritzky*[1], have received a great attention, because this moiety is presented in a great number of drugs and biologically active molecules, naturally occurred and synthetic compounds.[2] Furthermore nitro compounds are among the important groups of chemicals have been proven to be useful building blocks and widely used in biological, pharmaceutical and advanced materials science.[3] The side-chain nitration of alkylpyridines usually gives the products of electrophilic substitution, nitropyridines,[4] which are widely used in organic synthesis as precursors for pharmaceutical and agrochemical compounds.[4a,5] Moreover, the molecules with so-called "explosophoric~~s~~" groups stimulates the practical interest for the preparation of energetic materials by selective nitration of systems with pyridine fragments.[6]

*gem*-Dinitroalkyl pyridine derivatives are an unusual class of compounds. There are only a few methods for their preparation. Some examples for insertion of nitro groups in alkyl substitute of pyridines are already known,[4a,7] but the methods are given ~~only~~ for just a few ~~number of~~ substrates and have not been systemized. We were able to find only three publications with the description of direct side-chain nitration of 2-alkylpyridines into *gem*-di- and tri-nitro derivatives.[4a,7a,b] A significant disadvantage of these reactions was the low yields of the resulting products. The nitration of 2,5-dimethylpyridine with nitric acid in trifluoroacetic anhydride led to the formation of 5-methyl-2-(trinitromethyl)pyridine in 10% yield.[4a] Nitrogen dioxide reacted with 2-ethylpyridine in the presence of ozone in dichloromethane at room temperature with formation of only 8% ~~of~~ 2-(1,1-dinitroethyl)pyridine.[7a] The treatment of 6-methylpyrazino[2,3-*c*]isoquinoline by potassium nitrate in concentrated sulfuric acid gave 10-nitro-6-(trinitromethyl)pyrazino[2,3-*c*]isoquinoline in 31% yield.[7b] Using the described methods for the direct insertion of nitro group in the alkyl substituent of pyridine, only three *gem*-di- or tri-nitro compounds were obtained ~~only~~. [4a,7a,b]

Moreover, there are two methods for the indirect nitration of 2-alkylpyridines thorough the *gem*-trinitromethyl fragment insertion into the pyridinium salts by nitroform[7c,d] and using the Ponzio reaction variation~~s~~, under the action of nitrate or nitrogen oxides, to 2-pyridinecarbonyl oximes.[7e-g]

Many of these methods have one or more disadvantages such as long reaction times, low yields, formation of byproducts, tedious workup, and the use of explosive reagents leading to theserious environmental and safety problems. Therefore, the development of safe and simple methods for inserting of the nitro group into the α-alkyl substituent of the pyridine ring is a significant problem.

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## 2. Results/Discussion

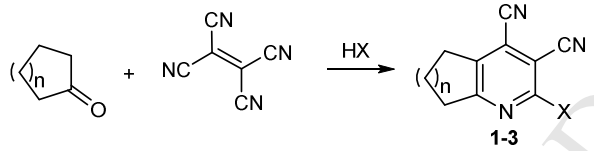
We suggested that alkylpyridines with electron-withdrawing groups should be easier to nitrate on the alkyl substituent in the second position of the pyridine ring. This assumption is based on the known fact that electron-withdrawing substituents increase the mobility of hydrogen atoms in the alkyl groups by pulling the electron density and make the compound ready for reactions.

Therefore, as the starting compounds readily available pyridines with two cyano groups were chosen, namely 2-halogenocycloalka[*b*]pyridine-3,4-dicarbonitriles **1-3**. This choice is influenced by the fact that these compounds contain an important pyridinecarboxylic acid structural moiety – specifically nicotinic (nicotinonitrile) and isonicotinic (isonicotinonitrile) acids. Moreover, readily replaceable halogen atom (X) commonly used for the directed synthesis are found in the products.[8a,b]

For the synthesis of starting compounds a multi-component coupling reactions strategy (MCRs) was used. 2-Halogenocycloalka[*b*]pyridine-3,4-dicarbonitriles **1-3** were prepared according to the earlier described method[8c] *via* three-component reaction: cycloalkanone – tetracyanoethylene (TCNE) – hydrogen halide. The reaction was carried at 60 °C in 1,4-dioxane using equimolar amounts of cycloalkanone and TCNE and an excess of hydrogen halide. During this investigation seven previously unknown halopyridines **1c**, **2a-d**, **3c**, **3d** were obtained to expand the range of examples for developed side-chain nitration method and to prove the universality (Table 1).

**Table 1**.

Three-component synthesis of 2-halogencycloalka[*b*]pyridine-3,4-dicarbonitriles **1-3**



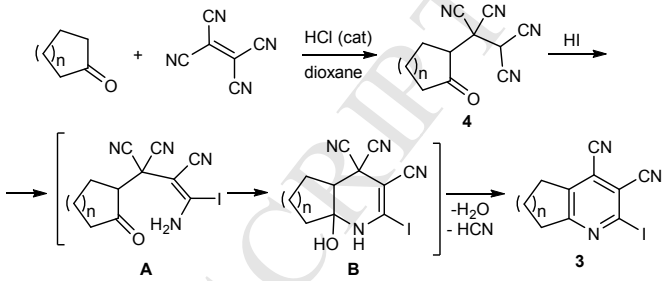

**1-3**

| Entry | n | X | Product | Yield[a] (%) | Yield[a] (%) **Scheme 1** |
|---|---|---|---|---|---|
| **1** | 1 | **Cl** | **1a** | 80 | - |
| **2** | 2 | **Cl** | **1b** | 97 | - |
| **3** | 3 | **Cl** | **1c** | 93 | - |
| **4** | 4 | **Cl** | **1d** | 94 | - |
| **5** | 1 | **Br** | **2a** | 82 | - |
| **6** | 2 | **Br** | **2b** | 77 | - |
| **7** | 3 | **Br** | **2c** | 67 | - |
| **8** | 4 | **Br** | **2d** | 66 | - |
| **9** | 1 | **I** | **3a** | 7 | 84 |
| **10** | 2 | **I** | **3b** | 12 | 81 |
| **11** | 3 | **I** | **3c** | 5 | 79 |
| **12** | 4 | **I** | **3d** | 2 | 76 |

[a] Isolated yield.

It is important to note that this approach works well when HCl and HBr were used (table 1, entries 1–8). However, the synthesis of iodine derivatives **3** did not proceed well under these conditions (table 1, entries 9–12). Probably, it is related with the reducing properties of hydrogen iodide, which is capable of converting TCNE into ethane-1,1,2,2-tetracarbonitrile. Correspondingly a two-step one-pot synthesis of 2-iodocycloalka[*b*]pyridine-3,4-dicarbonitriles **3** was developed to improve the yield by excluding the interaction of TCNE and HI. TCNE was treated at room temperature with equimolar amount of cycloalkanone in 1,4-dioxane in the presence of catalytic amount of hydrochloric acid. After the reaction completion (hydroquinone test – presence of unreacted TCNE gives a blue coloration) an excess of hydrogen iodide was added and the reaction mixture was stirred and heated at 50-60 °C for 1-2 hours. The reaction likely proceeds through ~~the~~ intermediate formation of 4-oxoalkane-1,1,2,2-tetracarbonitriles **4**, based on the involvement of compounds **4** in similar transformations.[9] During this investigation, tetracyanosubstituted derivatives of cycloheptanone **4c** (n = 3) and cyclooctanone **4d** (n = 4) were obtained and described at first time. They were yielded by pouring excess of water in the reaction mixture before the addition of hydrogen iodide.

**Scheme 1.** One-pot synthesis of 2-iodocycloalka[*b*]pyridine-3,4-dicarbonitriles **3**

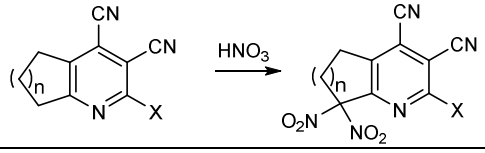



Pyridine **3** formation proceeds through the hyrogen halide addition to the terminal cyano group of compounds **4**, ring closure and aromatization by dehydration and dehydrocyanation. Pyridine structures **1-3** were confirmed by IR-, $^1$H NMR-spectroscopy and mass-spectrometry.

Studies have shown that for side-chain nitration of prepared nicotinonitriles **1-3** concentrated nitric acid can be used without any additional ~~enhancing~~ nitrating reagents. It was also found, that the reaction proceeds rapidly with heating for 4-5 min with good yields and leads to the regiospecific formation of *gem*-dinitro derivatives of α-alkyl substituents in 2-halogenocycloalka[*b*]pyridine-3,4-dicarbonitriles **5-7**.

**Table 2**.

Side-chain nitration of 2-halogencycloalka[*b*]pyridine-3,4-dicarbonitriles **5-7**.




| Entry | n | X | Product | Yield[a] (%) |
|---|---|---|---|---|
| **1** | 1 | **Cl** | **5a** | 74 |
| **2** | 2 | **Cl** | **5b** | 77 |
| **3** | 3 | **Cl** | **5c** | 73 |
| **4** | 4 | **Cl** | **5d** | 78 |
| **5** | 1 | **Br** | **6a** | 77 |
| **6** | 2 | **Br** | **6b** | 68 |
| **7** | 3 | **Br** | **6c** | 63 |
| **8** | 4 | **Br** | **6d** | 61 |
| **9** | 1 | **I** | **7a** | 83 |
| **10** | 2 | **I** | **7b** | 86 |
| **11** | 3 | **I** | **7c** | 84 |
| **12** | 4 | **I** | **7d** | 82 |

[a] Isolated yield.

It was found, that the applying of nitric acid in mixture with sulfuric acid (nitrating mixture) is complicated by the formation of cyano group hydrolysis byproducts. Among the compounds mixture, the product of α-alkylpyridine *gem*-dinitration was indicated by TLC. A similar is observed for other options mixtures used for nitration. Thus, when acetic acid or acetic anhydride were used as a co-solvent the decomposition products of **5-7** were found in the reaction mass, similar to the described for dinitrobarbituric acid.[10] It was found, that the best method is

the use of nitric acid with a concentration in a range of 50-60%. Moreover, it is the easiest and cheapest way, because this is the industrially available concentration of acid. It is interesting to note, that in this case the hydrolysis of cyano groups does not occur, even in trace amounts, despite ~~the~~ boiling in a medium of strong acid.

The structure of the pyridine **6c** established by the X-ray diffraction method (Fig. 1).[11] Structures of compounds **5-7** are considered with IR-, $^1$H NMR-spectroscopy and mass-spectrometry. The IR spectra of compounds **5-7** characterized with the intensive absorption bands of valent vibrations of conjugated C≡N in the area of 2235-2246 cm$^{-1}$, $NO_2$ in the area of 1536-1592 cm$^{-1}$. A characteristic distinction of the $^1$H NMR spectra of compounds **5-7** from corresponding starting pyridine **1-3** is the absence of signals of α-methylene protons. For the mass spectra of compounds **5-7** the presence of the fragment ion with weight equal to the difference of molecular weight and the nitro group $[M - 46(NO_2)]^+$ is usual. In the mass spectra of some 2-iododerivatives dinitro- compounds **7** the fragment ion with weight equal to the difference of molecular weight and two nitro groups $[M - 92(2NO_2)]^+$ is presented.

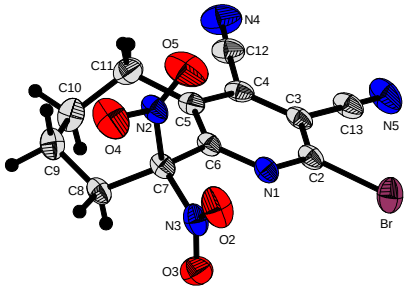
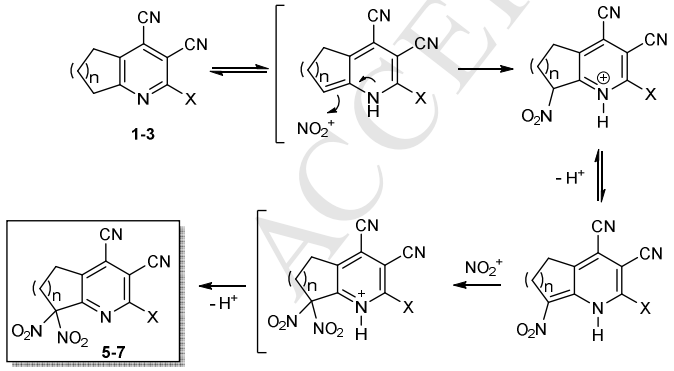



**Figure 1.** The molecular structure of 2-bromo-9,9-dinitro-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-3,4-dicarbonitrile (**6c**) with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are drawn as small spheres of arbitrary radii.

For the side-chain nitration of 2-halogenocycloalka[*b*]pyridine-3,4-dicarbonitriles **1-3** by nitric acid with concentration in the range of 50-60%, either a radical or an electrophilic mechanism can be proposed. The fact that only one product is formed and the absence of regioisomeric byproducts of the reaction, partially indicates the electrophilic nature of substitution.




**Scheme 2.** Proposed mechanism side-chain nitration

Probably, acid-catalyzed tautomerization of the α-alkylpyridine fragment occurs ~~at~~ first. Further, nitronium cation undergoes the electrophilic addition to the double bond and proton eliminates then. Substitution of the second hydrogen occurs in a similar way, even being much easier, because the acidity of the proton increases. This hypothesis explains the formation of dinitro- and the difficulty of making mononitro-derivatives under the same reaction conditions.

## 3. Conclusion

A simple and effective method to prepare *gem*-dinitro derivatives of 2-halogenocycloalka[*b*]pyridine-3,4-dicarbonitriles was investigated. This method includes the selective side-chain nitration of 2-halogenocycloalka[*b*]pyridine-3,4-dicarbonitriles with 60% nitric acid into the α-alkyl substitute of pyridine ring. The reaction proceeds rapidly (about 5 min) with good yields, making the method convenient for modification of pyridine derivatives.

## 4. Experimental Section

### 4.1. General information

The progress of reactions and the purity of the products were monitored by TLC on Sorbfil plates (spots were visualized under UV light, by treatment with iodine vapor, or by heating). The IR spectra were recorded on an FSM-1202 spectrometer with Fourier transform from samples dispersed in mineral oil. The NMR spectra were measured in DMSO-*d6* on a Bruker DRX-500 spectrometer using tetramethylsilane as an internal reference. The elemental compositions were determined on a CHN-analyzer vario Micro cube. The mass spectra (electron impact, 70 eV) were obtained on a Finnigan MAT INCOS-50 spectrometer. XRD study of a single crystal of compound **6c** was carried out on a diffractometer Cad-4 (Cu Kα emission, λ 1.54087Å, ω-scan). Correction for absorption was not used. The structure was solved and refined with SHELX[12a] program. The non-hydrogen atoms were refined by using the anisotropic full matrix least-square procedure. The hydrogen atoms were located from a difference Fourier map and refined freely. Molecular geometry calculations were performed with the SHELX program, and the molecular graphics were prepared by using DIAMOND[12b] software.

### 4.2. General procedure for the preparation of 2-halogenocycloalka[*b*]pyridine-3,4-dicarbonitriles (1-2)

To the solution of 0.006 mol appropriate ketone in 10 mL of 1,4-dioxane 0.64 g (0.005 mol) of TCNE and 3 mL of hydrohalic acid were added. Reaction mixture stirred at 60-70 °C for 1-2 h (indicated by TLC). Then mixture diluted with water, precipitated crystals filtered, washed with water and propan-2-ol. Recrystallized from propan-2-ol.

The analytical properties of compounds **1b,d** were identical to the previously reported literature data.[8c]

4.2.1. *2-Chloro-6,7-dihydro-5H-cyclopenta[b]pyridine-3,4-dicarbonitrile (**1a**).* Yield: 0.81 g (80%); mp 77-79 °C.[9b] IR (KBr): 2233 cm$^{-1}$. $^1$H NMR (500.13 MHz, DMSO-*d6*): δ = 2.18 (q, *J* = 7.7 Hz, 2H, $CH_2$), 3.14-3.21 (m, 4H, $2CH_2$). MS m/z (%): 203 ([M$^+$], 68), 204 ([M$^+$], 6), 205 ([M$^+$], 21). Anal. Calcd for $C_{10}H_6ClN_3$: C, 58.98; H, 2.97; N, 20.64. Found: C, 59.10; H, 2.98; N, 20.59.

4.2.2. *2-Chloro-6,7-dihydro-5H-cyclohepta[b]pyridine-3,4-dicarbonitrile (**1c**).* Yield: 1.15 g (93%); mp 90-92 °C. IR (KBr): 2235 cm$^{-1}$. $^1$H NMR (500.13 MHz, DMSO-*d6*): δ = 1.62-1.71 (m, 4H, $2CH_2$), 1.83-1.88 (m, 2H, $CH_2$), 3.04-3.07 (m, 2H, $CH_2$), 3.10-3.13 (m, 2H, $CH_2$). MS m/z (%): 231 ([M$^+$], 64), 232 ([M$^+$], 5), 233 ([M$^+$], 22). Anal. Calcd for $C_{12}H_{10}ClN_3$: C, 62.21; H, 4.35; N, 18.14. Found: C, 62.35; H, 4.37; N, 18.10.

4.2.3. *2-Bromo-6,7-dihydro-5H-cyclopenta[b]pyridine-3,4-dicarbonitrile (**2a**)*. Yield: 1.02 g (82%); mp 91-93 °C. IR (KBr): 2233 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 2.19 (q, *J* = 7.7 Hz, 2H, $CH_2$), 3.07-3.14 (m, 4H, $2CH_2$). MS m/z (%): 247 ([$M^+$], 28), 249 ([$M^+$], 25),. Anal. Calcd for $C_{10}H_6BrN_3$: C, 48.42; H, 2.44; N, 16.94. Found: C, 48.47; H, 2.46; N, 16.90.

4.2.4. *2-Bromo-5,6,7,8-tetrahydroquinoline-3,4-dicarbonitrile (**2b**)*. Yield: 1.01 g (77%); mp 99-101 °C. IR (KBr): 2231 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 1.79-1.85 (m, 4H, $2CH_2$), 2.87-2.90 (m, 2H, $CH_2$), 2.94-2.97 (m, 2H, $CH_2$). MS m/z (%): 261 ([$M^+$], 47), 263 ([$M^+$], 45). Anal. Calcd for $C_{11}H_8BrN_3$: C, 50.41; H, 3.08; N, 16.03. Found: C, 50.48; H, 3.09; N, 15.99.

4.2.5. *2-Bromo-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3,4-dicarbonitrile (**2c**)*. Yield: 0.92 g (67%); mp 112-114 °C. IR (KBr): 2234 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 1.63-1.70 (m, 4H, $2CH_2$), 1.82-1.87 (m, 2H, $CH_2$), 3.01-3.04 (m, 2H, $CH_2$), 3.10-3.13 (m, 2H, $CH_2$). MS m/z (%): 275 ([$M^+$], 73), 277 ([$M^+$], 70). Anal. Calcd for $C_{12}H_{10}BrN_3$: C, 52.20; H, 3.65; N, 15.22. Found: C, 52.26; H, 3.66; N, 15.19.

4.2.6. *2-Bromo-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3,4-dicarbonitrile (**2d**)*. Yield: 0.96 g (66%); mp 84-86 °C. IR (KBr): 2232 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 1.31-1.38 (m, 4H, $2CH_2$), 1.69-1.77 (m, 4H, $2CH_2$), 2.98-3.01 (m, 2H, $CH_2$), 3.02-3.05 (m, 2H, $CH_2$). MS m/z (%): 289 ([$M^+$], 21), 291 ([$M^+$], 20). Anal. Calcd for $C_{13}H_{12}BrN_3$: C, 53.81; H, 4.17; N, 14.48. Found: C, 53.88; H, 4.19; N, 14.44.

### 4.3. General procedure for the preparation of 2-iodocycloalka[b]pyridine-3,4-dicarbonitriles (3)

To the solution of 0.006 mol of the appropriate ketone in 10 mL of 1,4-dioxane 0.64 g (0.005 mol) of TCNE and 0.1 mL of hydrochloric acid were added. The reaction mixture stirred at room temperature and after the disappearance of TCNE (hydroquinone test) 3 mL of concentrated hydriodic acid was added. Mixture heated to 60-70 °C and continued stirring for 1-2 h (indicated by TLC). Precipitated crystals filtered, washed with water and propan-2-ol. Recrystallized from propan-2-ol

4.3.1. *2-Iodo-6,7-dihydro-5H-cyclopenta[b]pyridine-3,4-dicarbonitrile (**3a**)*. Yield: 1.24 g (84%); mp 102-103 °C.[9c] IR (KBr): 2235 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 2.15 (quin, *J* = 7.7 Hz, 2H, $CH_2$), 3.06 (t, *J* = 7.7 Hz, 2H, $CH_2$), 3.10 (t, *J* = 7.7 Hz, 2H, $CH_2$). MS m/z (%): 295 ([$M^+$], 21). Anal. Calcd for $C_{10}H_6IN_3$: C, 40.70; H, 2.05; N, 14.24. Found: C, 40.78; H, 2.06; N, 14.21.

4.3.2. *2-Iodo-5,6,7,8-tetrahydroquinoline-3,4-dicarbonitrile (**3b**)*. Yield: 1.25 g (81%); mp 103-104 °C.[9c] IR (KBr): 2225 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 1.77-1.84 (m, 4H, $2CH_2$), 2.84-2.87 (m, 2H, $CH_2$), 2.92-2.95 (m, 2H, $CH_2$). MS m/z (%): 309 ([$M^+$], 12). Anal. Calcd for $C_{11}H_8IN_3$: C, 42.74; H, 2.61; N, 13.59. Found: C, 42.80; H, 2.61; N, 13.56.

4.3.3. *2-Iodo-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3,4-dicarbonitrile (**3c**)*. Yield: 1.28 g (79%); mp 124-126 °C. IR (KBr): 2231 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 1.62-1.69 (m, 4H, $2CH_2$), 1.81-1.86 (m, 2H, $CH_2$), 2.97-3.00 (m, 2H, $CH_2$), 3.08-3.11 (m, 4H, $2CH_2$). MS m/z (%): 323 ([$M^+$], 97). Anal. Calcd for $C_{12}H_{10}IN_3$: C, 44.60; H, 3.12; N, 13.00. Found: C, 44.69; H, 3.13; N, 12.98.

4.3.4. *2-Iodo-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3,4-dicarbonitrile (**3d**)*. Yield: 1.28 g (76%); mp 96-98 °C. IR (KBr): 2232 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 1.30-1.38 (m, 4H, $2CH_2$), 1.81-1.86 (m, 2H, $CH_2$), 2.95-2.98 (m, 2H, $CH_2$), 3.00-3.03 (m, 4H, $2CH_2$). MS m/z (%): 337 ([$M^+$], 88). Anal. Calcd for $C_{13}H_{12}IN_3$: C, 46.31; H, 3.59; N, 12.46. Found: C, 46.37; H, 3.61; N, 12.42.

### 4.4. General procedure for the preparation of 4-oxoalcane-1,1,2,2-tetracarbonitriles (4)

1.28 g (0.01 mol) of TCNE was dissolved in a minimal amount of 1,4-dioxane (10 mL), then 0.015 mol of the appropriate ketone was added and mixture stirred until the complete dissolution then 1-2 drop of concentrated hydrochloric acid was added (d = 1.17-1.19). After the disappearance of TCNE (hydroquinone test) the mixture was poured into 100 mL of ice-cold water. The obtained oil crystallized with intensive stirring. The precipitated crystals were filtered, washed with water and ice-cold propan-2-ol. If it was needed, recrystallized from propan-2-ol.

4.4.1. *1-(2-Oxocycloheptyl)ethane-1,1,2,2-tetracarbonitrile (**4c**)*.Yield: 2.23 g (93%); mp 104-106 °C. IR (KBr): 2259, 1701 $cm^{-1}$. $^1H$ NMR (500.13 MHz, acetone-*d6*): δ = 1.47-1.55 (m, 1H, $CH_2$), 1.75-2.07 (m, 5H, $(CH_2)_3$), 2.35-2.40 (m, 1H, $CH_2$), 2.59-2.66 (m, 1H, $CH_2$), 2.81-2.87 (m, 1H, $COCH_2$), 3.16-3.21 (m, 1H, $CH_2CO$), 3.98-4.02 (m, 1H, CHCO), 5.93 (s, 1H, CHCN). MS m/z (%): 240 ([$M^+$], 8). Anal. Calcd for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 64.89; H, 5.05; N, 23.36.

4.4.2. *1-(2-Oxocyclooctyl)ethane-1,1,2,2-tetracarbonitrile (**4d**)*. Yield: 2.41 g (95%); mp 134-136 °C. IR (KBr): 2258, 1703 $cm^{-1}$. $^1H$ NMR (500.13 MHz, acetone-*d6*): δ = 1.12-1.20 (m, 1H, $CH_2$), 1.57-2.21 (m, 8H, $(CH_2)_4$), 2.48-2.54 (m, 1H, $CH_2$), 2.76-2.83 (m, 1H, $CH_2CO$), 2.89-2.99 (m, 1H, $CH_2CO$), 3.92-3.99 (m, 1H, CHCO), 5.88 (s, 1H, CHCN). MS m/z (%): 254 ([$M^+$], 3). Anal. Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.11; H, 5.54; N, 22.05.

### 4.5. General procedure for the preparation of gem-dinitro derivatives 2-halogenocycloalka[*b*]pyridine-3,4-dicarbonitriles

To ~~the~~ 0.005 mol of 2-halogenocycloalka[*b*]pyridine-3,4-dicarbonitriles (**1-3**) 5 mL of 60% nitric acid was added. Mixture refluxed for 4-5 min then allowed to cool and diluted with water. Precipitated crystals were filtered and then washed with water.

4.5.1. *2-Chloro-7,7-dinitro-6,7-dihydro-5H-cyclopenta[b]pyridine-3,4-dicarbonitrile (**5a**)*. Yield: 1.08 g (74%); mp 104-105 °C. IR (KBr): 2243, 1575 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 3.46-3.49 (m, 2H, $CH_2$), 3.60-3.63 (m, 2H, $CH_2$). MS m/z (%): 247 ([M-46]$^+$, 10), 249 ([M-46]$^+$, 3). Anal. Calcd for $C_{10}H_4ClN_5O_4$: C, 40.91; H, 1.37; N, 23.85. Found: C, 41.00; H, 1.37; N, 23.81.

4.5.2. *2-Chloro-8,8-dinitro-5,6,7,8-tetrahydroquinoline-3,4-dicarbonitrile (**5b**)*. Yield: 1.18 g (77%); mp 148-150 °C. IR (KBr): 2245, 1561 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 1.96-2.01 (m, 2H, $CH_2$), 3.19 (t, *J* = 6.4 Hz, 2H, $CH_2$), 3.23-3.26 (m, 2H, $CH_2$). MS m/z (%): 261 ([M-46]$^+$, 13), 263 ([M-46]$^+$, 4).

Anal. Calcd for $C_{11}H_6ClN_5O_4$: C, 42.95; H, 1.97; N, 22.76. Found: C, 43.05; H, 1.98; N, 22.71.

4.5.3. *2-Chloro-9,9-dinitro-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3,4-dicarbonitrile (**5c**)*. Yield: 1.17 g (73%); mp 185-187 °C. IR (KBr): 2235, 1554 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 1.78-1.82 (m, 2H, $CH_2$), 1.89-1.94 (m, 2H, $CH_2$), 2.97-3.00 (m, 2H, $CH_2$), 3.08-3.11 (m, 2H, $CH_2$). MS m/z (%): 275 ($[M-46]^+$, 11), 277 ($[M-46]^+$, 3). Anal. Calcd for $C_{12}H_8ClN_5O_4$: C, 44.81; H, 2.51; N, 21.77. Found: C, 44.91; H, 2.52; N, 21.72.

4.5.4. *2-Chloro-10,10-dinitro-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3,4-dicarbonitrile (**5d**)*. Yield: 1.30 g (78%); mp 197-199 °C. IR (KBr): 2237, 1556 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 1.34-1.38 (m, 2H, $CH_2$), 1.81-1.85 (m, 4H, $2CH_2$), 2.98 (t, *J* = 6.6 Hz, 2H, $CH_2$), 3.26-3.28 (m, 2H, $CH_2$). MS m/z (%): 289 ($[M-46]^+$, 5). Anal. Calcd for $C_{13}H_{10}ClN_5O_4$: C, 46.51; H, 3.00; N, 20.86. Found: C, 46.63; H, 3.01; N, 20.81.

4.5.5. *2-Bromo-7,7-dinitro-6,7-dihydro-5H-cyclopenta[b]pyridine-3,4-dicarbonitrile (**6a**)*. Yield: 1.29 g (77%); mp 135-137 °C. IR (KBr): 2246, 1589 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 3.42-3.45 (m, 2H, $CH_2$), 3.59-3.62 (m, 2H, $CH_2$). MS m/z (%): 291 ($[M-46]^+$, 29), 293 ($[M-46]^+$, 30). Anal. Calcd for $C_{10}H_4BrN_5O_4$: C, 35.53; H, 1.19; N, 20.72. Found: C, 35.61; H, 1.20; N, 20.67.

4.5.6. *2-Bromo-8,8-dinitro-5,6,7,8-tetrahydroquinoline-3,4-dicarbonitrile (**6b**)*. Yield: 1.19 g (68%); mp 153-155 °C. IR (KBr): 2239, 1569 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 1.95-2.00 (m, 2H, $CH_2$), 3.15 (t, *J* = 6.4 Hz, 2H, $CH_2$), 3.23-3.25 (m, 2H, $CH_2$). MS m/z (%): 305 ($[M-46]^+$, 21), 307 ($[M-46]^+$, 20). Anal. Calcd for $C_{11}H_6BrN_5O_4$: C, 37.52; H, 1.72; N, 19.89. Found: C, 37.61; H, 1.73; N, 19.84.

4.5.7. *2-Bromo-9,9-dinitro-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3,4-dicarbonitrile (**6c**)*. Yield: 1.15 g (63%); mp 172-174 °C. IR (KBr): 2241, 1564 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 1.77-1.81 (m, 2H, $CH_2$), 1.88-1.93 (m, 2H, $CH_2$), 2.96-2.99 (m, 2H, $CH_2$), 3.07-3.10 (m, 2H, $CH_2$). MS m/z (%): 319 ($[M-46]^+$, 18), 321 ($[M-46]^+$, 17). Anal. Calcd for $C_{12}H_8BrN_5O_4$: C, 39.37; H, 2.20; N, 19.13. Found: C, 39.46; H, 2.21; N, 19.08.

4.5.8. *2-Bromo-10,10-dinitro-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3,4-dicarbonitrile (**6d**)*. Yield: 1.16 g (61%); mp 187-188 °C. IR (KBr): 2238, 1567 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 1.36-1.40 (m, 2H, $CH_2$), 1.81-1.86 (m, 4H, $2CH_2$), 2.98 (t, *J* = 6.5 Hz, 2H, $CH_2$), 3.27-3.29 (m, 2H, $CH_2$). MS m/z (%): 333 ($[M-46]^+$, 24), 335 ($[M-46]^+$, 24). Anal. Calcd for $C_{13}H_{10}BrN_5O_4$: C, 41.07; H, 2.65; N, 18.42. Found: C, 41.16; H, 2.67; N, 18.37.

4.5.9. *2-Iodo-7,7-dinitro-6,7-dihydro-5H-cyclopenta[b]pyridine-3,4-dicarbonitrile (**7a**)*. Yield: 1.59 g (83%); mp 197-198 °C. IR (KBr): 2241, 1589 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 3.37-3.40 (m, 2H, $CH_2$), 3.55-3.58 (m, 2H, $CH_2$). MS m/z (%): 339 ($[M-46]^+$, 23). Anal. Calcd for $C_{10}H_4IN_5O_4$: C, 31.19; H, 1.05; N, 18.19. Found: C, 31.27; H, 1.06; N, 18.14.

4.5.10. *2-Iodo-8,8-dinitro-5,6,7,8-tetrahydroquinoline-3,4-dicarbonitrile (**7b**)*. Yield: 1.71 g (86%); mp 207-210 °C. IR (KBr): 2239, 1588 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 1.92-1.97 (m, 2H, $CH_2$), 3.10 (t, *J* = 6.4 Hz, 2H, $CH_2$), 3.20-3.23 (m, 2H, $CH_2$). MS m/z (%): 307 ($[M-92]^+$, 11). Anal. Calcd for $C_{11}H_6IN_5O_4$: C, 33.10; H, 1.52; N, 17.55. Found: C, 33.17; H, 1.53; N, 17.51.

4.5.11. *2-Iodo-9,9-dinitro-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3,4-dicarbonitrile (**7c**)*. Yield: 1.73 g (84%); mp 194-196 °C. IR (KBr): 2239, 1592 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 1.76-1.80 (m, 2H, $CH_2$), 1.87-1.92 (m, 2H, $CH_2$), 2.88-2.91 (m, 2H, $CH_2$), 3.05-3.08 (m, 2H, $CH_2$). MS m/z (%): 321 ($[M-92]^+$, 14). Anal. Calcd for $C_{12}H_8IN_5O_4$: C, 34.89; H, 1.95; N, 16.95. Found: C, 35.06; H, 1.95; N, 16.90.

4.5.12. *2-Iodo-10,10-dinitro-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3,4-dicarbonitrile (**7d**)*. Yield: 1.74 g (82%); mp 180-182 °C. IR (KBr): 2235, 1569 $cm^{-1}$. $^1H$ NMR (500.13 MHz, DMSO-*d6*): δ = 1.38-1.40 (m, 2H, $CH_2$), 1.79-1.85 (m, 4H, $2CH_2$), 2.92 (t, *J* = 6.5 Hz, 2H, $CH_2$), 3.25-3.28 (m, 2H, $CH_2$). MS m/z (%): 381 ($[M-46]^+$, 39). Anal. Calcd for $C_{13}H_{10}IN_5O_4$: C, 36.55; H, 2.36; N, 16.40. Found: C, 36.62; H, 2.37; N, 16.36.

**Acknowledgements**

This work was supported by Russian Fund for Basic Research, Grant No. 15-33-21087.

The XRD study was carried out using the equipment purchased from the funds of the Program of development of Moscow University and within the framework of the Agreement on collaboration between the Chemical Department of the Lomonsov Moscow State University and the Chemical-Pharmaceutical Department of the I.N. Ulyanov Chuvash State University.

**Supplementary data**

Supplementary data (Copies of $^1H$ NMR spectra for compounds **1**-**7**) associated with this article can be found in the online version, at http://

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11. CCDC No. 1402024. CCDC 1402024 contains supplementary crystallographic data for **6c**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: þ44 1223 336033.

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## Supporting information

# Regiospecific synthesis of *gem*-dinitro derivatives of 2-halogenocycloalka[*b*]pyridine-3,4-dicarbonitriles

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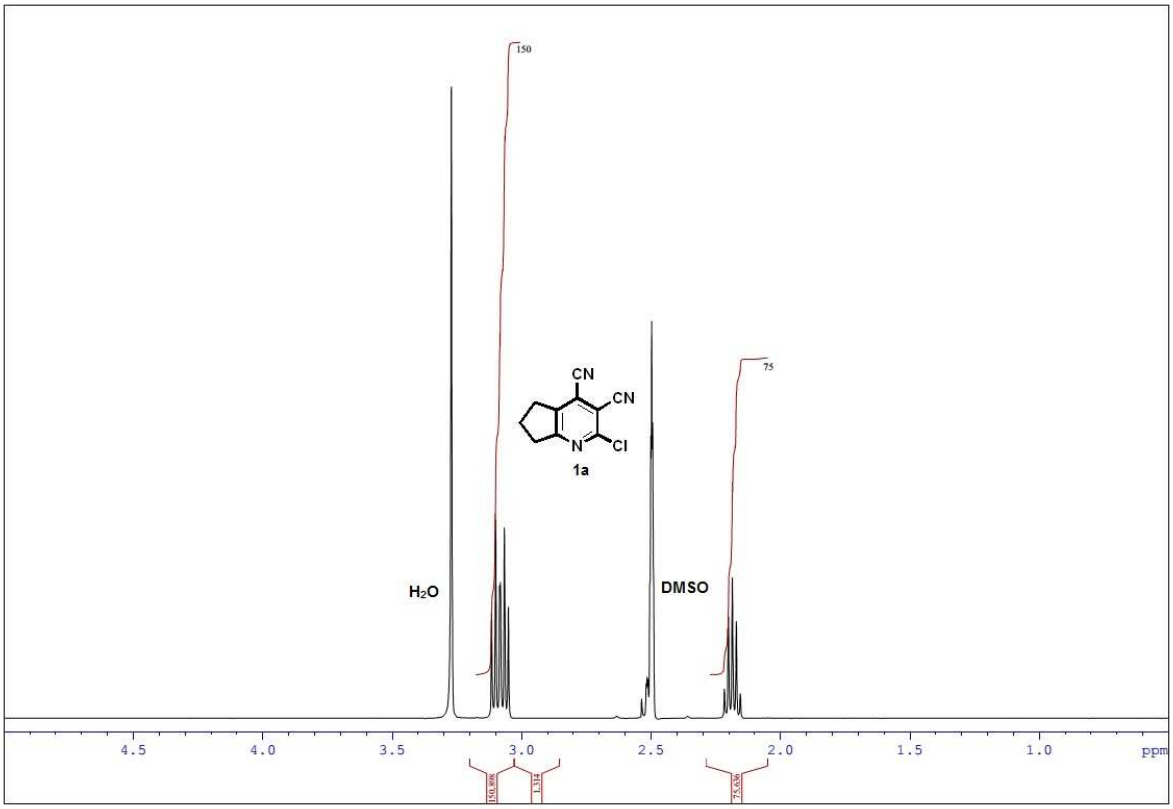
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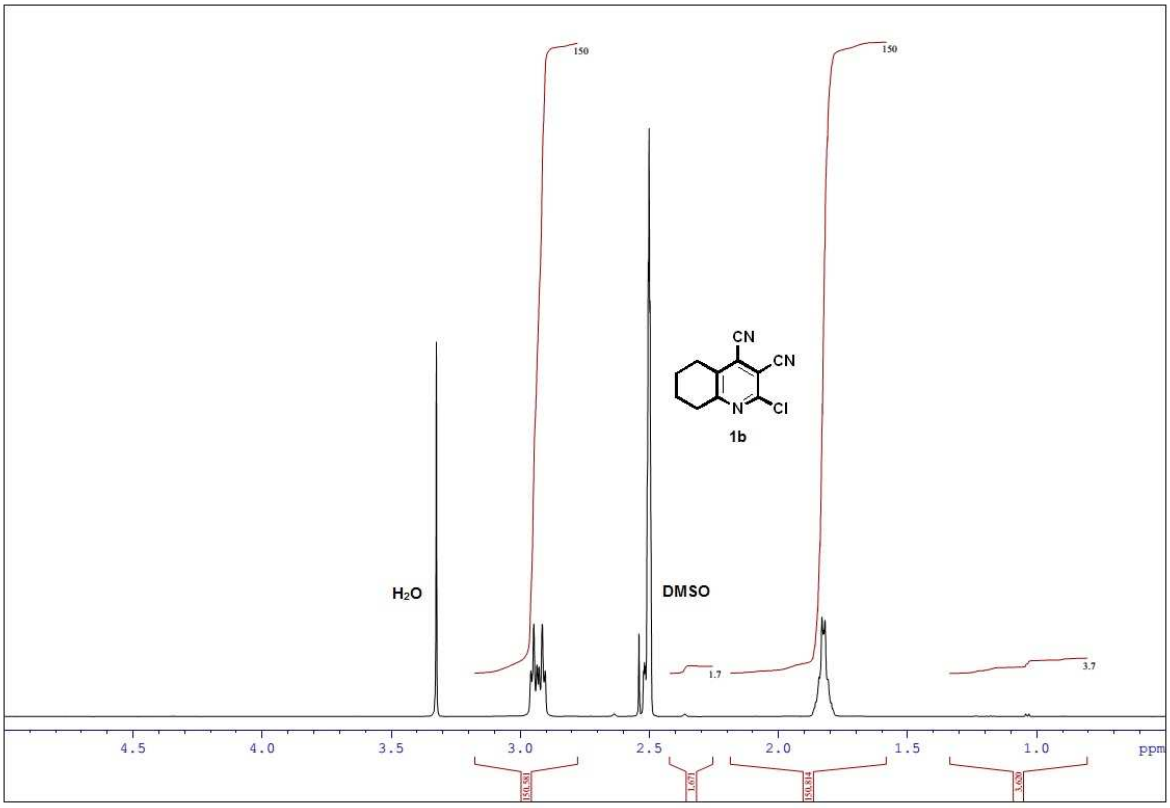
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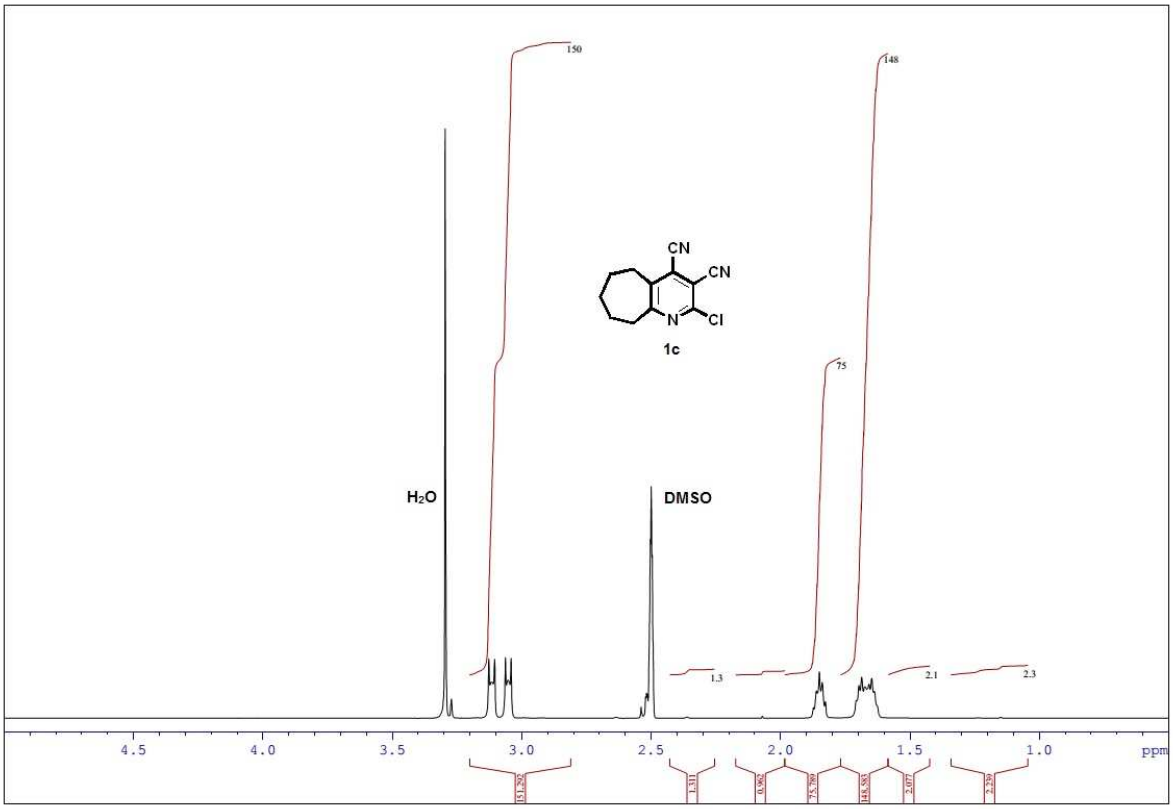
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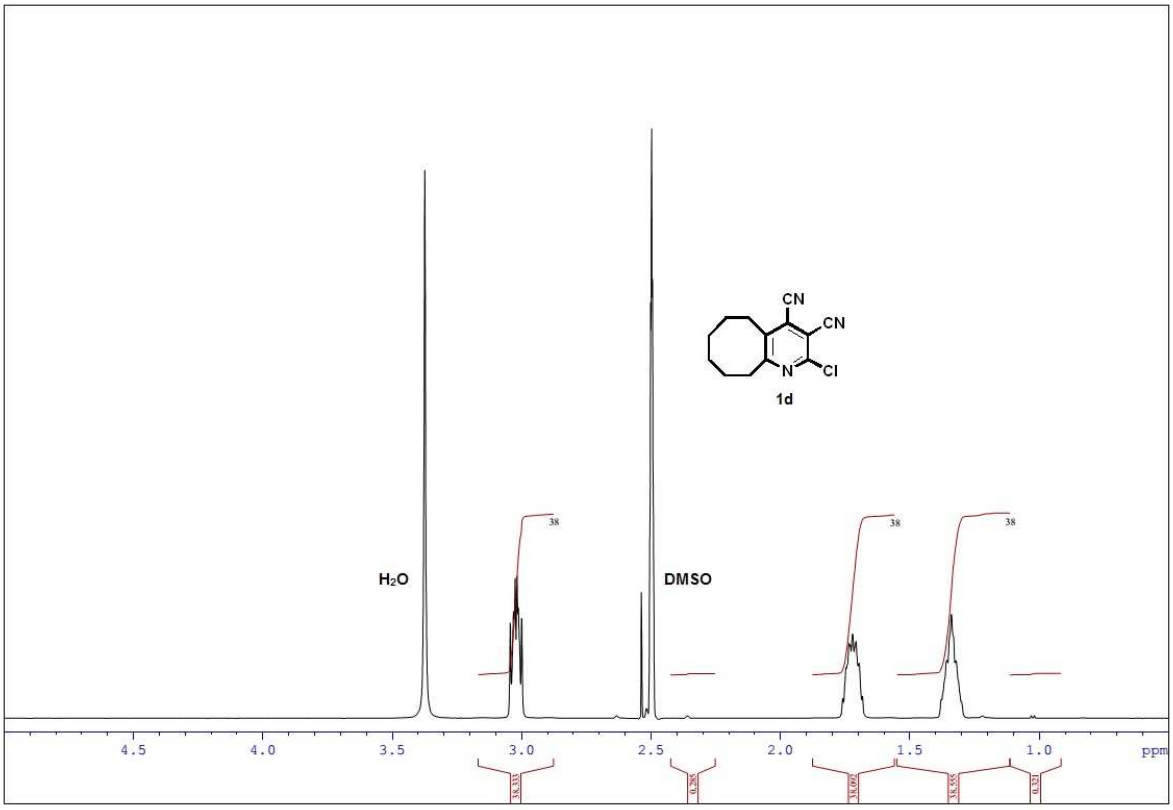
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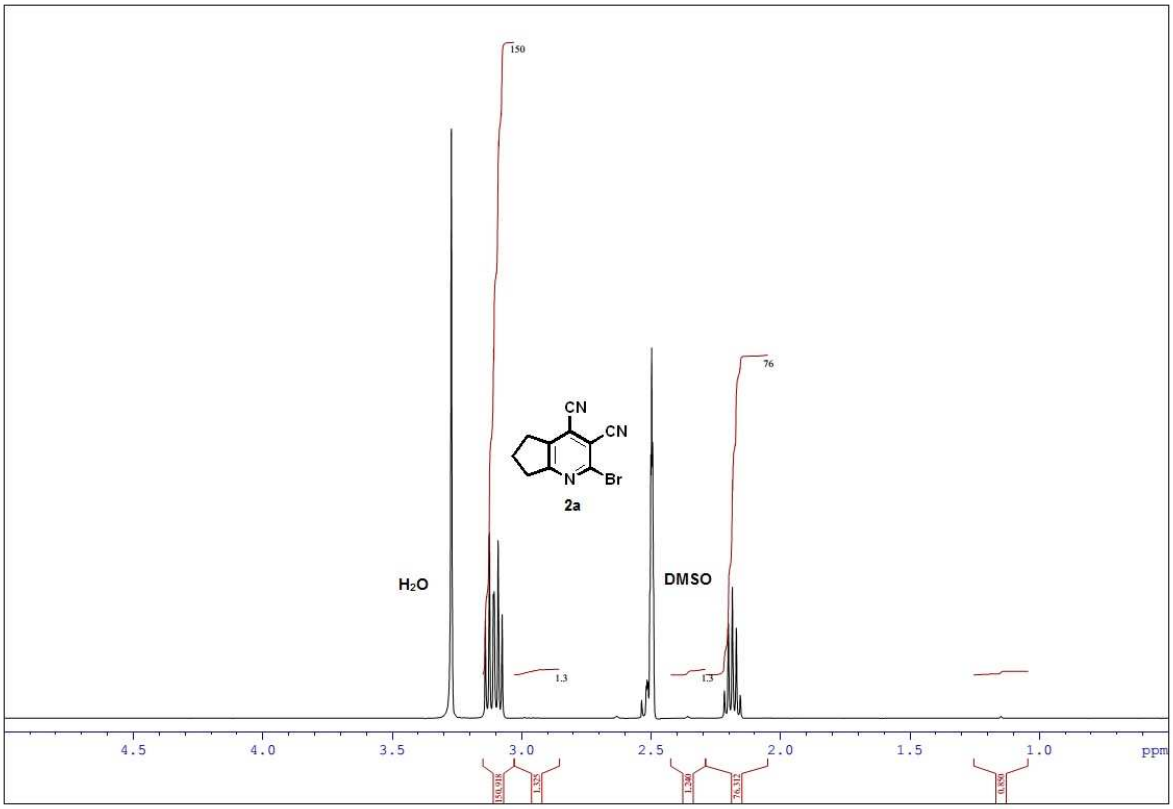
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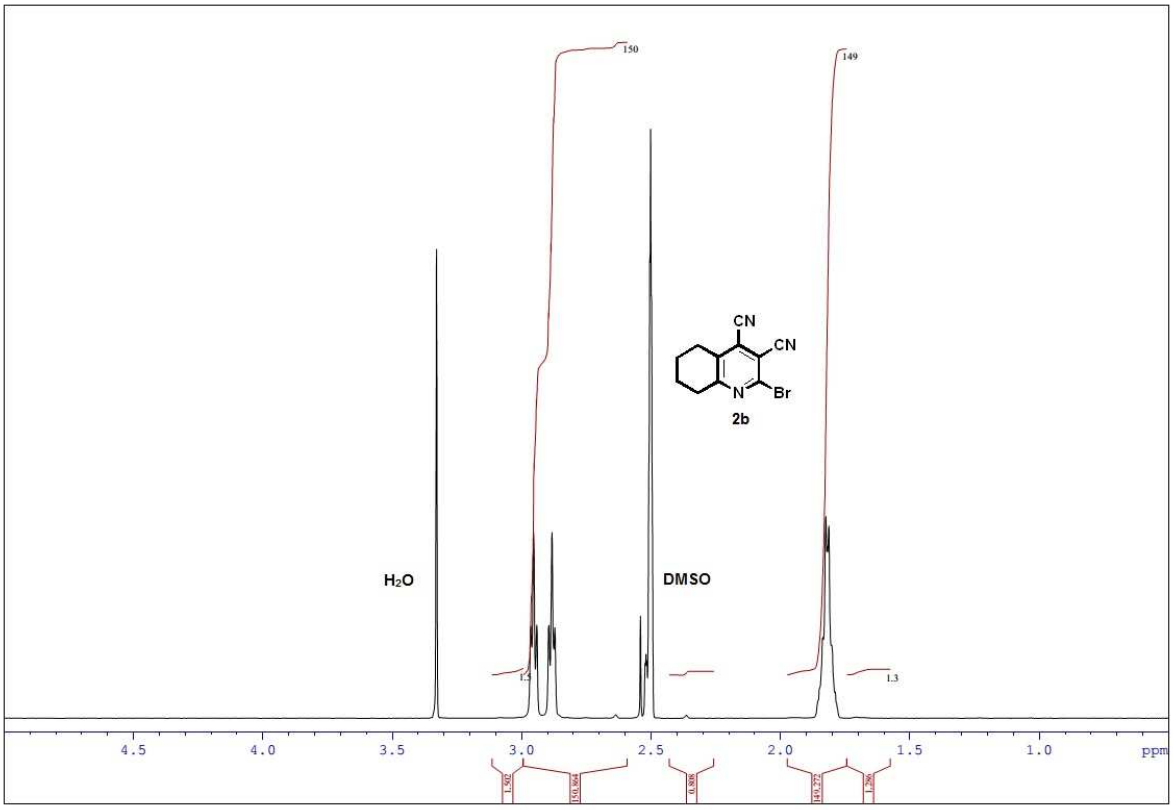
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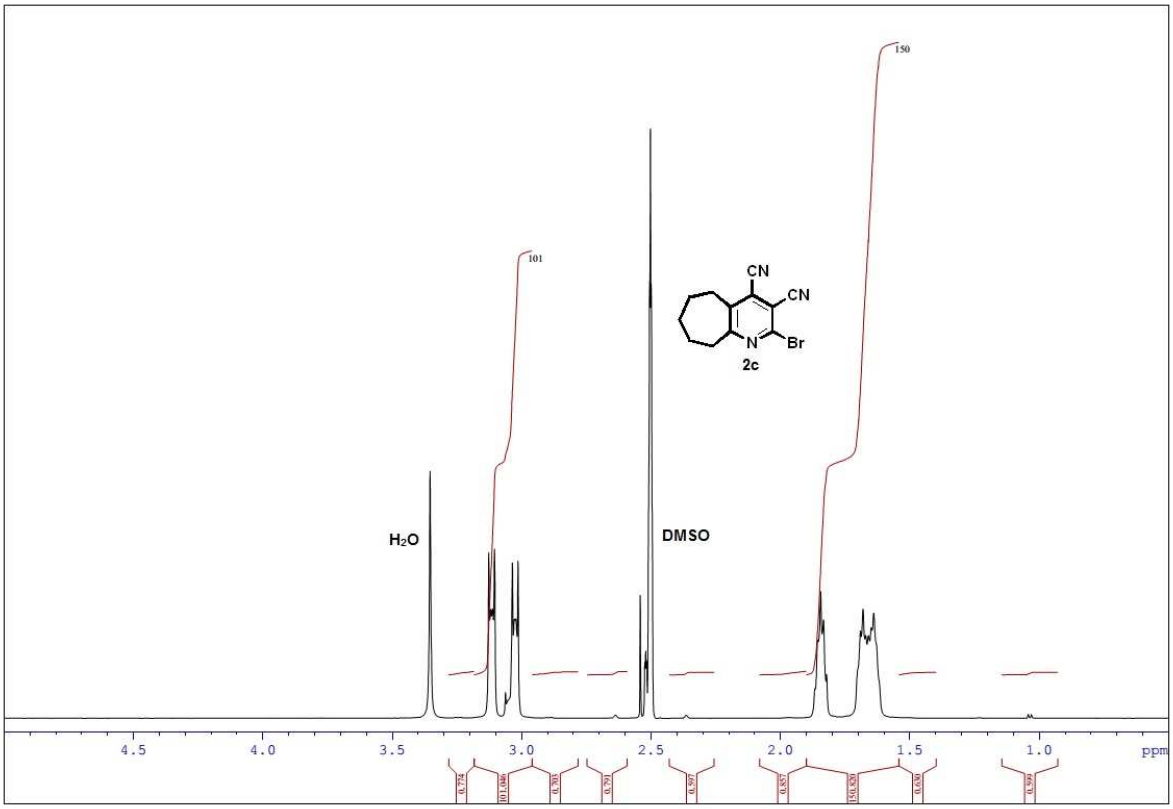
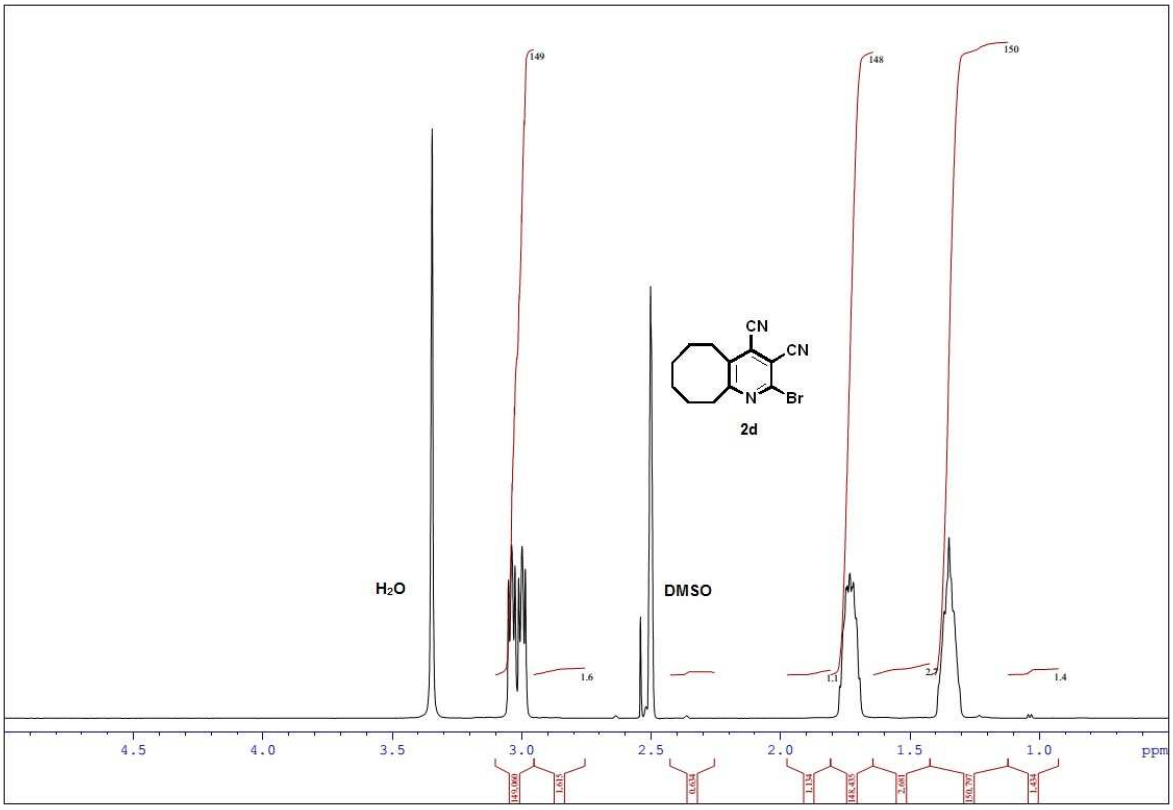
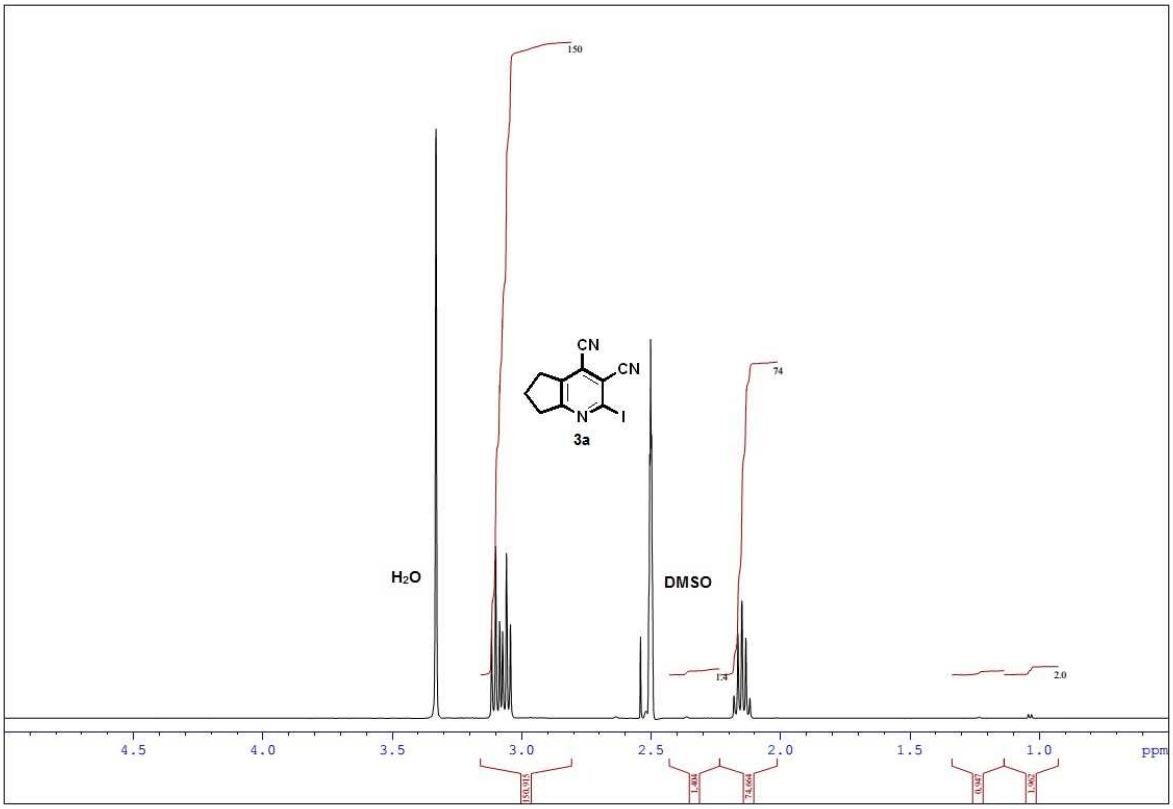
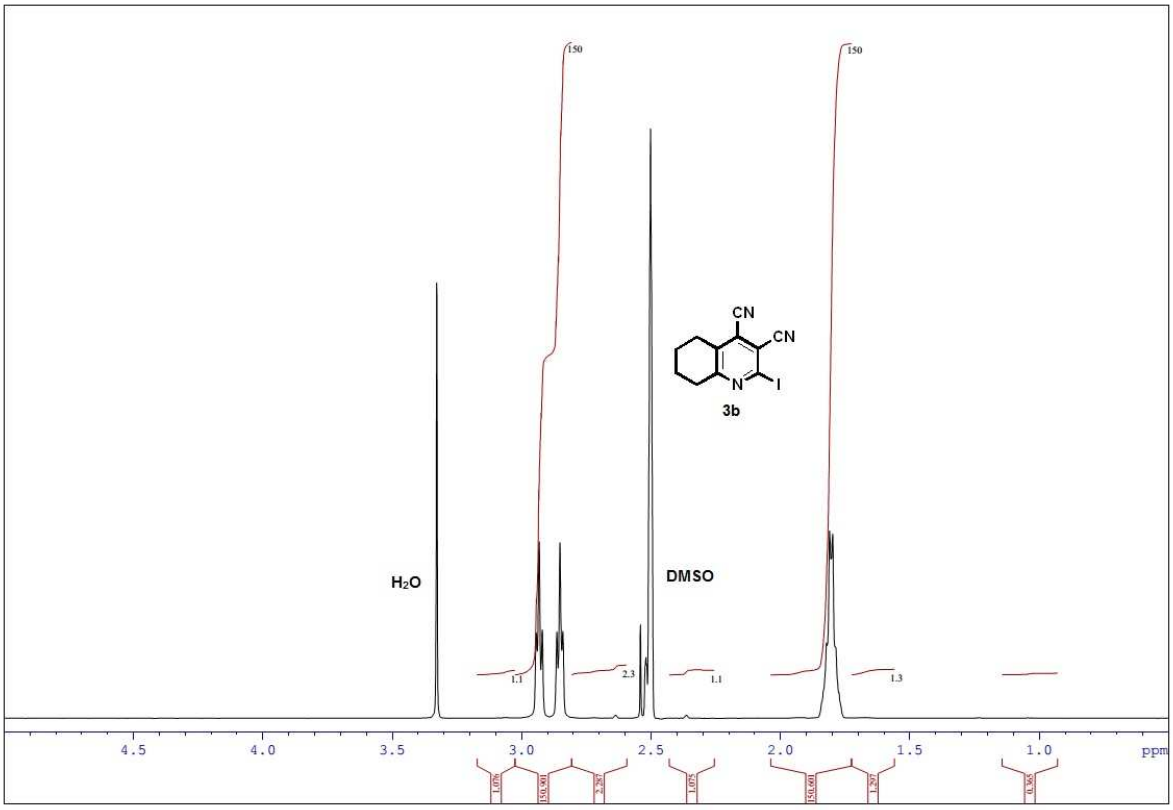
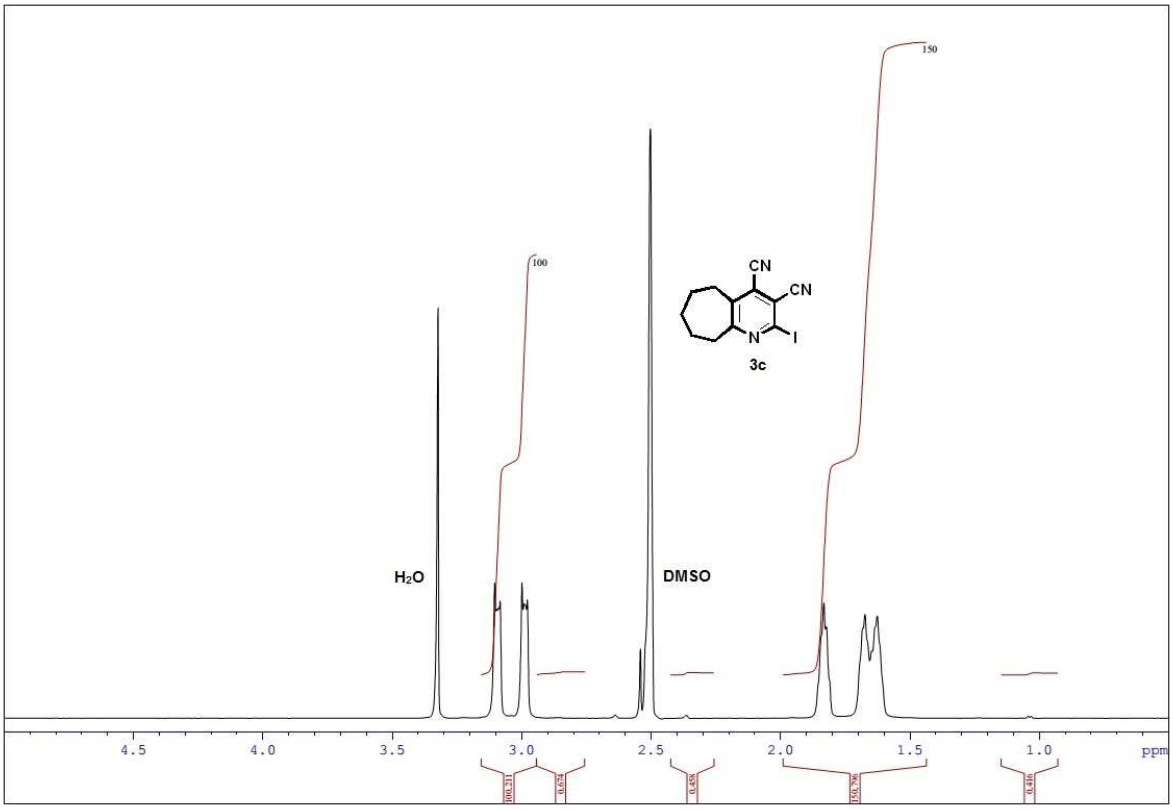
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

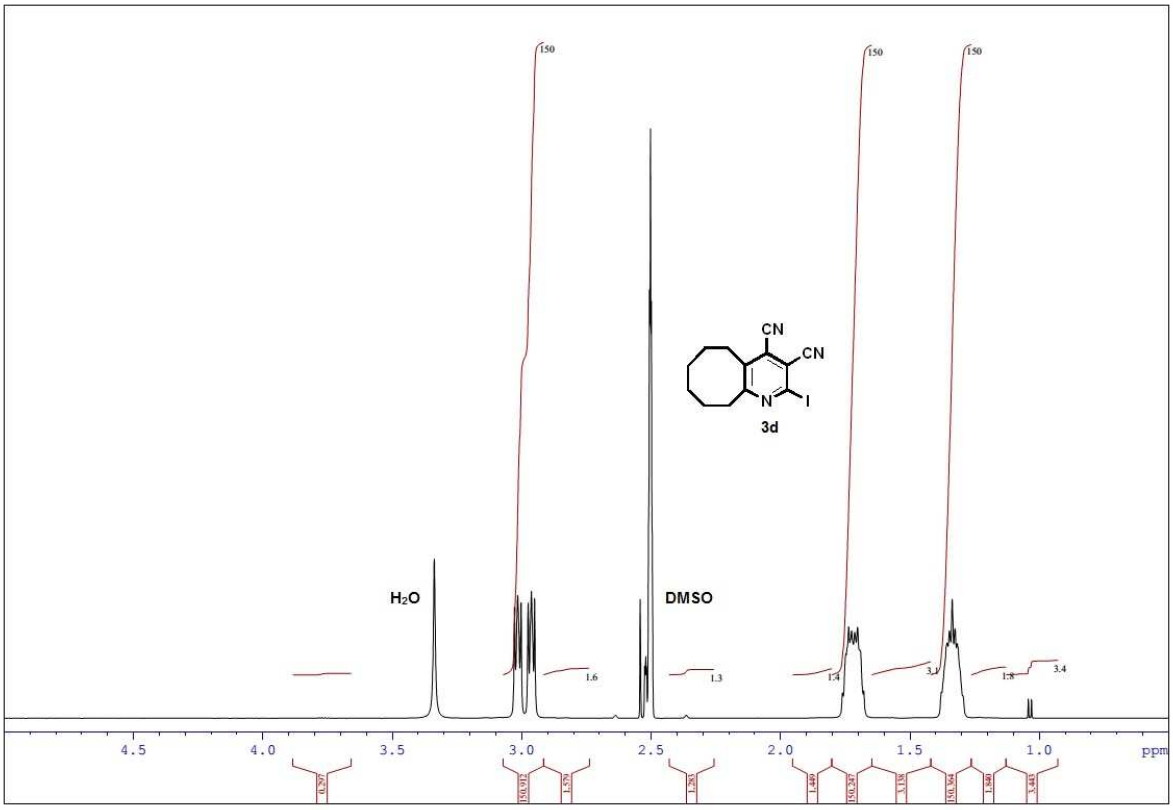

150
101
CN
CN
N
Br
2c
H₂O
DMSO
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

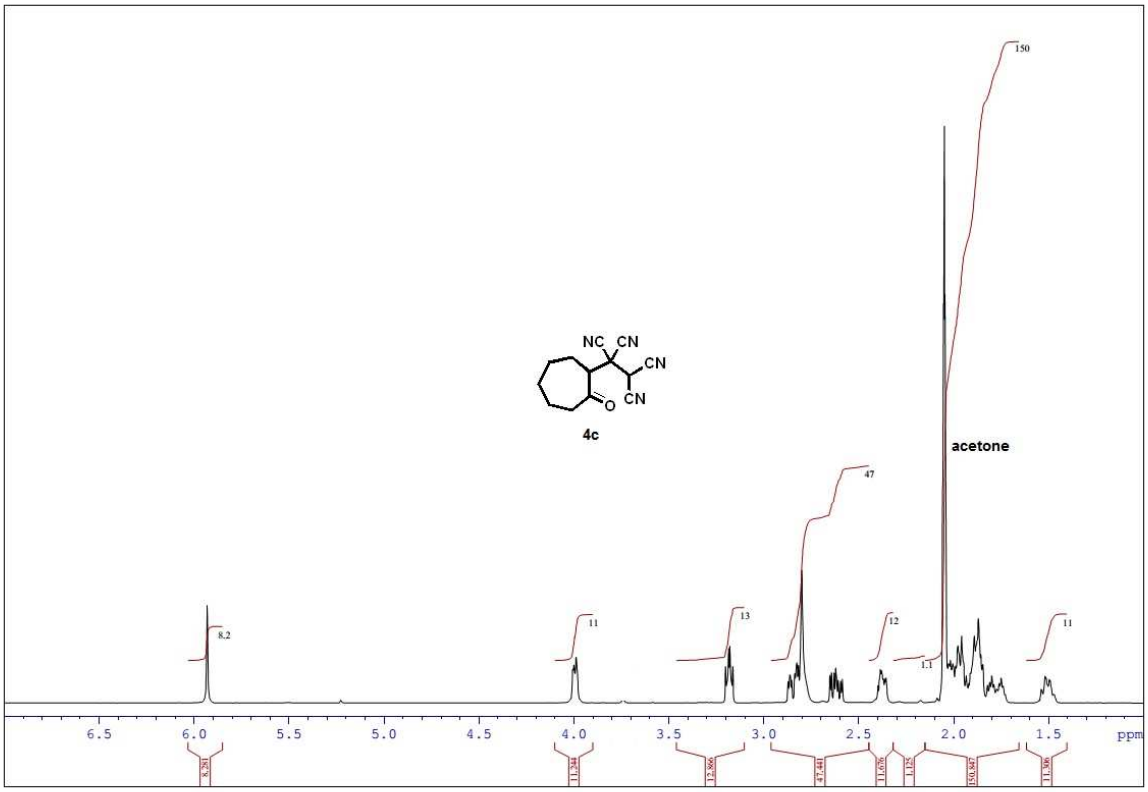

149
148
150
CN
CN
N
Br
2d
H₂O
DMSO
1.6
1.1
2.7
1.4
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

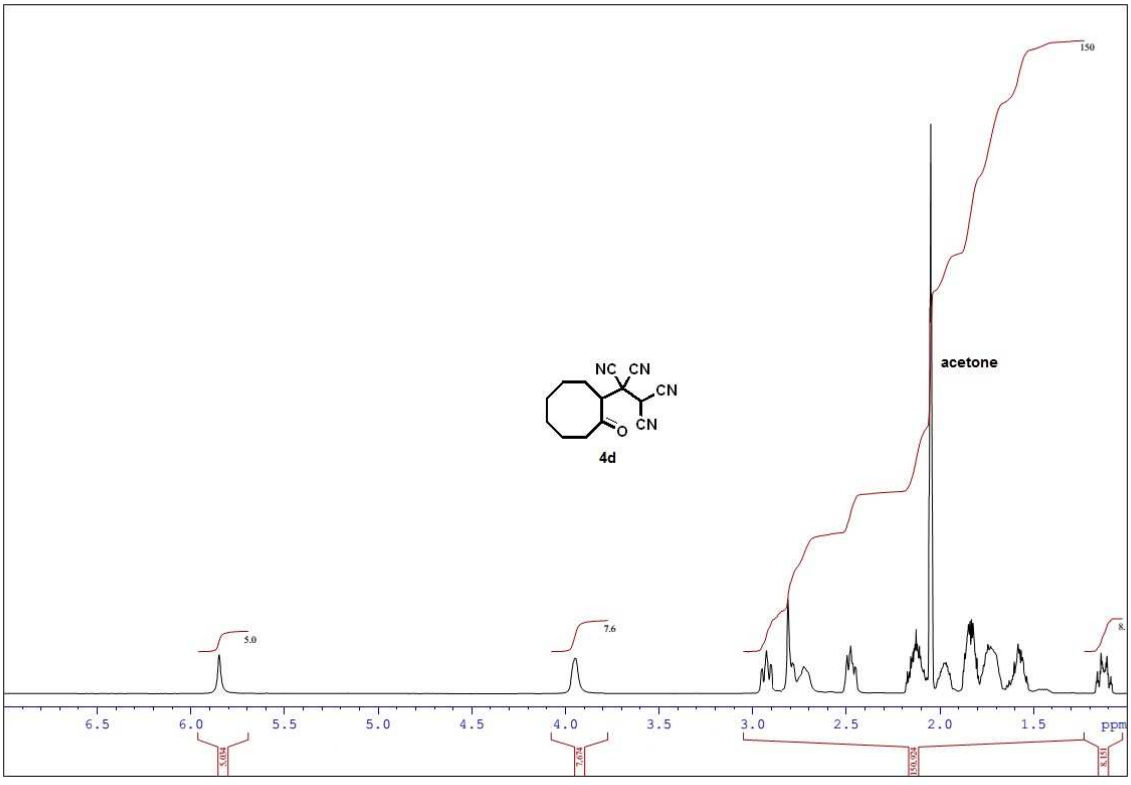

150
CN
CN
N
I
3a
74
H2O
DMSO
1.4
2.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

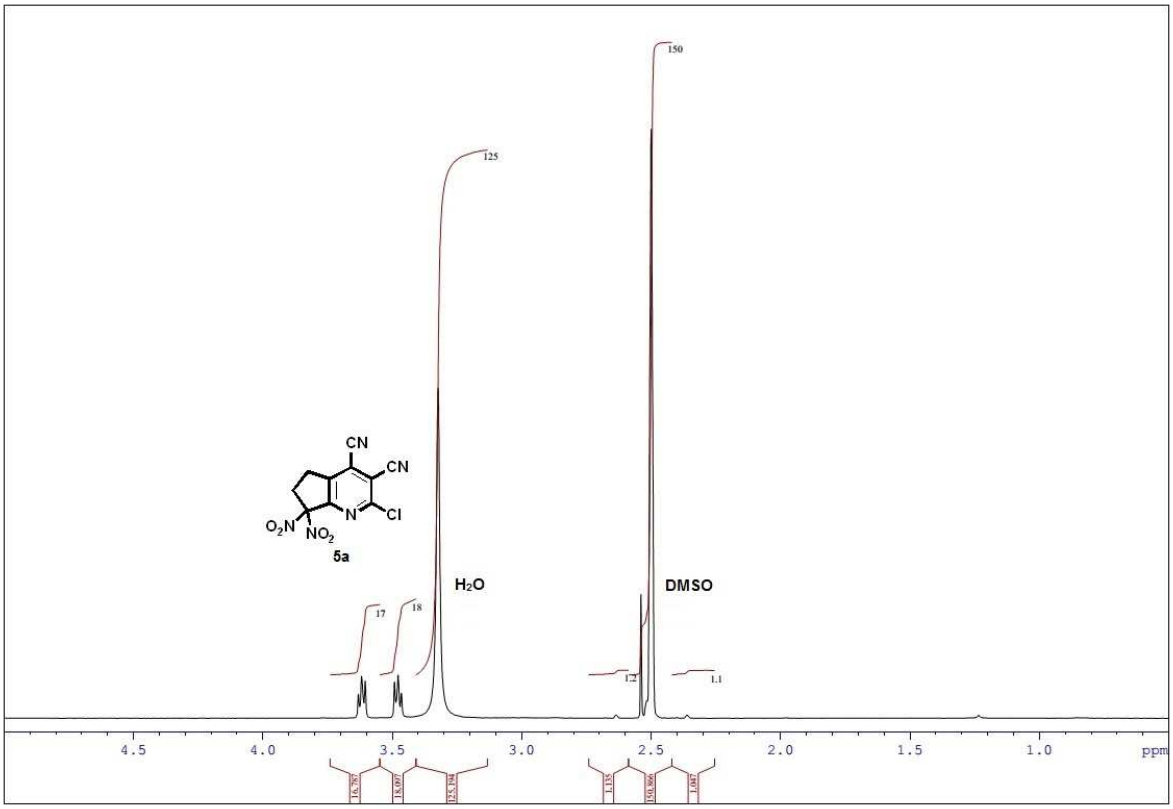

150
150
CN
CN
N
I
3b
H2O
DMSO
1.1
2.3
1.1
1.3
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

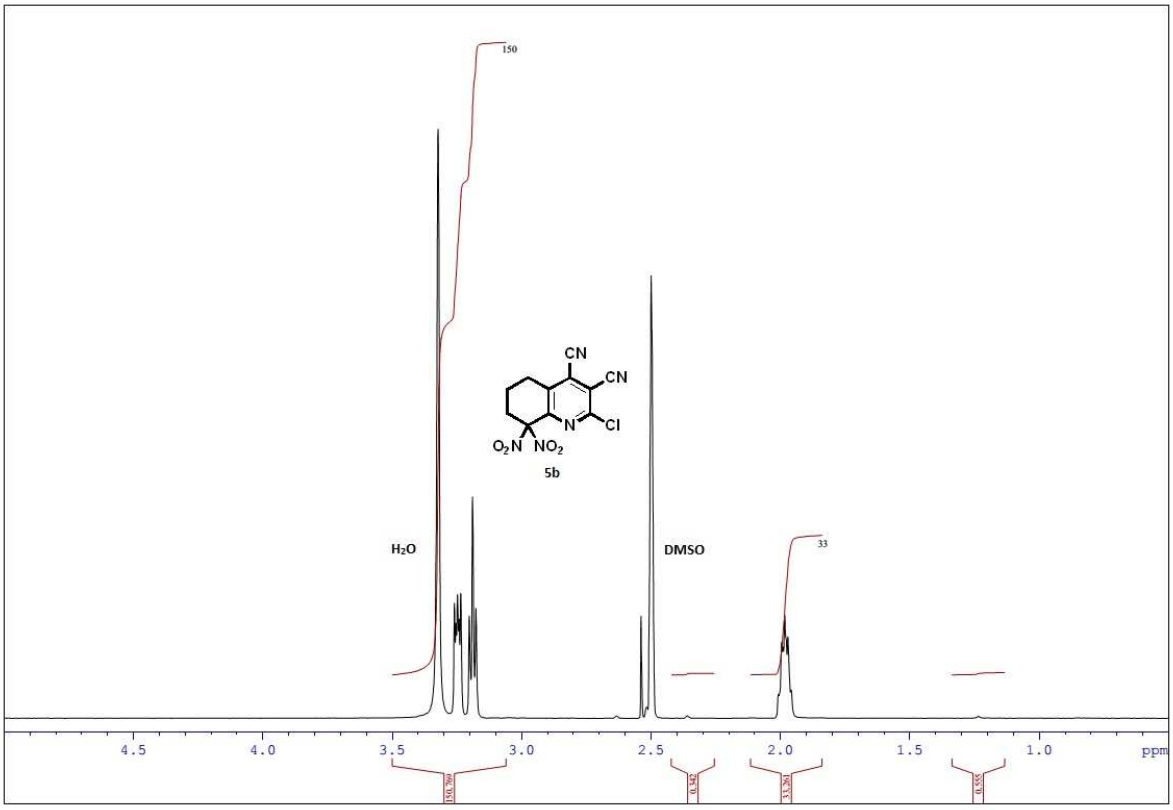

150
100
CN
CN
N
I
3c
H2O
DMSO
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

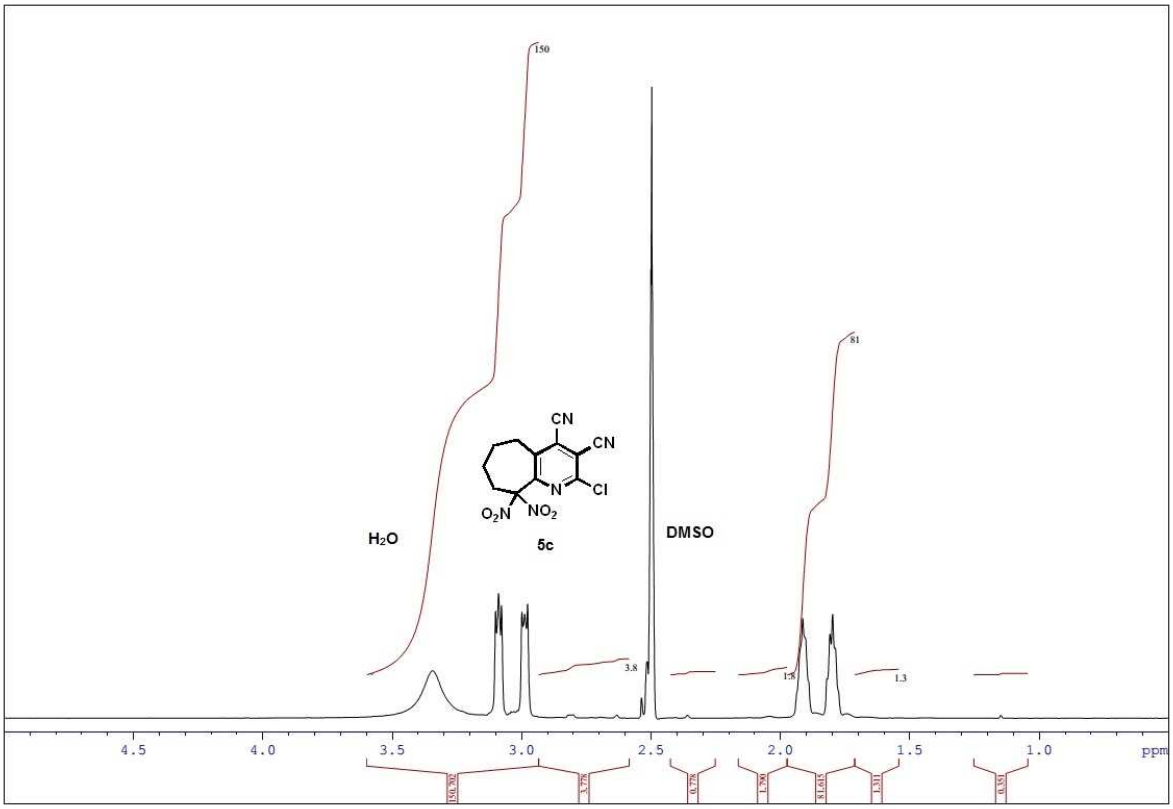

150
150
150
CN
CN
N
I
3d
H2O
DMSO
1.6
1.3
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

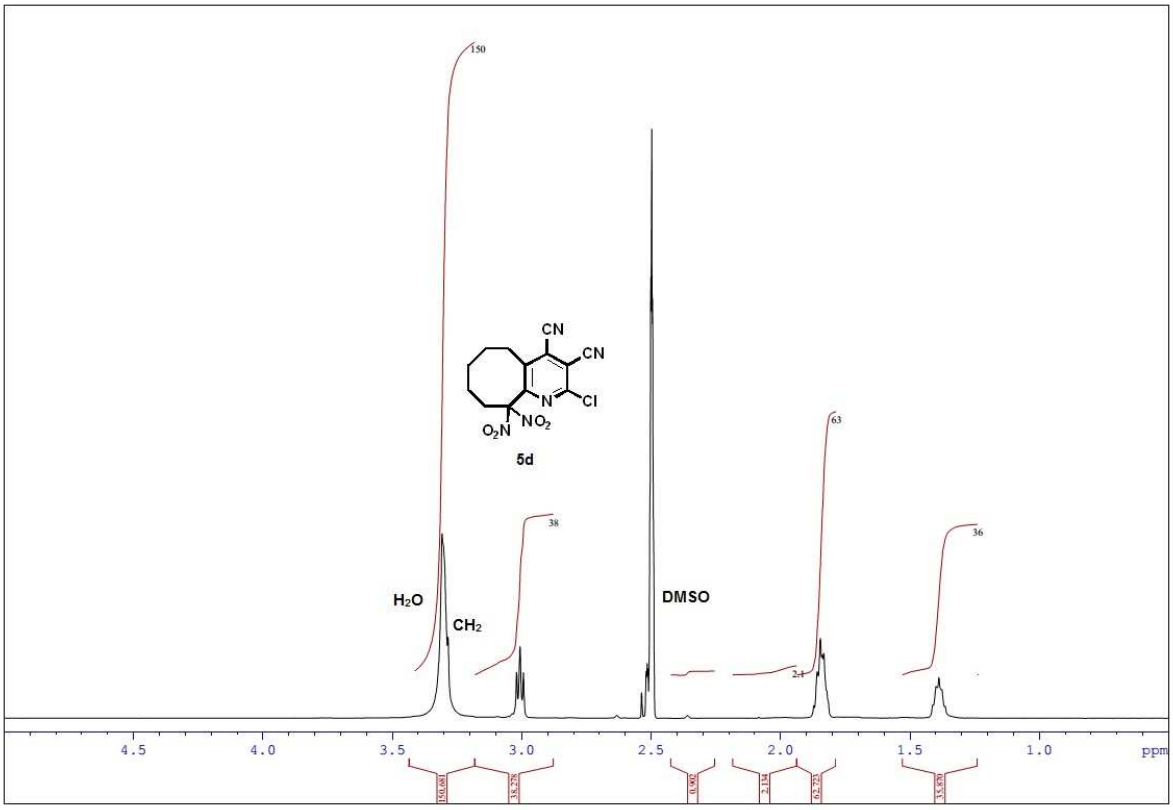

NC CN
CN
CN
O
4c
acetone
150
47
8.2
11
13
12
1.1
11
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

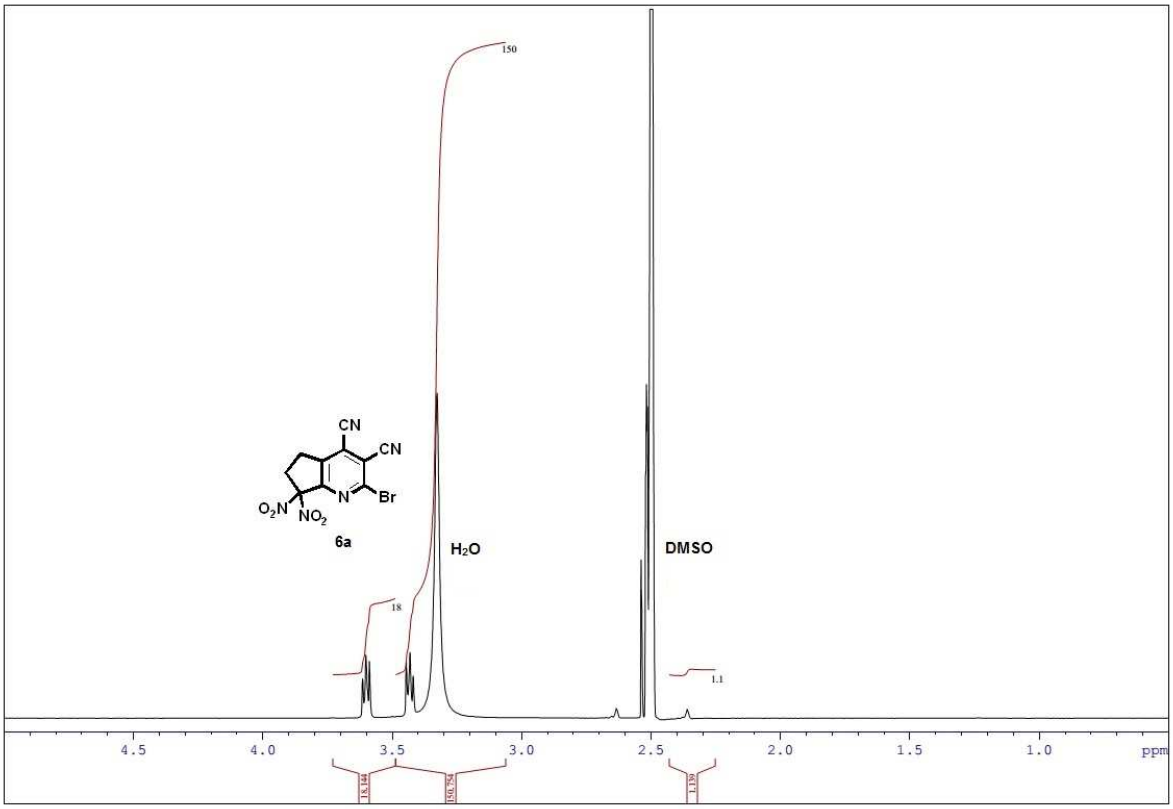

NC CN
CN
CN
O
4d
acetone
150
5.0
7.6
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

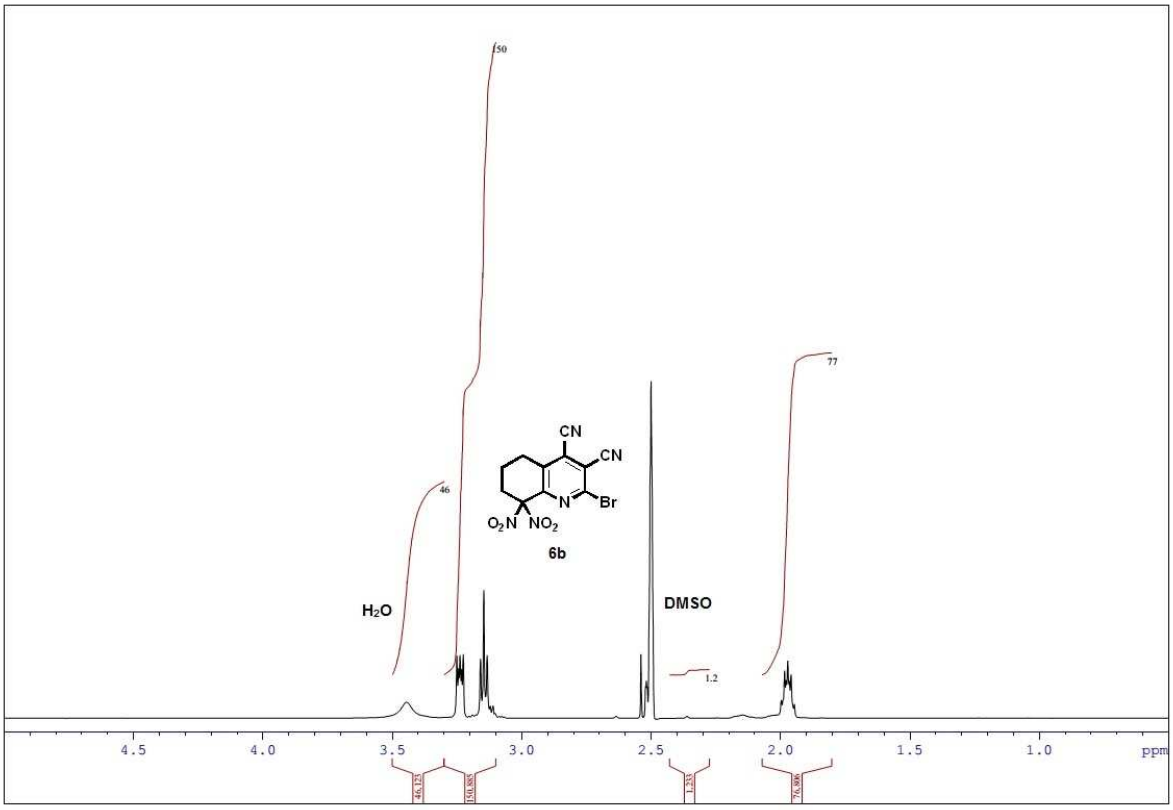

CN
CN
Cl
N
O2N
NO2
5a
H2O
DMSO
150
125
17
18
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

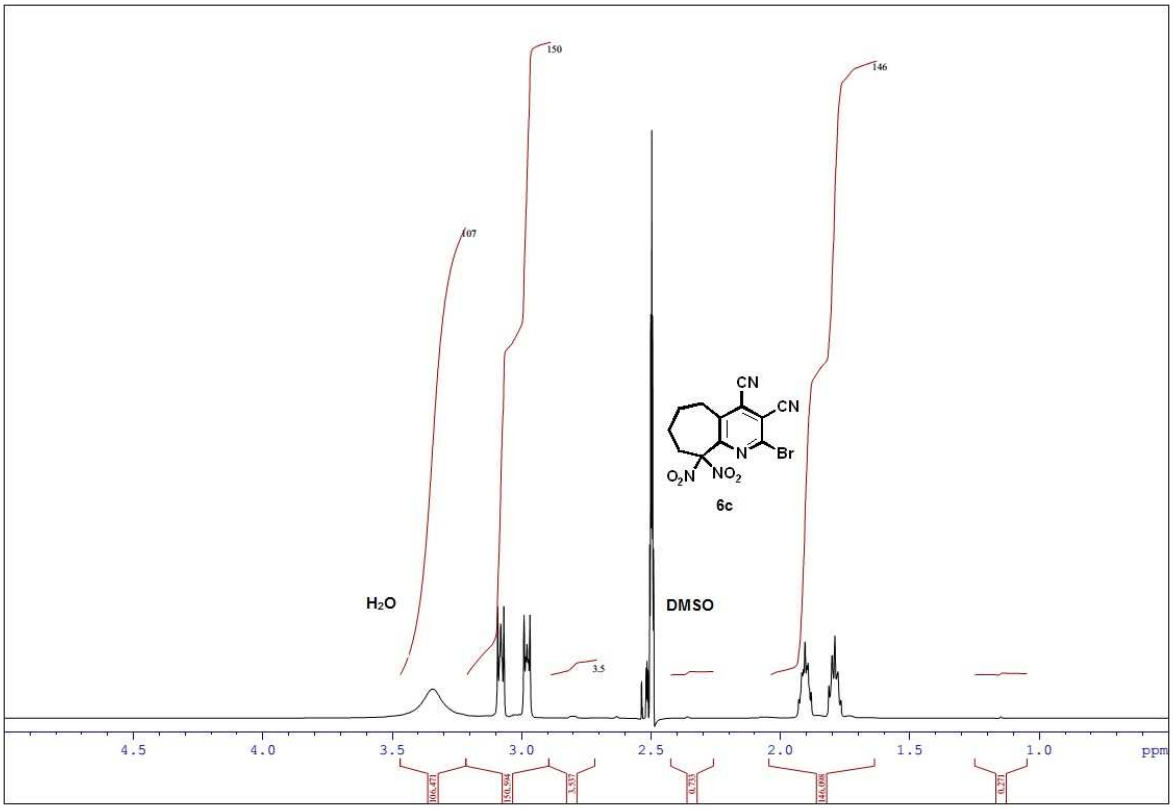

CN
CN
Cl
N
O2N
NO2
5b
H2O
DMSO
150
33
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

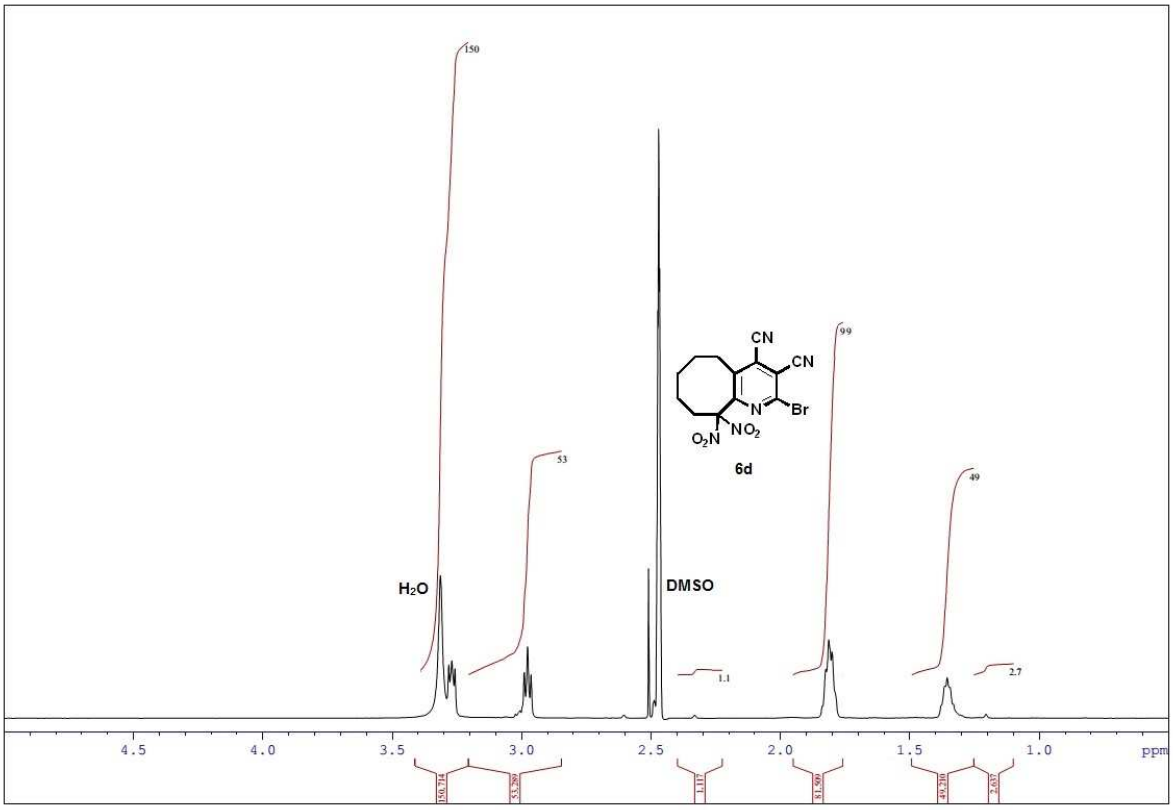

150
81
CN
CN
Cl
N
O2N
NO2
5c
H2O
DMSO
3.8
1.8
1.3
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

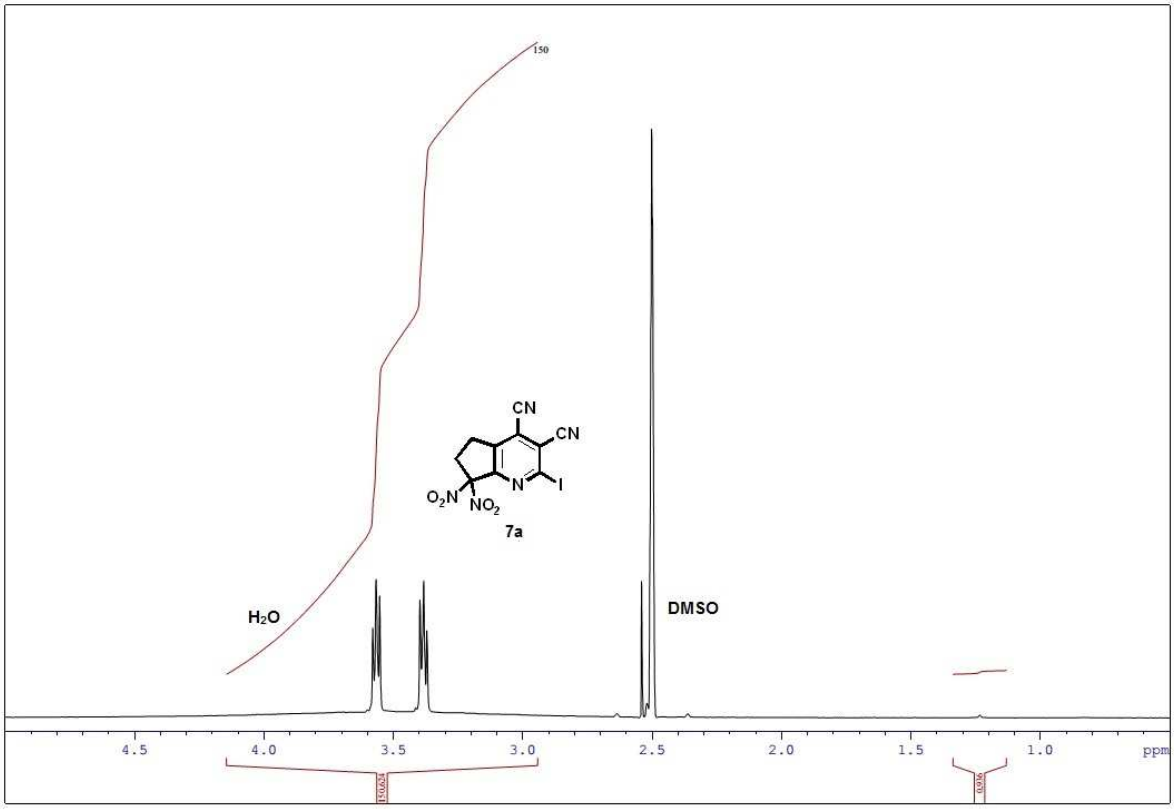

150
CN
CN
Cl
N
O2N
NO2
5d
63
38
36
H2O
CH2
DMSO
2.1
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

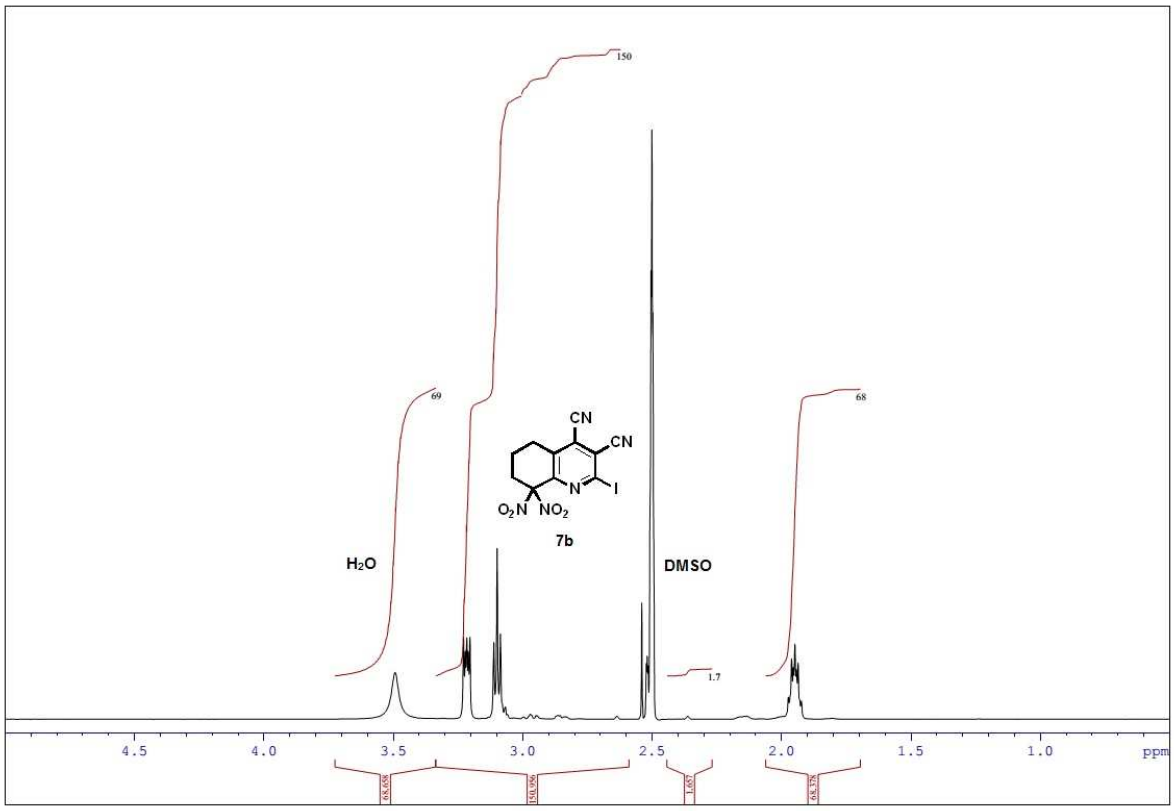

150
CN
CN
Br
N
$O_2N$ $NO_2$
6a
$H_2O$
DMSO
18
1.1
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
18.144
158.794
1.139

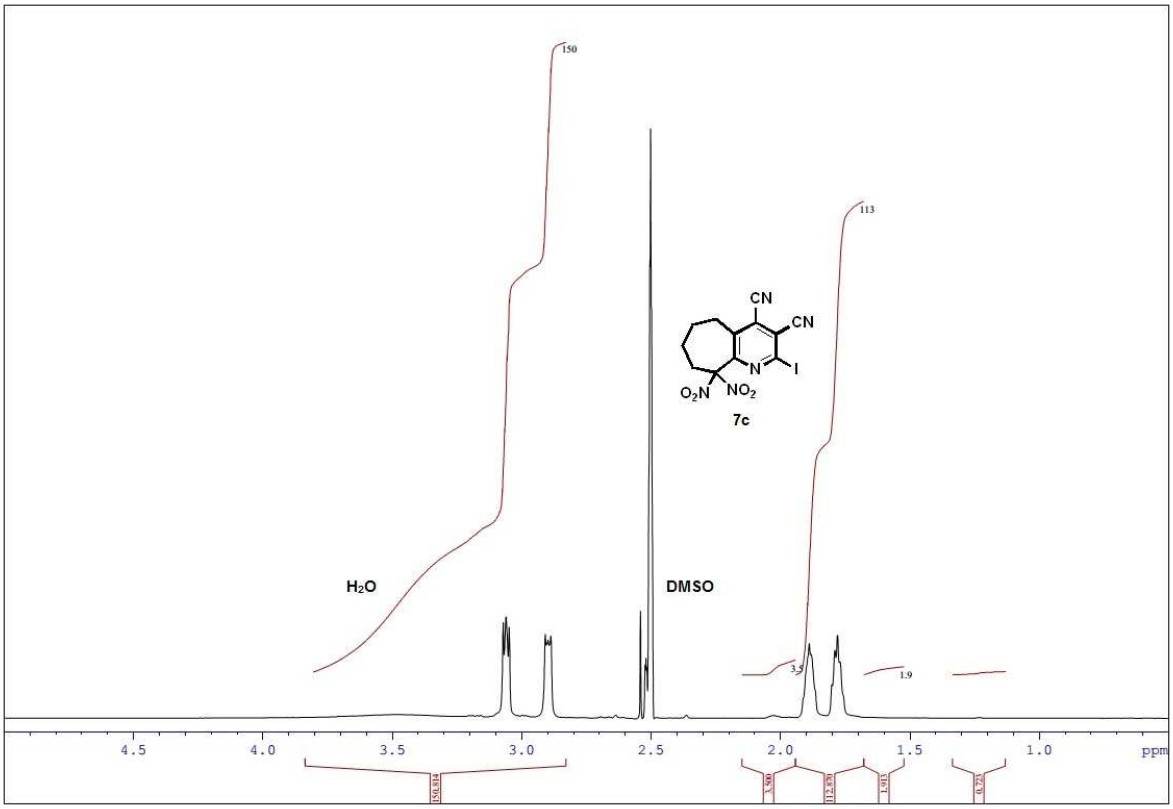

150
77
46
CN
CN
Br
N
$O_2N$ $NO_2$
6b
$H_2O$
DMSO
1.2
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
46.125
150.885
1.325
76.886

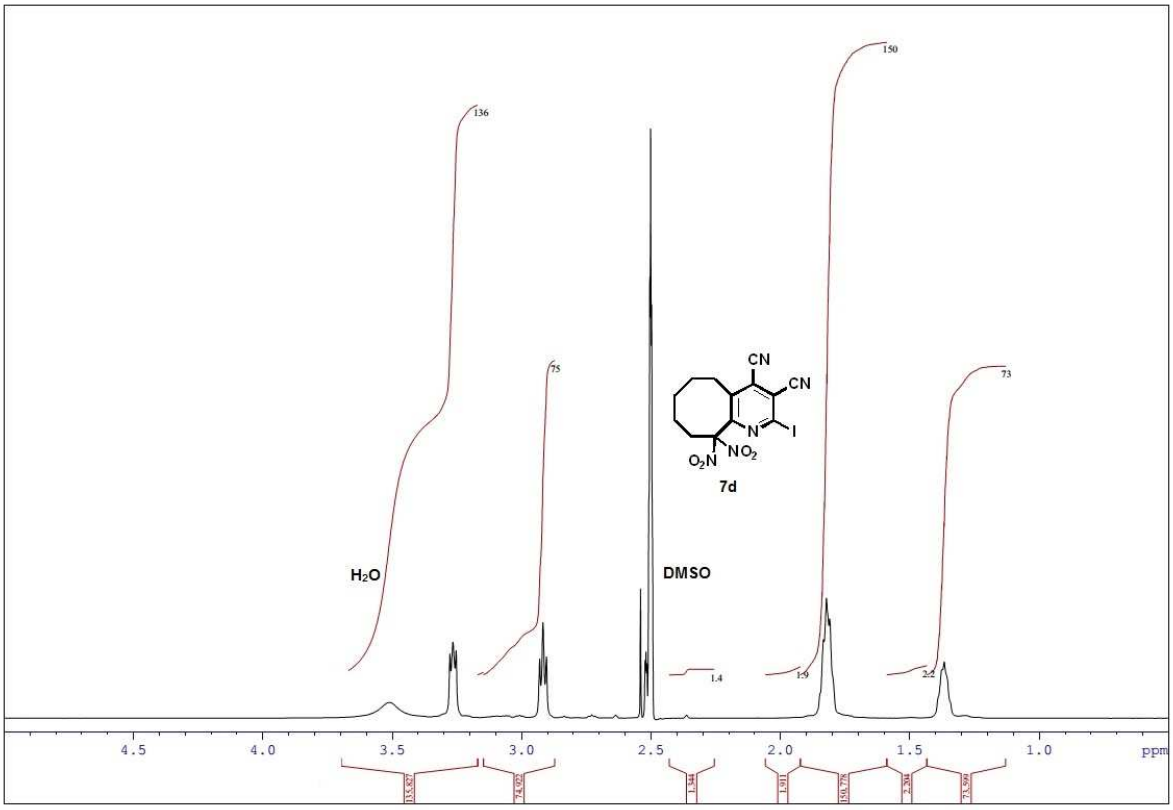

150
146
107
CN
CN
Br
N
O2N
NO2
6c
H2O
DMSO
3.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


150
99
53
49
CN
CN
Br
N
O2N
NO2
6d
H2O
DMSO
1.1
2.7
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


150
CN
CN
I
N
O2N
NO2
7a
H2O
DMSO
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
150.00
0.96


150
69
68
CN
CN
I
N
O2N
NO2
7b
H2O
DMSO
1.7
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
68.88
141.96
1.67
68.35


150
113
CN
CN
I
N
O2N
NO2
7c
H2O
DMSO
3.2
1.9
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


150
136
75
73
CN
CN
I
N
O2N
NO2
7d
H2O
DMSO
1.4
1.9
2.2
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm