

## Short Note

# 3,3'-(4,11-Bis(4-(trifluoromethyl)benzyl)-1,4,8,11-Tetraazacyclotetradecane-1,8-diyl)dipropanenitrile

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**Abstract:** The cyclam derivative (NCCH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>(<sup>4</sup>-CF<sub>3</sub>PhCH<sub>2</sub>)<sub>2</sub>Cyclam was prepared by the reaction of H<sub>2</sub>(<sup>4</sup>-CF<sub>3</sub>PhCH<sub>2</sub>)<sub>2</sub>Cyclam with acrylonitrile in methanol. The compound was fully characterized by elemental analysis, mass spectrometry as well as IR and NMR spectroscopy. Crystals of (NCCH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>(<sup>4</sup>-CF<sub>3</sub>PhCH<sub>2</sub>)<sub>2</sub>Cyclam suitable for single-crystal X-ray diffraction were obtained by the slow evaporation of a chloroform solution of the compound. The establishment of non-classical hydrogen bonds and unusual nitrile–nitrile and  $\pi(\text{CN}) \cdots \pi$  interactions determined the solid-state supramolecular architecture of (NCCH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>(<sup>4</sup>-CF<sub>3</sub>PhCH<sub>2</sub>)<sub>2</sub>Cyclam.

**Keywords:** cyclam; C–H $\cdots$ N; nitrile–nitrile;  $\pi(\text{CN}) \cdots \pi$ ; single-crystal X-ray diffraction



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## 1. Introduction

Cyclams have received considerable attention over the last few years due to their chemical and biological properties. The high kinetic and thermodynamic stability exhibited by metal complexes supported by cyclam derivatives led to their application as catalysts [1–6], radiopharmaceuticals [7–13] and metallodrugs [14–20]. The modification of the macrocyclic backbone by the attachment of substituents to nitrogen atoms is essential for the optimization of their electronic and stereochemical properties. Despite a large number of tetrasubstituted cyclams of formula R<sub>4</sub>Cyclam being described in the literature, derivatives of the type *trans,trans*-R<sub>2</sub>R'<sub>2</sub>Cyclam are much less commonly reported [11,12,20–29].

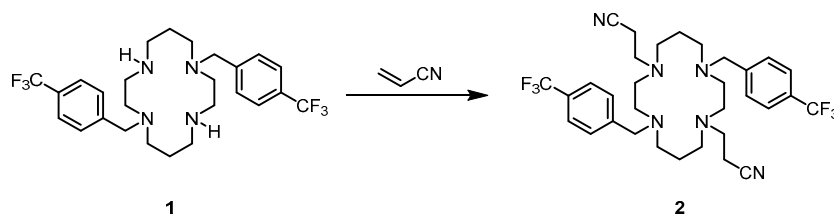
Aiming to contribute to the continuous development of cyclam-based compounds, we present herein the synthesis and structural characterization of a new tetrasubstituted cyclam derivative of formula (NCCH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>(<sup>4</sup>-CF<sub>3</sub>PhCH<sub>2</sub>)<sub>2</sub>Cyclam. By exploring the undiscovered functionalities of this type of compounds, it might be possible to unlock hidden potential applications in fields ranging from medicine to materials science.

## 2. Results and Discussion

Refluxing a methanolic solution of H<sub>2</sub>(<sup>4</sup>-CF<sub>3</sub>PhCH<sub>2</sub>)<sub>2</sub>Cyclam, **1**, with excess of acrylonitrile afforded (NCCH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>(<sup>4</sup>-CF<sub>3</sub>PhCH<sub>2</sub>)<sub>2</sub>Cyclam, **2**, in a moderated yield, as shown in Scheme 1.

The <sup>1</sup>H NMR spectrum of **2** (see Figure S1) shows five multiples for the methylene protons of the cyclam ring along with a set of resonances corresponding to the protons of the <sup>4</sup>-CF<sub>3</sub>PhCH<sub>2</sub> and NCCH<sub>2</sub>CH<sub>2</sub> pendant arms of the macrocycle. The <sup>19</sup>F NMR spectrum (see Figure S2) shows one singlet at –62.3 ppm attributed to the CF<sub>3</sub> groups of the <sup>4</sup>-CF<sub>3</sub>PhCH<sub>2</sub> pendant arms of the cyclam ring. The <sup>13</sup>C{<sup>1</sup>H} NMR spectrum (see Figure S3) is

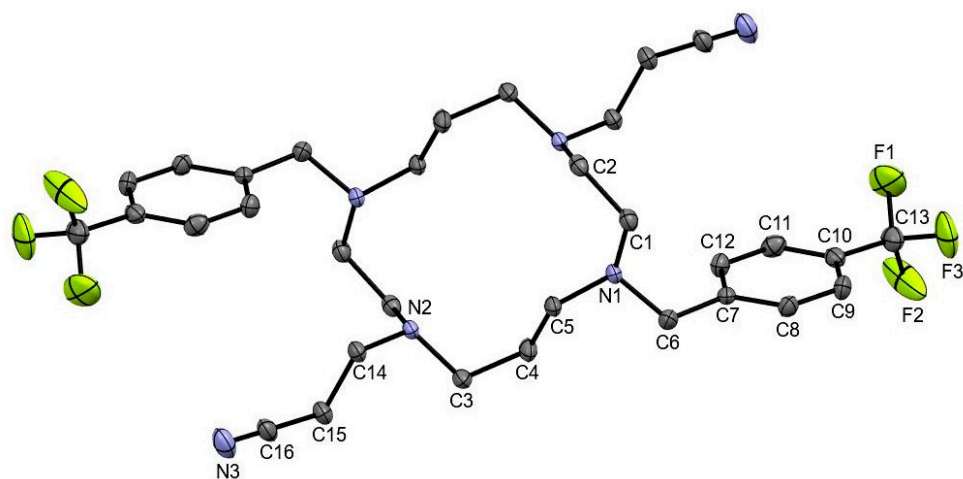
in accordance with the pattern observed in the  $^1\text{H}$  and  $^{19}\text{F}$  NMR spectra and, thus, confirms the  $C_{2v}$  symmetry of **2** in solution.



**Scheme 1.** Synthetic route for the preparation of  $(\text{NCCH}_2\text{CH}_2)_2(4\text{-CF}_3\text{PhCH}_2)_2\text{Cyclam}$ , **2**.

The infrared spectrum of compound **2** (see Figure S4) shows bands between  $2945$  and  $2797\text{ cm}^{-1}$  assigned to the  $\nu_{\text{C-H}}$  asymmetric/symmetric stretching vibrational modes of the methylene groups. The band at  $2249\text{ cm}^{-1}$  is assigned to the  $\nu_{\text{C}\equiv\text{N}}$  of the nitrile group of the  $\text{CH}_2\text{CH}_2\text{CN}$  pendant arms of the macrocycle. The  $\nu_{\text{C-C}}$  stretching (in-ring) band observed at  $1615\text{ cm}^{-1}$  is assigned to the aromatic rings. The strong absorption bands between  $1319$  and  $1156\text{ cm}^{-1}$  are due to the combination of the  $\nu_{\text{C-C}}$  and  $\nu_{\text{C-N}}$  stretching vibrational modes of the cyclam ring. The  $\nu_{\text{C-F}}$  stretching vibrational modes of the  $\text{CF}_3$  groups are observed as strong absorption bands ranging from  $1115$  to  $1063\text{ cm}^{-1}$ . The absorption band observed at  $830\text{ cm}^{-1}$  is characteristic of 1,4-disubstituted aromatic rings.

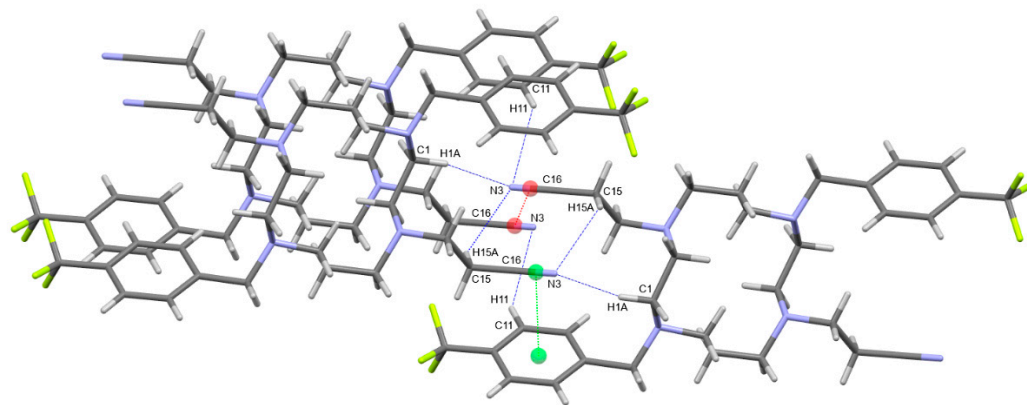
Crystals of **2** suitable for single-crystal X-ray diffraction were obtained from the slow evaporation of a chloroform solution. Crystal data for **2** ( $M = 622.70\text{ g/mol}$ ) were obtained and used in all calculations: monoclinic, space group  $C2/c$  (no. 15),  $a = 25.328(2)\text{ \AA}$ ,  $b = 5.7081(5)\text{ \AA}$ ,  $c = 24.491(2)\text{ \AA}$ ,  $\beta = 118.384(4)^\circ$ ,  $V = 3115.1(5)\text{ \AA}^3$ ,  $Z = 4$ ,  $T = 150(2)\text{ K}$ ,  $\mu(\text{MoK}\alpha) = 0.105\text{ mm}^{-1}$ ,  $D_{\text{calc}} = 1.328\text{ g/cm}^3$ , 10,078 reflections measured ( $1.905^\circ \leq \Theta \leq 27.180^\circ$ ), 3475 unique ( $R_{\text{int}} = 0.0579$ ,  $R_{\text{sigma}} = 0.0820$ ). The final  $R_1$  was 0.0642 ( $I > 2\sigma(I)$ ) and  $wR_2$  was 0.1729 (all data). The ORTEP diagram of the solid-state molecular structure of **2** is shown in Figure 1. The overall molecular shape of the macrocycle is remarkably flat and disk-like with the four nitrogen atoms coplanar, as observed in other tetrasubstituted cyclams [30]. The  $\text{N}(1)\cdots\text{N}(1\#)$  and  $\text{N}(2)\cdots\text{N}(2\#)$  transannular distances are 5.59 and 4.95  $\text{\AA}$ , respectively, which correspond to a cavity size smaller than 1.95  $\text{\AA}$  calculated from the sum [ $1.5 + 1.5 = 3.0\text{ \AA}$ ] of the van der Waals radii of two nitrogen atoms [31].



**Figure 1.** ORTEP diagram of  $(\text{NCCH}_2\text{CH}_2)_2(4\text{-CF}_3\text{PhCH}_2)_2\text{Cyclam}$ , **2**, showing thermal ellipsoids at 40% probability level. Hydrogen atoms were omitted for clarity. Half-molecule is generated by the symmetry operation  $-x + 2, -y, -z + 1$ .

The solid-state molecular structure of **2** reveals the formation of non-classical  $\text{C-H}\cdots\text{N}$  hydrogen bonds between the  $\text{C}(1)\text{-H}(1\text{A})$ ,  $\text{C}(11)\text{-H}(11)$  and  $\text{C}(15)\text{-H}(15\text{A})$  moieties and the acceptor nitrogen atom  $\text{N}(3)$  of neighboring molecules with distances of 2.520, 2.731

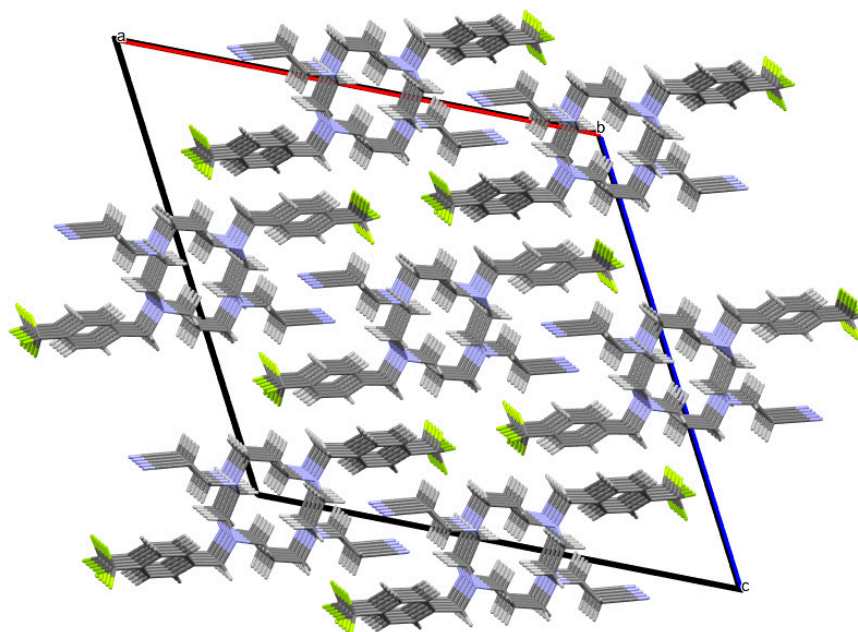
and 2.645 Å, respectively (see Table S1 for details). Unconventional antiparallel nitrile–nitrile interactions are observed with centroid-to-centroid distances of 3.563 Å between the  $\pi$ -systems of the nitrile fragments of two neighboring molecules. The corresponding C(15)–C(16) $\equiv$ N(3) angle of 179.32° attests its linearity. Unusual  $\pi$ -stacking interactions are also observed between the  $\pi$ -electrons of the nitrile group and the aromatic ring of a neighboring molecule having centroid-to-centroid distances of 3.790 Å. A detailed view of the supramolecular interactions in compound **2** is depicted in Figure 2.



**Figure 2.** Detailed view of the C–H $\cdots$ N (blue dashed lines), nitrile–nitrile (red dashed lines) and  $\pi$ (CN) $\cdots\pi$  (green dashed lines) interactions in compound **2**.

Similar C–H $\cdots$ N interactions can be observed in other cyclam derivatives containing CH<sub>2</sub>CH<sub>2</sub>CN pendant arms (NUPZII [32], ICALON [33] and ICALON01 [34]). Nevertheless, antiparallel nitrile–nitrile interactions are only observed in 3,3′-(5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane-1,8-diyl)dipropenenitrile (NUPZII) but with longer centroid-to-centroid distances (3.653 Å) [32].

The above-mentioned interactions are responsible for the tridimensional arrangement of **2** at a supramolecular level that reveals tubular chains growing along the *b* direction (see Figure 3).



**Figure 3.** View of the supramolecular assembly of compound **2** along the *b* axis.

### 3. Materials and Methods

#### 3.1. General Considerations

Compound **1** was prepared according to a previously published procedure [6]. All other reagents and solvents were commercial grade and used without purification. NMR spectra were recorded in a Bruker AVANCE II 300 MHz spectrometer, at 296 K, referenced internally to residual proton-solvent ( $^1\text{H}$ ) or solvent ( $^{13}\text{C}$ ) resonances, and reported relative to tetramethylsilane (0 ppm). Two-dimensional NMR experiments such as  $^1\text{H}$ - $^{13}\text{C}$  HSQC and  $^1\text{H}$ - $^1\text{H}$  COSY were carried out to make all the assignments. The infrared spectrum was acquired using a Bruker ALPHA II ATR spectrometer with an individual diamond in the range of  $3400\text{--}400\text{ cm}^{-1}$  at a resolution of  $4\text{ cm}^{-1}$ . Elemental analysis was performed at the SSADS-CACTI UVIGO Laboratory, Spain, using a FISON EA-1108 automatic analyzer instrument. The mass spectrum was performed at the Structural Analysis Lab of the Faculty of Pharmacy of the University of Lisbon, Portugal, using a Acquity<sup>TM</sup> triple-quadrupole mass spectrometer (Waters®, Wexford, Ireland) operating with an electrospray ionization (ESI) source at  $120\text{ }^\circ\text{C}$  and applying a capillary voltage of 3.0 kV and a sampling-cone voltage of 60 V. Acetonitrile was used as the solvent and nitrogen was used as both the drying and nebulizing gas.

#### 3.2. Synthesis and Characterization

$(\text{NCCH}_2\text{CH}_2)_2(^4\text{-CF}_3\text{PhCH}_2)_2\text{Cyclam}$ , **2**: Compound **1** (0.47 g, 0.91 mmol) was dissolved in methanol (15 mL) and acrylonitrile was added (0.30 mL, 4.58 mmol). The reaction mixture was refluxed overnight. The volume of the solution was reduced by the evaporation of the solvent in a rotavapor, and the concentrated solution was placed in the freezer. The product precipitated out of solution as a white solid that was isolated by filtration, washed with diethyl ether, and dried in vacuum. Yield: 58% (0.33 g, 0.53 mmol).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300.1 MHz, 296 K):  $\delta$  (ppm) 7.58 (d, 4H,  $^3J_{\text{H-H}} = 8.1\text{ Hz}$ , Ph), 7.47 (d, 4H,  $^3J_{\text{H-H}} = 7.8\text{ Hz}$ , Ph), 3.58 (s, 4H,  $\text{CH}_2\text{Ph}$ ), 2.64–2.56 (overlapping, 16H total, 4H,  $[\text{C}3]\text{CH}_2\text{N}$ , 8H,  $[\text{C}2]\text{CH}_2\text{N}$  and 4H,  $\alpha\text{-CH}_2$ ), 2.52–2.47 (m, 4H,  $[\text{C}3]\text{CH}_2\text{N}$ ), 2.35 (t,  $^3J_{\text{H-H}} = 6.7\text{ Hz}$ , 4H,  $\beta\text{-CH}_2$ ), 1.74–1.68 (m, 4H,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ).  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz, 296 K):  $\delta$  (ppm) 144.2 (*i*-Ph), 129.4 (q,  $^2J_{\text{C-F}} = 32.5\text{ Hz}$ , *p*-Ph), 129.2 (*o*-Ph), 125.3 (q,  $^3J_{\text{C-F}} = 3.8\text{ Hz}$ , *m*-Ph), 124.4 (q,  $^1J_{\text{C-F}} = 271.8\text{ Hz}$ ,  $\text{CF}_3$ ), 119.2 (CN), 59.2 ( $\text{CH}_2\text{Ph}$ ), 51.5 ( $\text{CH}_2$ ), 51.4 ( $\text{CH}_2$ ), 51.3 ( $\text{CH}_2$ ), 51.1 ( $\text{CH}_2$ ), 50.0 ( $\text{CH}_2$ ), 24.5 ( $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 16.4 ( $\beta\text{-CH}_2$ ).  $^{19}\text{F}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 282.2 MHz, 296 K):  $\delta$  (ppm) -62.3 ( $\text{CF}_3$ ). FT-IR (ATR,  $\text{cm}^{-1}$ ): 2945 ( $\nu_{\text{C-H}}$ ), 2797 ( $\nu_{\text{C-H}}$ ), 2249 ( $\nu_{\text{C}\equiv\text{N}}$ ), 1615 ( $\nu_{\text{C}=\text{C}}$ ), 1355 ( $\nu_{\text{C-C}}$ ,  $\nu_{\text{C-N}}$ ), 1319 ( $\nu_{\text{C-C}}$ ,  $\nu_{\text{C-N}}$ ), 1279 ( $\nu_{\text{C-C}}$ ,  $\nu_{\text{C-N}}$ ), 1156 ( $\nu_{\text{C-C}}$ ,  $\nu_{\text{C-N}}$ ), 1115 ( $\nu_{\text{C-F}}$ ), 1102 ( $\nu_{\text{C-F}}$ ), 1063 ( $\nu_{\text{C-F}}$ ), 830 ( $\nu_{\text{C}=\text{C}}$ ). ESI-MS ( $m/z$ ): 623  $[\text{C}_{32}\text{H}_{41}\text{F}_6\text{N}_6]^+$ , 465  $[\text{C}_{24}\text{H}_{36}\text{F}_3\text{N}_6]^+$ . Anal. calcd for  $\text{C}_{32}\text{H}_{40}\text{F}_6\text{N}_6\cdot\text{H}_2\text{O}$ : C, 59.99; H, 6.61; N, 13.12. Found: C, 60.29; H, 7.19; N, 13.90.

#### 3.3. General Procedure for Single Crystal X-ray Crystallography

Crystals of compound **2** suitable for single-crystal X-ray diffraction were coated and mounted on a loop with Fomblin<sup>®</sup> oil. Data were collected using graphite-monochromated Mo-K $\alpha$  radiation ( $\lambda = 0.71073\text{ \AA}$ ) on a Bruker AXS-KAPPA APEX II diffractometer (Bruker AXS Inc., Madison, WI, USA) equipped with an Oxford Cryosystem open-flow nitrogen cryostat at 150(2) K. Data were corrected for Lorentzian polarization and absorption effects using the SAINT [35] and SADABS [36] programs. SIR2004 [37] was used for structure solution and SHELXL-2014/7 [38] was used for full-matrix least-squares refinement on  $F^2$ . These programs are included in the WinGX-Version 2023.1 program package [39]. The hydrogen atoms were inserted in idealized positions and allowed to refine in the parent carbon atom. Crystallographic and experimental details of data collection and crystal structure determinations are available in Table S2. Illustrations of the molecular structures were made with MERCURY 2022.3.0 [40].



**Supplementary Materials:** Crystallographic data (Tables S1 and S2), NMR spectra (Figures S1–S3), IR spectrum (Figure S4) and ESI-MS spectrum (Figure S5) of compound 2 are presented as supporting information and can be downloaded online Data for 2 was deposited in the Cambridge Crystallographic Data Centre (CCDC) under the deposit number 2337050 and can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html>.

**Author Contributions:** I.M.N. and L.G.A. performed the synthesis and characterization of the compound; L.G.A. and E.R.S. supervised the experiments and wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

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**Data Availability Statement:** The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

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**Conflicts of Interest:** The authors declare no conflicts of interest.

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