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Structural and spectroscopic investigation on a new potentially bioactive di-hydrazone containing thiophene heterocyclic rings

Vanessa de S. Nogueira [a], Maria Clara Ramalho Freitas [b], Wellington S. Cruz [a], Tatiana S. Ribeiro [c], Jackson A.L.C. Resende [b], Nicolás A. Rey [a, *]

[a] Department of Chemistry, PUC-Rio, Rua Marquês de São Vicente, 225, 22453-900, Rio de Janeiro, RJ, Brazil
[b] Institute of Chemistry, UFF, Outeiro de São João Batista, s/n, 24020-141, Niterói, RJ, Brazil
[c] DCNME, UFSCar, Rodovia Anhanguera, km 174, 13600-970, Araras, SP, Brazil

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ABSTRACT

Hydrazones and several substituted hydrazones are associated with a broad spectrum of biological activities, as well as compounds containing the thiophene ring. In this context, a novel di-hydrazone derived from 2-thiophenecarboxylic acid hydrazide was synthesized and completely characterized by elemental analysis, XRD, FT-IR, Raman and UV–Vis spectroscopies, thermogravimetry, ^{1}H NMR, ^{1}H–^{1}H COSY and ^{1}H–^{1}H ROESY. A preliminary *in silico* pharmacological evaluation was also performed in order to assess the performance of the new compound regarding some molecular properties relevant for a drug's pharmacokinetics in the human body.

1. Introduction

Hydrazones are a class of organic compounds defined by the presence of the functional group $R_1R_2C{=}N{-}NR_3R_4$ [1]. Literature studies reveal that hydrazones and several substituted hydrazones are associated with a broad spectrum of biological activities, such as analgesic [2], antihypertensive [3], anticonvulsant [4], anti-inflammatory [5], anti-TB [6,7], antitumor [8,9], anti-HIV [10,11], antimalarial [12], antidepressant [13], and vasodilatory [14]. Very recently, anti-Alzheimer activity was also reported for hydrazones derived from 8-hydroxyquinoline-2-carboxaldehyde [15,16]. It is known that the interesting biological properties of carbonyl-containing hydrazones are related to the presence of the $R_1R_2C{=}N{-}NH{-}CO{-}$ pharmacophore [1], which also allows for those compounds to act as bidentate ligands, coordinating biometals through the azomethine nitrogen and the carbonyl oxygen. Our research group at the Pontifical Catholic University of Rio de Janeiro (PUC-Rio) has some experience in the synthesis of heterocyclic hydrazones [17,18].

On the other hand, thiophene belongs to a class of heterocyclic sulfur compounds containing a five-membered ring [19]. Its structure is similar to that of pyrrole and constitutes one of the most important classes of heterocycles, presenting a variety of actions [20], such as antimicrobial [21,22], antitumoral [23], analgesic and anti-inflammatory [24], antihypertensive [25], anti-diabetes [26], inhibitory activity of cholesterol [27], anti-allergic [28], insecticide [29] and antioxidant [30]. Thiophene can be attached to various heterocyclic systems giving rise to new compounds, which exhibit a broad range of biological effects, and reduced toxicity [31].

In view of the intrinsic biological relevance of both hydrazones and thiophene, and based on the well-known concept of hybrid drugs, this paper reports on the synthesis of a novel di-hydrazone, obtained by condensation between 2,5-dimethoxytereph thalaldehyde and 2-thiophenecarboxylic acid hydrazide. This compound was characterized by elemental analysis, X-ray crystallography, FT-IR, Raman and UV–Vis spectroscopies, thermogravimetry, ^{1}H NMR, ^{1}H–^{1}H COSY and ^{1}H–^{1}H ROESY experiments. A preliminary *in silico* (computational) pharmacological evaluation was also performed in order to assess the performance of the synthesized compound regarding some molecular properties relevant for a drug's pharmacokinetics in the human body.

* Corresponding author.
E-mail address: nicoarey@puc-rio.br (N.A. Rey).

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2. Experimental methods

2.1. Syntheses of the target compound and its precursors

For the preparation of the desired di-hydrazone, we chose a protocol that involves the synthesis of a symmetrical precursor center, namely, 2,5-dimethoxyterephthalaldehyde, which is obtained from 2,5-bis(chloromethyl)-1,4-dimethoxybenzene. This compound was, in turn, prepared from the starting material 1,4-dimethoxybenzene (Scheme 1, top). All chemicals were purchased from commercial sources and used without further purification.

2.1.1. 2,5-bis(chloromethyl)-1,4-dimethoxybenzene (*I*)

This compound was prepared in the way described in literature [32]. Yield: 39.3 g (23%) of a white powder, m.p. 164 °C (literature m.p.: 165 °C). **Main IR bands** (KBr): 3050, 3019, 2966, 2938, 2837, 1512, 1464, 1432, 1409, 1319, 1259, 1224, 1179, 1136, 1041, 913, 877, 736, 680, 609, 475 cm^{-1}. **^{1}H NMR** (DMSO-d_6, 300 MHz): 3.78 ppm (s, 6H, $-OCH_3$); 4.67 ppm (s, 4H, $-CH_2Cl$); 7.12 ppm (s, 2H, aromatic ring).

2.1.2. 2,5-dimethoxyterephthalaldehyde (*II*)

This precursor center was prepared in three synthetic steps, from a procedure involving small modifications of the method already reported [33]. Initially, we dissolved 24.1 g (0.10 mol) of **I** and 30.0 g (0.21 mol) of urotropine (hexamethylenetetramine) in 200 mL of chloroform. The mixture was refluxed overnight. At the end of this first stage, after leaving the mixture cool to room temperature, the solvent was removed under reduced pressure and the solid residue obtained was dissolved in 320 mL of a 50% acetic acid aqueous solution, being refluxed subsequently for 12 h. In the last part of the process, 25 mL of concentrated HCl was dropwise added to the solution, which was then refluxed for 8 h. After cooling, we observed the formation of a yellow precipitate, which was filtered off, washed with cold water and ethanol and dried under vacuum. Yield: 2.1 g (~10%), m.p. 207 °C (literature m.p.: 207 °C). From the filtrate, an additional 0.8 g of the product could be obtained; its m.p. was 200 °C. The substance was used in the next step without further purification. Elemental analysis – Percentages found: C, 61.9; H, 5.2. Calcd. for $C_{10}H_{10}O_4$: C, 61.9; H, 5.2. **Main IR bands** (KBr): 3435, 3069, 3048, 2992, 2953, 2932, 2870, 2833, 1679, 1503, 1483, 1466, 1408, 1398, 1302, 1131, 1042, 878, 660 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 300 MHz): 3.93 ppm (s, 6H, $-OCH_3$); 7.44 ppm (s, 2H, aromatic ring); 10.48 ppm (s, 2H, $-CHO$).

2.1.3. 2,5-dimethoxyterephthalaldehyde bis(thiophene-2-carbonyl hydrazone)

A 1.0 mmol (0.142 g) 2-thiophenecarboxylic acid hydrazide methanolic solution was added, under constant stirring, to another solution containing 0.5 mmol (0.097 g) of **II** in 10 mL of methanol (Scheme 1, bottom). The mixture was refluxed for 2 h and a yellow solid was formed during this time. The precipitated was filtered off and washed with cold methanol. The resulting yellow solution was maintained at room temperature and, after 7 days, pale orange crystals suitable for X-ray diffraction were separated by filtration. Yield: 0.17 g (76%), m.p. 357–358 °C. Elemental analysis – Percentages found: C, 54.3%; H, 4.1%; N, 12.8%; S, 14.2%. Calcd. for $C_{20}H_{18}O_4N_4S_2$: C, 54.3%; H, 4.1%; N, 12.7%; S, 14.5%. The infrared spectrum of this compound, as well as the 1D and 2D NMR assignments, will be discussed in the Results and Discussion section.

2.2. Instruments and methodology

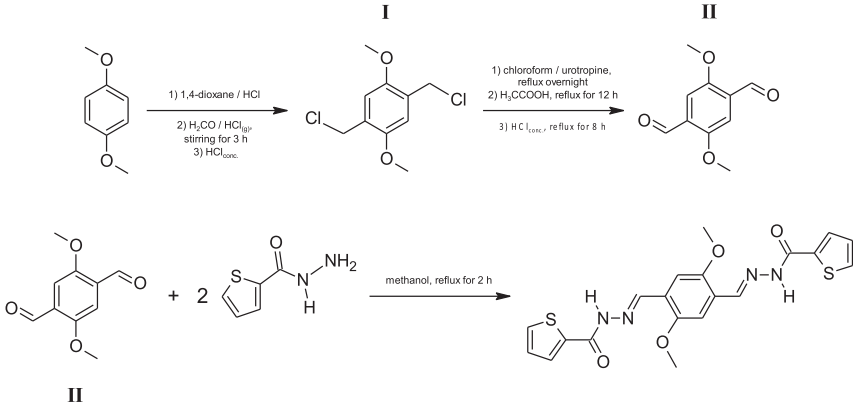
The determination of carbon, hydrogen, nitrogen and sulfur were performed on a Thermo Electron Corporation CHNS analyzer, model Flash EA 1112. Melting point was determined with a MS TECNOPON Additional equipment LTDA, PMF-11 model, and series 8276.

2.2.1. X-ray crystallography

Single crystal X-ray diffraction (XRD) data for the di-hydrazone were collected on a Bruker D8 Venture diffractometer at room temperature, using Incoatec IμS microfocus X-ray source, MoKα radiation (λ = 0.71069 Å). The crystal was mounted on a Kappa Goniometer, and reflections collected using a PHOTON 100 detector. Data collection and cell refinement were performed with Bruker Instrument Service APEX2 v4.2.2 [34]. Data integration was carried out using SAINT [35]. Empirical multiscan absorption correction employing equivalent reflections was achieved with the SADABS program [36]. The structure solutions and full-matrix least-squares refinements based on F^2 were performed with the SHELXS-2013 and SHELXL-2013 program packages [37]. Anisotropic parameters were refined to all non-hydrogen atoms. Positions concerning the hydrogen atoms were constrained to neutral diffraction distances values [38].

2.2.2. Spectroscopic analyses (FT-IR, Raman, UV–Vis and NMR)

Infrared spectra were recorded on a Perkin–Elmer FT-IR 2000 apparatus. Samples were measured from 4000 to 450 cm^{-1} as KBr pellets. Raman spectra of the solid sample of the di-hydrazone were performed on a Perkin–Elmer Raman Station 400, using the 785 nm line for excitation. Electronic spectra were obtained on a



Scheme 1. Chemical synthesis of 2,5-dimethoxyterephthalaldehyde bis(thiophene-2-carbonyl hydrazone).