Structural Chemistry (2021) 32:1231–1245
https://doi.org/10.1007/s11224-020-01700-y

ORIGINAL RESEARCH

Synthesis, physicochemical characterization, and TD–DFT calculations of monothiocarbohydrazone derivatives

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Received: 18 September 2020 / Accepted: 2 December 2020 / Published online: 7 January 2021

Abstract

Derivatives of thiocarbohydrazone studied so far have shown great biological activity such as antioxidant, antimicrobial, and anticancer. Most of these compounds are bis-substituted derivatives, while monothiocarbohydrazones are much less investigated. Eighteen monothiocarbohydrazones were synthesized and subjected to physicochemical characterization in order to facilitate the examination of their potential biological activity and application in future studies. The structure of synthesized derivatives was confirmed with NMR and FT–IR spectroscopy, and with elemental analysis. For one of the compounds, single-crystal X-ray diffraction analysis was performed. Specific and non-specific molecular interactions were interpreted by LSER principles, using *Catalan's* model. For additional information about the dominance and influence of the interactions presented, correlations with *Hansen's* solubility parameters were calculated. Influence of the type and position of the substituent on absorption maxima was determined with LFER (linear free-energy relationship) principles, using *Hammett's* equation. Acidity constants of the synthesized compounds were theoretically calculated and experimentally determined. Moreover, the excitation of a molecule by a photon of UV–Vis light was interpreted by time-dependent density functional theory (TD–DFT) calculations of UV absorption bands, and intramolecular charge transfer (ICT) was quantified by calculations of the charge transfer distances (D_{CT}).

Keywords Acidity constants · LSER · LFER · Monothiocarbohydrazones · TD–DFT · X-ray

Introduction

Derivatives of thiocarbohydrazone are synthesized by condensation of thiocarbohydrazide with appropriate aldehyde or ketone. Depending on the molar ratio of the reactants (1:1 or 1:2), mono- or bis-substituted thiocarbohydrazones can be obtained [1, 2]. Many of these compounds tested so far have shown exceptionally good antimicrobial [3–5], antioxidant [6, 7], and antitumor [8, 9] activity. Due to their structure, more specifically to the presence of nitrogen and sulfur atoms, they are easily coordinated and can build complexes with many transition metals [10, 11]. Most of the derivatives synthesized and investigated so far belong to bis-compounds, while monothiocarbohydrazones (mTCHs) are less investigated. Some studies have shown that mono-derivatives can show better biological activity than bis-compounds due to the contribution of existence of free hydrazine end (–NH–NH_2 group) [1]. Considering all facts stated above, the aim of this work was synthesis, physicochemical characterization, and cognition of properties of monothiocarbohydrazones in order to facilitate the examination of their potential biological activity and possible application in future studies. Eighteen compounds of mTCHs have been synthesized under controlled conditions in order to avoid the formation of bis-compounds. Structure of the compounds obtained has been confirmed by NMR and FT–IR spectroscopy, as well as with elemental analysis. For one of the synthesized compounds (**17**), single-crystal X-ray diffraction analysis was also performed. Solvents' effect on the

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UV–Vis absorption spectra was interpreted by LSER (linear solvation energy relationship) principles with the use of *Catalan's* model. Also, for additional information about the dominance and influence of the interactions presented, correlations with *Hansen's* solubility parameters were obtained. Influence of the type and position of the substituent present on the benzene ring on absorption maxima was determined by LFER (linear free-energy relationship) principles, using *Hammett's* equation. Moreover, acidity constants—pK_a values of synthesized compounds—were experimentally determined and compared with values theoretically calculated. In this research, the nature of the electronic transitions and electronic structure of mTCHs have been investigated by using computational theoretical methods which include MP2 geometry optimizations and TD–DFT calculations.

Experimental

Materials and instruments

All chemicals used for synthesis were purchased from *Sigma Aldrich* and with quality for synthesis. Thiocarbohydrazide (dhS), basic compound for synthesis of mTCHs, was prepared according to a known procedure [12]. Melting points of synthesized mTCHs were determined with *Kofler's* device. IR spectra were recorded on a *Nicolet Nexus 670 FTIR* (Thermo Fisher Scientific) spectrophotometer, in the 400–4000 cm^{-1} range using the KBr pellet technique. NMR spectra (^1H and ^{13}C) were recorded in DMSO-d_6 on a *Bruker AVANCE III 400* spectrometer operating at 400 MHz (^1H) and 100 MHz (^{13}C), and residual solvent signals were used for the chemical shift (ppm; δ-scale) calibration. The elemental analysis was performed using a *Vario El III* elemental analyzer. Diffraction experiments were performed on a *Gemini S* goniometer (*Oxford Diffraction*) equipped with a sealed X-ray tube ($\lambda = 1.5418$ Å) and a *Sapphire CCD* detector. UV–Vis absorption spectra were recorded on *Shimadzu UV–1800* spectrophotometer in 1.00 cm cells at 25.0 ± 0.1 °C with concentration of 4×10^{-5} mol dm^{-3}. Solvents used were also from *Sigma-Aldrich*, with quality for spectrophotometric measurements. pH values were measured using *Crison pH-Burette 24 2S* equipped with a micro-combined pH electrode (*Crison pH electrode 50 29*). The electrode was calibrated by standard *Crison* buffer solutions (pH 4.01, 7.00, and 9.21).

General procedure for synthesis of monothiocarbohydrazones

Thiocarbohydrazide (dhS) 1.0 mmol was dissolved in warm 70% ethanol (30 mL). After dissolution, the corresponding benzaldehyde (0.5 mmol) and one drop of glacial acetic acid were added to the solution, and the reaction mixture was heated under reflux for 3 h. The resulting products were crystalized by cooling to the room temperature and then recrystallized from a suitable solvent, and the crystals were washed and dried with ether and methanol. For the compounds **4**–**9**, **11**, **12**, **14**, **16**, and **17**, there is no complete literary characterization, so it is presented in the main text, while the characterization of compounds **1**–**3**, **10**, **13**, **15**, and **18** is given in Supplementary material.

4-hydroxydobenzaldehyde thiocarbohydrazone (4)

White substance, recrystallized from ethanol. Yield: 69%. M.p. 203 °C. Elemental analysis: Calculated for $C_8H_{10}ON_4S$ ($Mw = 210.54$ g mol^{-1}): C, 45.34; H, 4.80; N, 26.73; O, 7.60; S, 15.23%. Found: C, 45.42; H, 4.83; N, 26.27; O, 7.84; S, 15.64%. IR (KBr, cm^{-1}): ν(OH): 3441s, ν(NH_2): 3275s, ν(NH): 3170s, ν(C=N): 1599s, ν(C=S): 1274s, ν(Ar-OH): 1251s. ^1H NMR (400 MHz, DMSO-d_6, δ (ppm)): 4.80 (s, 2H, H2–N4), 6.76 (d, 2H, H–2, H–6), 7.63 (d, 2H, H–3, H–5), 7.89 (s, 1H, H–7), 9.60 (s, 1H, H–OH), 9.83 (s, 1H, H–N2), 11.21 (s, 1H, H–N3). ^{13}C NMR (100 MHz, DMSO-d_6, δ (ppm)): 115.8 (C2; C6), 125.9 (C1), 129.6 (C5; C3), 143.2 (C7), 159.7 (C4), 176.3 (C8).

2-methylbenzaldehyde thiocarbohydrazone (5)

Pale yellow substance, recrystallized from ethanol. Yield: 66%. M.p. 192 °C. Elemental analysis: Calculated for $C_9H_{12}N_4S$ ($Mw = 208.57$ g mol^{-1}): C, 51.83; H, 5.81; N, 26.98; S, 15.38%. Found: C, 51.74; H, 5.87; N, 26.82; S, 15.57%. IR (KBr, cm^{-1}): ν(NH_2): 3296s, ν(NH): 3170s, ν(C=N): 1538s, ν(C=S): 1254s. ^1H NMR (400 MHz, DMSO-d_6, δ (ppm)): 2.35 (s, 3H, H–CH_3), 4.85 (s, 2H, H2–N4), 7.17–7.27 (m, 3H, H–C3, H–C4, H–C5), 8.11 (d, 1H, H–C6), 8.34 (s, 1H, H–C7), 9.71 (s, 1H, H–N2), 11.32 (s, 1H, H–N3). ^{13}C NMR (100 MHz, DMSO-d_6, δ (ppm)): 19.2 (C–CH_3), 126.4 (C4), 126.5 (C6), 129.9 (C5), 131.1 (C3), 132.6 (C2), 137.1 (C1), 141.2 (C7), 176.2 (C8).

3-methylbenzaldehyde thiocarbohydrazone (6)

White substance, recrystallized from ethanol. Yield: 77%. M.p. 175 °C. Elemental analysis: Calculated for $C_9H_{12}N_4S$ ($Mw = 208.57$ g mol^{-1}): C, 51.83; H, 5.81; N, 26.98; S, 15.38%. Found: C, 51.77; H, 5.69; N, 27.11; S, 15.43%. IR (KBr, cm^{-1}): ν(NH_2): 3274s, ν(NH): 2982m, ν(C=N): 1637s, ν(C=S): 1283s. ^1H NMR (400 MHz, DMSO-d_6, δ (ppm)): 2.31 (s, 3H, H–CH_3), 4.82 (s, 2H, H2–N4), 7.18 (d, 1H, H–C4), 7.26 (t, 1H, H–C3), 7.55 (d, 1H, H–C2), 7.69 (s, 1H, H–C6), 7.96 (s, 1H, H–C7), 9.78 (s, 1H, H–N2), 11.38 (s, 1H, H–N3). ^{13}C NMR (100 MHz, DMSO-d_6, δ (ppm)): 21.5 (C–CH_3), 125.3 (C2), 128.1 (C6), 129.0 (C3), 130.8 (C4), 134.7 (C5), 138.3 (C1), 142.7 (C7), 1766 (C8).

4-methylbenzaldehyde thiocarbohydrazone (7)

Yellow substance, recrystallized from ethanol. Yield: 59%. M.p. 186 °C. Elemental analysis: Calculated for $C_9H_{12}N_4S$ ($Mw = 208.57$ g mol^{-1}): C, 51.83; H, 5.81; N, 26.98; S, 15.38%. Found: C, 51.28; H, 5.99; N, 26.64; S, 16.09%. IR (KBr, cm^{-1}): ν(NH_2): 3283s, ν(NH): 3179s, ν(C=N): 1604s, ν(C=S): 1237s. ^{1}H NMR (400 MHz, DMSO-d_6, δ (ppm)): 2.30 (s, 3H, H–CH_3), 4.84 (s, 2H, H2–N4), 7.19 (d, 2H, H–C5, H–C3), 7.70 (d, 2H, H–C2, H–C6), 7.96 (s, 1H, H–C7), 9.74 (s, 1H, H–N2), 11.34 (s, 1H, H–N3). ^{13}C NMR (100 MHz, DMSO-d_6, δ (ppm)): 21.5 (C–CH_3), 127.8 (C2; C6), 129.7 (C5; C3), 132.0 (C4), 139.9 (C1), 142.7 (C7), 176.3 (C8).

2-nitrobenzaldehyde thiocarbohydrazone (8)

Yellow substance, recrystallized from ethanol. Yield: 68%. M.p. 222 °C. Elemental analysis: Calculated for $C_8H_9N_5O_2S$ ($Mw = 239.60$ g mol^{-1}): C, 40.11; H, 3.79; N, 29.36; O, 13.36; S, 13.38%. Found: C, 39.98; H, 3.77; N, 29.64; O, 13.47; S, 13.14%. IR (KBr, cm^{-1}): ν(NH_2): 3296s, ν(NH): 3138m, ν(C=N): 1610s, ν(NO): 1524s and 1346s, ν(C=S): 1272s. ^{1}H NMR (400 MHz, DMSO-d_6, δ (ppm)): 4.93 (s, 2H, H2–N4), 7.61 (m, 1H, H–C4), 7.74 (m, 1H, H–C5), 8.02 (dd, 1H, H–C6), 8.44 (s, 1H, H–C7), 8.56 (dd, 1H, H–C3), 10.03 (s, 1H, H–N2), 11.74 (s, 1H, H–N3). ^{13}C NMR (100 MHz, DMSO-d_6, δ (ppm)): 124.9 (C3), 128.8 (C5), 129.0 (C4), 130.6 (C6), 133.7 (C1), 137.3 (C7), 148.7 (C2), 176.3 (C8).

3-nitrobenzaldehyde thiocarbohydrazone (9)

Yellow substance, recrystallized from ethanol. Yield: 54%. M.p. 236 °C. Elemental analysis: Calculated for $C_8H_9N_5O_2S$ ($Mw = 239.60$ g mol^{-1}): C, 40.11; H, 3.79; N, 29.36; O, 13.36; S, 13.38%. Found: C, 40.12; H, 3.64; N, 29.57; O, 13.44; S, 13.23%. IR (KBr, cm^{-1}): ν(NH_2): 3282s, ν(NH): 3063m, ν(C=N): 1606s, ν(NO): 1518s and 1347s, ν(C=S): 1248s. ^{1}H NMR (400 MHz, DMSO-d_6, δ (ppm)): 4.91 (s, 2H, H2–N4), 7.66 (t, 1H, H–C5), 8.09 (s, 1H, H–C7), 8.17 (d, 1H, H–C4), 8.22 (d, 1H, H–C6), 8.73 (s, 1H, H–C2), 10.17 (s, 1H, H–N2), 11.60 (s, 1H, H–N3). ^{13}C NMR (100 MHz, DMSO-d_6, δ (ppm)): 121.9 (C2), 124.5 (C4), 130.8 (C5), 134.3 (C6), 136.9 (C1), 140.4 (C7), 149.0 (C3), 176.6 (C8).

2-metoxybenzaldehyde thiocarbohydrazone (11)

Pale yellow substance, recrystallized from ethanol. Yield: 85%. M.p. 184 °C. Elemental analysis: Calculated for $C_9H_{12}N_4OS$ ($Mw = 224.57$ g mol^{-1}): C, 48.14; H, 5.40; N, 25.06; O, 7.03; S, 14.32%. Found: C, 48.23; H, 5.31; N, 25.11; O, 7.03; S, 14.32%. IR (KBr, cm^{-1}):ν(NH_2): 3274s, ν(NH): 3178s, ν(O-CH3): 2963m, 2837m and 1464m, ν(C=N): 1604s, ν(C=S): 1251s. ^{1}H NMR (400 MHz, DMSO-d_6, δ (ppm)): 3.82 (s, 3H, H–OCH_3), 6.95 (t, 1H, H–C5), 7.04 (d, 1H, H–C3), 7.36 (m, 1H, H–C4), 8.18 (dd, 1H, H–C6), 8.36 (s, 1H, H–C7), 9.74 (s, 1H, H–N2), 11.40 (s, 1H, H–N3). ^{13}C NMR (100 MHz, DMSO-d_6, δ (ppm)): 56.1 (C-OCH_3), 112.0 (C3), 121.0 (C6), 122.7 (C4), 126.8 (C5), 131.6 (C1), 138.1 (C7), 158.1 (C2), 176.2 (C8).

3-metoxybenzaldehyde thiocarbohydrazone (12)

Pale yellow substance, recrystallized from ethanol. Yield: 91%. M.p. 204 °C. Elemental analysis: Calculated for $C_9H_{12}N_4OS$ ($Mw = 224.57$ g mol^{-1}): C, 48.14; H, 5.40; N, 25.06; O, 7.03; S, 14.32%. Found: C, 48.21; H, 5.36; N, 25.11; O, 7.02; S, 14.30%. IR (KBr, cm^{-1}): ν(NH_2): 3249s, ν(NH): 3160m, ν(O-CH3): 2964m, 2832m, and 1429m, ν(C=N): 1579s, ν(C=S): 1279s. ^{1}H NMR (400 MHz, DMSO-d_6, δ (ppm)): 3.79 (s, 3H, H–OCH_3), 4.86 (s, 2H, H2–N4), 6.93 (m, 1H, H–C6), 7.20–7.33 (m, 2H, H–C4, H–C5), 7.51 (s, 1H, H–C2), 7.96 (s, 1H, H–C7), 9.88 (s, 1H, H–N2), 11.41 (s, 1H, H–N3). ^{13}C NMR (100 MHz, DMSO-d_6, δ (ppm)): 56.0 (C-OCH_3), 111.4 (C2), 117.2 (C6), 121.2 (C4), 130.3 (C5), 136.2 (C1), 142.5 (C7), 160.2 (C3), 176.6 (C8).

3-chlorobenzaldehyde thiocarbohydrazone (14)

White substance, recrystallized from ethanol. Yield: 66%. M.p. 213 °C. Elemental analysis: Calculated for $C_8H_9N_4SCl$ ($Mw = 228.98$ g mol^{-1}): C, 41.96; H, 3.97; N, 24.58; S, 14.01; Cl, 15.48%. Found: C, 41.77; H, 3.88; N, 24.66; S, 14.07; Cl, 15.62%. IR (KBr, cm^{-1}): ν(NH_2): 3235m, ν(NH): 3172m, ν(C=N): 1604s, ν(C=S):1279s, ν(C–Cl): 784m. ^{1}H NMR (400 MHz, DMSO-d_6, δ (ppm)): 4.88 (s, 2H, H2–N4), 7.35–7.43 (m, 2H, H–C4, H–C2), 7.63 (m, 1H, H–C3), 7.96 (s, 1H, H–C6), 8.14 (s, 1H, H–C7), 10.02 (s, 1H, H–N2), 11.49 (s, 1H, H–N3). ^{13}C NMR (100 MHz, DMSO-d_6, δ (ppm)): 126.4 (C7), 127.2 (C3), 129.7 (C2), 130.8 (C4), 134.3 (C1), 137.1 (C5), 140.7 (C6), 176.3 (C8).

3-bromobenzaldehyde thiocarbohydrazone (16)

Yellow substance, recrystallized from ethanol. Yield: 61%. M.p. 215 °C. Elemental analysis: Calculated for $C_8H_9N_4SBr$ ($Mw = 273.43$ g mol^{-1}): C, 35.14; H, 3.32; N, 20.58; S, 11.73; Br, 29.22%. Found: C, 35.08; H, 3.37; N, 20.42; S, 11.64; Br, 29.46%. IR (KBr, cm^{-1}): ν(NH_2): 3282m, ν(NH): 3170m, ν(C=N): 1602s, ν(C=S): 1244s, ν(C-Br): 595m. ^{1}H NMR (400 MHz, DMSO-d_6, δ (ppm)): 4.87 (s, 2H, H2–N4), 7.33 (t, 1H; H–C3), 7.53 (m, 1H; H–C4), 7.67 (d, 1H, H–C2), 7.94 (s, 1H, H–C7), 8.27 (s, 1H, H–C6), 10.03 (s, 1H, H–N2), 11.49 (s, 1H, H–N3). ^{13}C NMR (100 MHz, DMSO-d_6, δ (ppm)): 122.8 (C1), 127.6 (C2), 129.3 (C6), 131.1 (C3), 132.6 (C4), 137.3 (C5), 140.7 (C7), 176.2 (C8).

4-bromobenzaldehyde thiocarbohydrazone (17)

Pale yellow substance, recrystallized from ethanol. Yield: 88%. M.p. 205 °C. Elemental analysis: Calculated for $C_8H_9N_4SBr$ ($Mw = 273.43$ g mol^{-1}): C, 35.14; H, 3.32; N, 20.58; S, 11.73; Br, 29.22%. Found: C, 35.11; H, 3.28; N, 20.39; S, 11.80; Br, 29.42%. IR (KBr, cm^{-1}): ν(NH_2): 3267 m, ν(NH): 3168 m, ν(C=N): 1590s, ν(C=S): 1246s, ν(C-Br): 508m. ^{1}H NMR (400 MHz, DMSO-d_6, δ (ppm)): 4.86 (s, 2H, H2–N4), 7.57 (d, 2H, H–C2, H–C6), 7.79 (d, 2H, H–C3, H–C5) 7.95 (s, 1H, H–C7), 9.90 (s, 1H, H–N2), 11.46 (s, 1H, H–N3).^{13}C NMR (100 MHz, DMSO-d_6, δ (ppm)): 123.3 (C4), 129.7 (C3; C5), 132.0 (C2; C6), 134.1(C1), 141.1 (C7), 176.2 (C8).

X–ray diffraction analysis

Single-crystal X-ray diffraction data for the compound **17** were collected on an Oxford Gemini S diffractometer equipped with a CCD detector, using monochromatized CuK_α radiation ($\lambda = 1.54184$ Å). Data reduction and empirical absorption correction were performed with CrysAlis^{PRO} [13]. The structure was solved by SHELXT [14] and refined by using the full-matrix least-squares method implemented in SHELXL [15]. The positions of the nonhydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed at geometrically ideal distances (N–H = 0.86, O–H = 0.82, C–H = 0.93, and 0.97 Å for CH_3 and CH, respectively), and their positions were refined using a riding atom model, with fixed isotropic displacement parameters. Images of the obtained structures of monothiocarbohydrazone were made using the *Mercury* program [16]. Table with crystallographic data and some refinement parameters is given in the supplementary material (Table S1). Crystallographic and refinement details are deposited in the Cambridge Crystallographic Data Centre under CCDC 2031024, obtainable free of charge from https://www.ccdc.cam.ac.uk//structures/.

UV–Vis measurements

Solvents used for UV–Vis measurements were 2-choloroethanol (2-ClEtOH), methanol, ethanol, *n*-propanol, *n*-butanol, *n*-pentanol, *i*-propanol, *i*-butanol, *t*-butanol, acetic acid, acetonitrile (ACN), dimethyl-sulfoxide (DMSO), *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), dichloromethane (DCM), chloroform, ethyl-acetate (EtAc), tetrahydrofuran (THF), 1,4-dioxane, and diethyl-ether. Obtained spectrophotometric data were processed with *Excel 97–2003*.

pK_a determination

Most of the synthesized compounds were sparingly soluble in water; thus, the working solutions of mTCHs were prepared in a methanol: water mixture (1:1, V:V) in the concentration range (4.0024–6.3284) × 10^{-4} M. Investigated compounds were dissolved in methanol, and solution was diluted with aqueous NaCl (0.2 M) to maintain a constant ionic strength ($I = 0.1$ M). Prior to titration, a certain volume of standard 0.09510 M HCl solution was added to 4.00 mL of every working compound solution (n_{HCL}: $n_{comp} = 1.2$:1) to reach the full compound protonation. Titrations were performed with 2.0 μL increments of standard 0.09720 M NaOH solution in 2.50–12.20 pH range in argon flow at $t = 25 \pm 1$ °C. NaOH and HCl standard solutions were also prepared in a methanol: water mixture (1:1, V:V) and standardized by potentiometric titrations. For each compound, four titrations were performed, and obtained results are shown as an average. System calibration was performed according to *Grann's* method, using the *GLEE (Glass Electrode Evaluation)* software [17]. Experimentally obtained values were processed with the software package *HYPERQUAD 2008* [18].

Computational methods

The geometries of the *E* and *Z* isomers of all synthetized compounds were fully optimized using the ab initio MP2 calculations with a 6-311G(d,p) basis set in the gas phase. The *theoretical* UV–Vis spectra were calculated on MP2/6-311G(d,p) optimized geometries with a time-dependent (TD) density functional theory (DFT) method. TD–DFT calculations were performed in DMSO with CAM-B3LYP functional and 6-311G(d,p) basis set. Solvent effects have been simulated using the self-consistent reaction field (SCRF)/isodensity surface polarized continuum model (IPCM). Qualitative charge transfer index—the charge transfer distance (D_{CT}) was estimated according to the method proposed by *Le Bahers* et al. [19]. All quantum chemical calculations were performed using the *Gaussian 09* program package [20].

Results and discussion

Characterization of monothiocarbohydrazones

Purity of the obtained compound was checked by melting point, NMR, FT–IR spectroscopy, and elemental analysis. All synthesized compounds are already known except compound **5**. Compounds **1**, **2**, **3**, **10**, **13**, **15**, and **18** [21–24] are known and partly characterized, while the rest are known but uncharacterized. In this research, both previous and new results are systematically presented and thoroughly discussed. Results obtained for partly characterized compounds are in

agreement with literature data. Chemical reaction used for synthesis, the list of obtained compounds, and the numbering of the atoms of interest are shown in Scheme 1.

Results of the elemental analysis were within ± 0.5% of the theoretical values. The FT–IR spectra of synthesized mTCHs absorption between 3063 and 3188 cm^{-1} were assigned to N–H vibrations. ν(C=N) for all compounds were in the range from 1538 to 1637 cm^{-1}, while signals recorded from 1237 to 1284 cm^{-1} were attributed to ν(C=S) band. One of the proofs that all synthesized compounds belong to the derivatives of monothiocarbohydrazones and that bis-compounds were not formed is the existence of ν(NH_2) vibrations that were recorded in the range of 3235–3300 cm^{-1}. ^1H and ^{13}C NMR spectra of uncharacterized mTCHs showed a great match with the signals expected for hydrogen and carbon atoms. Also, ^1H NMR spectra for partly characterized mTCHs showed extraordinarily well superposition with the literature data. Another proof that these compounds belong to mono-derivatives is expressed through the existence of a signal in the region between 4.70 and 4.91 ppm (^1H NMR spectra) for every synthesized compound, assigned to the NH_2 group.

Some previous studies have shown that mTCHs have several possible solution structures including configurational (*E* or *Z*) isomers around imine bond and thione/thiol tautomers [25]. Careful analysis of the ^1H NMR spectra of the mTCHs concluded that all of the synthesized compounds in DMSO-d_6 solution exist in thione form and that there is no mixture of two isomers—*E* and *Z*.

X–ray structural analysis of monothiocarbohydrazones

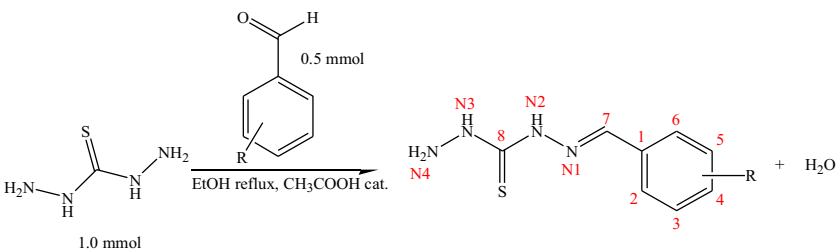
Compound **17** (4-bromobenzaldehyde thiocarbohydrazone) was successfully obtained in the form of single crystals by recrystallization in a suitable solvent and slow evaporation. Molecular structure obtained for this compound is shown in Fig. 1, while Table 1 presents lengths of the selected bonds, values of the angles formed between them, and torsion angles.

The length of the C7–N1 bond indicates the existence of a localized double bond between these atoms, while the C8–N2 and C8–N3 bonds are, due to delocalization, longer than double (1.29 Å) and shorter than single bonds (1.47 Å). Also, the smallest angle with adjacent atoms is formed by the unprotonated nitrogen atom N1, while the angles around the protonated N2 and N3 are larger, around 120° and more. Observing the values of the torsion angles shown in Table 1, it can be seen that within the structure of compound **17**, the greatest torsion occurs at the free hydrazone end.

Since the optimization of the structures of all eighteen compounds was performed, it is important to compare the experimentally obtained results with the theoretically predicted ones. Within the *E* isomer of compound **17**, the dihedral angle between the benzene ring and the thiocarbohydrazone moiety is 7.57° (Table S2) and shows good agreement with the experimentally confirmed structure where this angle amounts 6.68°. The overlay of the two structures is shown in Fig. 2.

Geometry optimization of monothiocarbohydrazones

All the isomers of mTCHs differing in configuration at the C7=N1 double bond were optimized by quantum chemical calculation at the second-order *Møller–Plesset* perturbation theory (MP2) level using 6-311G(d,p) basis set in the gas phase. The geometric structure of *E* isomers shows a nearly planar configuration with the dihedral angles between phenyl group and thiocarbohydrazone moiety from 5.77 to 9.12° (Table S2), except for three compounds with *ortho* substituents: **2**, **8**, and **11** (18.14°–27.90°). In compound **2**, intramolecular hydrogen bond between –OH substituent in *ortho* position and N1 is formed inducing deviation from planarity. Compounds **8** and **11** have bulky polar substituents present in *ortho* position (–NO_2 and –OCH_3, respectively) and strong repulsive electrostatic interaction with thiocarbohydrazone



Scheme 1 Synthesis procedure and numbering of atoms of monothiocarbohydrazones

Compound	Reactant (**R**)
1	H
2/3/4	*o*/*m*/*p* - OH
5/6/7	*o*/*m*/*p* - CH_3
8/9/10	*o*/*m*/*p* - NO_2
11/12/13	*o*/*m*/*p* - OCH_3
14/15	*m*/*p* - Cl
16/17	*m*/*p* - Br
18	*p* - F

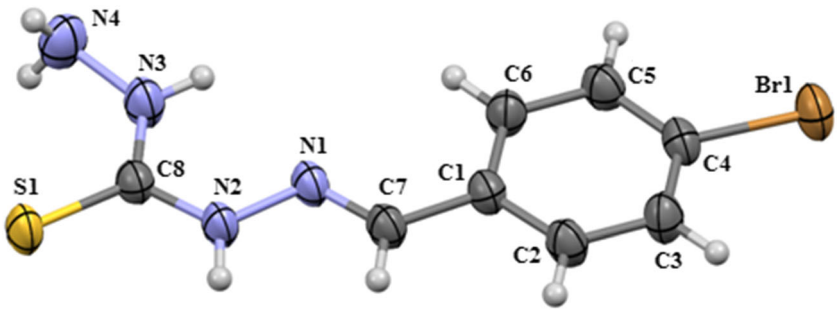


Fig. 1 Molecular structure of the compound **17**

moiety. Thus, the most stable conformation for these compounds is with substituent rotated away from thiocarbohydrazone moiety, and the deviation from planarity is a consequence of steric repulsion between hydrogen on C7 atom and substituent in ortho position (Fig. S1). In compound **5**, nonpolar $-CH_3$ group is in *ortho* position, so it can be oriented towards thiocarbohydrazone moiety and retain planar geometry (Table S2). On the other hand, *Z* isomers have much larger deviations from planarity (52.28–70.70°) due to present steric clash/hindrance between a hydrogen atom from N2 and hydrogen atoms or substituents in *ortho* position from phenyl group. Optimized structures of both isomers of all investigated compounds are represented on Fig. S1.

Solvents' effect on the absorption spectra of monothiocarbohydrazones

Effects of specific and nonspecific solvent–solute interactions on the absorption maxima of the mTCHs were studied by multiple regression analysis (LSER principles) using *Catalan's* solvatochromic model [26, 27], described with Eq. 1:

$$\nu = \nu_0 + \mathrm{aSA} + \mathrm{bSB} + \mathrm{cSP} + \mathrm{dSdP} \quad (1)$$

where ν is the frequency in a given solvent, ν_0 is the solute property of the reference system, cyclohexane, *SA* represents the hydrogen bond donating ability (HBD, acidity of the solvent), *SB* is a measure of the hydrogen bond accepting ability (HBA, basicity of the solvent), *SP* describes the polarizability, and *SdP* represents dipolarity of the solvent. Correlation coefficients **a**, **b**, **c**, and **d** describe the sensitivity of the absorption maxima to different types of solvent–solute interactions.

UV–Vis absorption spectra of the synthesized monothiocarbohydrazones were recorded within the 200–400 nm range within twenty-one solvent of various properties. As an example, spectrum of compound **5** in protic (a) and aprotic (b) solvents is shown on Fig. 3. Similar spectra were obtained for all other compounds.

After the deconvolution of the recorded spectra, maxima that were considered in further analysis were in the 280–310-nm range. The reason of this wide range of wavelengths is the variety of substituents present, as well as the properties of the solvents used. Absorption frequencies (wave numbers, $\nu_{max} \cdot 10^{-3}$, cm^{-1}) and calculated values of molar absorptivity of eighteen investigated monothiocarbohydrazones in all solvents used are represented in Table S3.

Observing the values in Table S3, it can be seen that with the increase of the solvent's polarity absorption maxima of the mTCHs shift hypsochromically, that is, the values of the absorption frequencies of the tested compounds increase. In order to confirm this fact, correlations with empirical polarity parameter (E_T^N [28], Table S4) of the solvents used have been made. An example of the obtained linear dependencies is shown in Fig. 4. For all other compounds tested, similar dependencies were obtained.

Results of the quantitative analysis of specific and nonspecific interactions represented between solvents used and investigated mTCHs obtained with *Catalan's* solvatochromic model are given in Table 2.

As can be seen from Table 2, the obtained correlation coefficients for each compound are high, in the range 0.902–

Table 1 Geometric parameters of the compound **17**

Bond	Bond lengths (Å)	Bond	Angle (°)	Bond	Torsion angle. τ (°)
C7–N1	1.275 (3)	N4–N3–C8	122.9 (2)	C7–N1–N2–C8	176.3 (2)
N2–C8	1.344 (3)	N3–C8–S1	123.5 (2)	N2–C8–N3–N4	− 171.4 (2)
C8–S1	1.681 (2)	S1–C8–N2	120.4 (1)	C6–C1–C7–N1	− 179.2 (2)
C8–N3	1.335 (3)	C8–N2–N1	120.0 (2)		
C4–Br1	1.899 (2)	N2–N1–C7	115.2 (2)		
		C7–C1–C6	118.0 (2)		

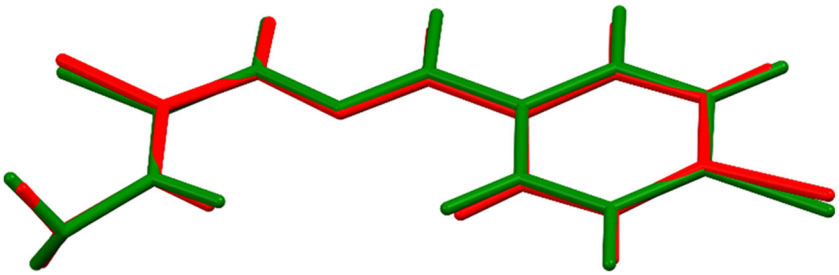


Fig. 2 Overlay of the optimized structure (red) **17** with the structure obtained by single-crystal XRD (green)

0.975, and it is assumed that the model used is suitable for describing intermolecular interactions between the tested compounds and the surrounding medium. Regression coefficient **a** has the biggest values, which means that the greatest impact on spectral changes of the mTCHs has the acidity of the solvent used (exceptions are compounds **2** and **10** where polarizability of the solvent is the most dominant). Somewhat smaller effects on maxima shifting have polarizability and dipolarity of the solvent, presented with regression coefficients **c** and **d**, while basicity of the solvent has the slightest impact on spectral changes of the investigated derivatives (values of the regression coefficient **b**). A positive sign in front of regression coefficients **a**, **b**, and **d** indicates that with increasing of the solvent's acidity, basicity, and dipolarity, hypsochromic shifting of the maxima will occur. On the other hand, the negative sign in front of the coefficient **c** indicates that increasing solvent polarizability will result in a bathochromic shifting of the investigated derivatives absorption maxima.

In order to confirm the accuracy of the applied model, correlations between the experimentally obtained and theoretically calculated results were made. Obtained linear dependence is presented in Fig. 5. Correlation coefficient is high (0.979), leading to conclusion that the used model is suitable for the interpretation of the interactions between investigated mTCHs and surrounding medium.

In addition to the solvent effect, correlations of the absorption maxima with *Hansen's* solubility parameters [29] of the solvents used were obtained by the Eq. 2.

$$\nu_{max} = \nu_0 + d\delta_D + p\delta_P + h\delta_H \quad (2)$$

where δ_D represents energy from dispersion forces, δ_P is energy from dipolar forces, and δ_H ability of building hydrogen bonds, while **d**, **p**, and **h** are regression coefficients that show measures of the impact of these forces on intermolecular interactions that occur between the tested mTCHs and surrounding medium. Results obtained by correlations of absorption frequencies of mTCHs (Table S3) and *Hansen's* solubility parameters (Table S4) are presented in Table 3.The highest values were obtained for the regression coefficient **d**, which means that the dispersion forces are the most dominant interactions between the examined monothiocarbohydrazones and the surrounding medium. They are followed by the influence of hydrogen bond construction (regression coefficient **h**), and finally, with the smallest impact, dipolar forces are present (the coefficient **p** for all compounds has the smallest value). A positive sign in front of the coefficients **p** and **h** indicates that with the increase of the influence of dipolar forces and the possibility of building a hydrogen bond, a hypsochromic shift of absorption maxima will occur. A negative sign in front of the coefficient **d** indicates a possible bathochromic shift with an increase of the influence of dispersion forces.

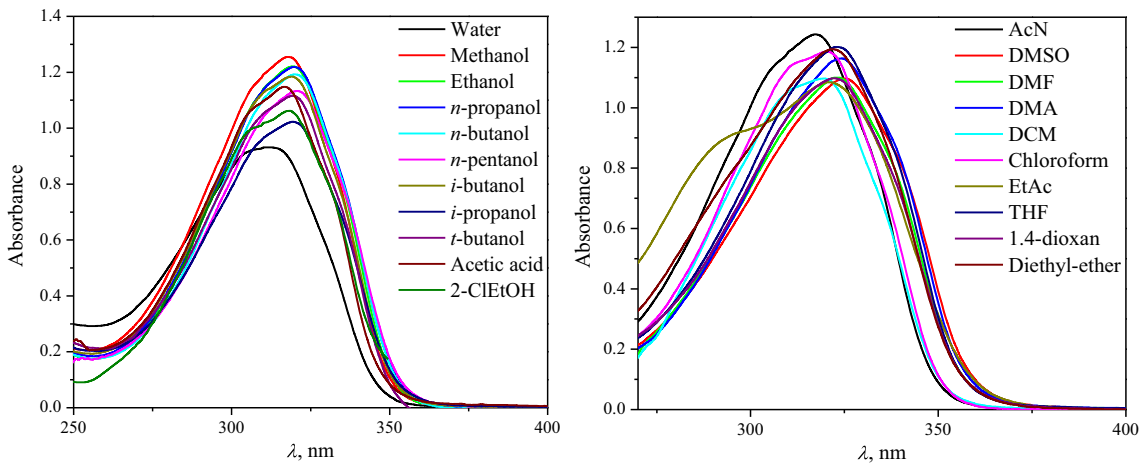


Fig. 3 UV–Vis absorption spectra of compound **5**, 2-methylbenzaldehyde thiocarbohydrazone, in protic (**a**) and aprotic (**b**) solvents

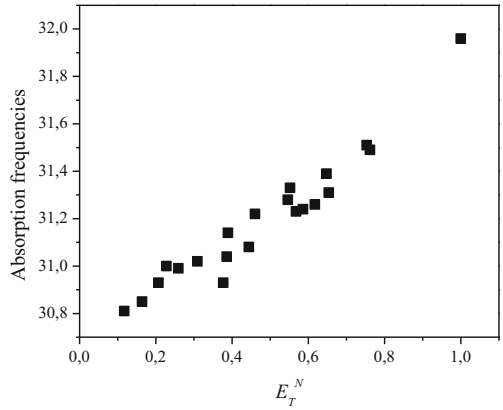


Fig. 4 Correlation of absorption frequencies of compound **5** with E_T^N

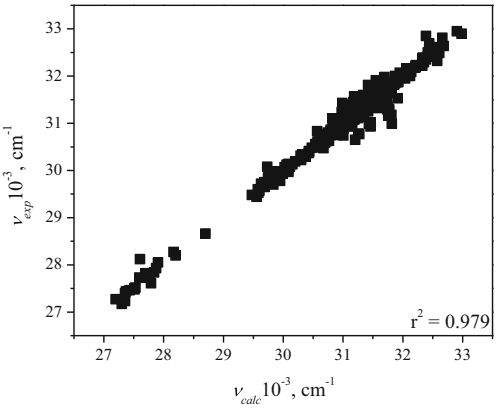


Fig. 5 Correlation of experimentally obtained with theoretical results of *Catalan's* model

The effect of substituent on UV–Vis absorption spectra of monothiocarbohydrazones

The influence of the substituent on the appearance of the UV–Vis absorption spectra is reflected in its type and position on the benzene ring. Quantitative analysis of this impact was determined with the help of *Hammett's* equation [30], by applying LFER principles:

$$\nu_{max} = \nu_0 + \rho\sigma_{m,p} \quad (3)$$

where ν_{max} is absorption frequency at the maximum absorbance, ν_0 represents the wave number in the irrespective solvent, and ρ is a proportionality constant reflecting the sensitivity of the spectral data to the substituent effects, described by the substituent constant, $\sigma_{m,p}$ (*Hammett's* constant). In Fig. 6 spectra of all compounds recorded in water are represented.

Observing Fig. 6 and Table S3, it can be noted that all tested compounds have more or less bathochromic displacement relative to the unsubstituted compound (**1**). The exceptions are compounds **8** and **18** where some hypsochromic shifts have been reported. Table S5 shows the values of *Hammett's* substituent constants with exceptions for *ortho-*

Table 2 Values of the regression coefficients of *Catalan's* solvatochromic model

Compound	$v_0 \cdot 10^{-3}$. (cm^{-1})	a·10^{-3}. (cm^{-1})	b·10^{-3}. (cm^{-1})	c·10^{-3}. (cm^{-1})	d·10^{-3}. (cm^{-1})	r^2	sd	F	Solvents excluded
1	31.575 (± 0.154)	0.713 (± 0.046)	/[1]	−0.305 (±0.211)	0.283 (± 0.059)	0.971	0.046	125	2
2	29.717 (± 0.265)	0.553 (± 0.073)	/	−0.459 (±0.444)	0.311 (± 0.062)	0.908	0.070	34	2, 3
3	31.531 (± 0.361)	0.921 (± 0.092)	/	−0.988 (±0.419)	0.518 (± 0.118)	0.945	0.091	64	2
4	30.426 (± 0.142)	0.610 (± 0.039)	/	−0.269 (±0.185)	0.305 (± 0.039)	0.975	0.037	134	2, 3
5	31.093 (± 0.245)	0.750 (± 0.073)	/	−0.482 (±0.335)	0.344 (± 0.094)	0.940	0.072	59	2
6	31.631 (± 0.173)	0.667 (± 0.048)	/	−0.460 (±0.225)	0.191 (± 0.062)	0.967	0.046	102	2, 3
7	31.236 (± 0.246)	0.584 (± 0.068)	0.103 (± 0.064)	−0.355 (± 0.320)	0.203 (± 0.088)	0.916	0.065	38	2, 3
8	32.240 (± 0.361)	1.039 (± 0.132)	/	− 0.702 (± 0.471)	0.601 (± 0.127)	0.921	0.092	38	2, 3
9	31.403 (± 0.215)	0.746 (± 0.065)	/	− 0.384 (± 0.295)	0.282 (± 0.083)	0.949	0.064	70	2
10	27.488 (± 0.314)	1.098 (± 0.094)	/	− 0.583 (± 0.429)	0.445 (± 0.120)	0.950	0.093	72	2
11	30.226 (± 0.149)	0.244 (± 0.041)	/	− 0.573 (± 0.193)	0.195 (± 0.053)	0.902	0.039	32	2, 3
12	30.967 (± 0.274)	0.826 (± 0.076)	0.079 (± 0.072)	− 0.601 (± 0.356)	0.423 (± 0.098)	0.951	0.072	69	2, 3
13	30.795 (± 0.152)	0.575 (± 0.042)	/	− 0.234 (± 0.198)	0.128 (± 0.054)	0.963	0.0470	90	2, 3
14	31.261 (± 0.327)	0.943 (± 0.098)	/	− 0.734 (± 0.448)	0.347 (± 0.126)	0.930	0.097	50	2
15	31.004 (± 0.287)	0.920 (± 0.086)	/	− 0.702 (± 0.3939)	0.404 (± 0.110)	0.944	0.085	63	2
16	31.246 (± 0.310)	0.813 (± 0.093)	/	− 0.652 (± 0.424)	0.303 (± 0.119)	0.918	0.092	42	2
17	30.945 (± 0.244)	0.772 (± 0.073)	/	− 0.480 (± 0.333)	0.306 (± 0.094)	0.942	0.072	61	2
18	31.388 (± 0.313)	0.801 (± 0.094)	/	− 0.477 (± 0.429)	0.475 (± 0.120)	0.919	0.093	43	2

The values in parentheses represent the determination error; r^2 correlation coefficient, *sd* standard deviation, *F* Fischer's coefficient; 1, error greater than the value; 2, 2-ClEtOH; 3, diethyl-ether

Table 3 Results of correlations of absorption frequencies of monothiocarbohydrazones with *Hansen's* parameters

Compound	$\nu_0 \cdot 10^{-3}$. cm^{-1}	d·10^{-3}. cm^{-1}	p·10^{-3}. cm^{-1}	h·10^{-3}. cm^{-1}	r^2	sd	F	Solvents excluded
1	32.354 (± 0.347)	− 0.056 (± 0.020)	0.007 (± 0.005)	0.021 (± 0.003)	0.903	0.091	37	1
2	33.580 (± 0.141)	− 0.065 (± 0.008)	/	0.017 (± 0.001)	0.982	0.032	165	1, 2, 3
3	33.205 (± 0.494)	− 0.123 (± 0.028)	/	0.023 (± 0.004)	0.911	0.124	34	1, 2, 3
4	31.180 (± 0.289)	− 0.051 (± 0.016)	0.007 (± 0.004)	0.017 (± 0.002)	0.916	0.073	40	1, 2
5	31.859 (± 0.285)	− 0.062 (± 0.016)	0.008 (± 0.004)	0.022 (± 0.002)	0.942	0.075	65	1
6	32.341 (± 0.308)	− 0.061 (± 0.017)	0.005 (± 0.004)	0.019 (± 0.003)	0.914	0.081	43	1
7	32.556 (± 0.314)	− 0.082 (± 0.017)	/	0.012 (± 0.003)	0.918	0.074	33	1, 2, 3, 4
8	33.787 (± 0.440)	− 0.105 (± 0.023)	0.012 (± 0.005)	0.028 (± 0.006)	0.938	0.086	46	1, 2, 3, 5
9	32.292 (± 0.338)	− 0.061 (± 0.019)	/	0.020 (± 0.003)	0.916	0.085	36	1, 2, 3
10	29.315 (± 0.511)	− 0.118 (± 0.028)	/	0.027 (± 0.004)	0.918	0.128	37	1, 2, 3
11	30.434 (± 0.164)	− 0.034 (± 0.009)	/	0.009 (± 0.001)	0.902	0.042	34	1, 6
12	32.202 (± 0.384)	− 0.086 (± 0.022)	/	0.023 (± 0.003)	0.924	0.097	45	1, 2
13	31.440 (± 0.291)	− 0.048 (± 0.016)	/	0.019 (± 0.003)	0.918	0.073	41	1, 2
14	32.478 (± 0.455)	− 0.096 (± 0.026)	/	0.027 (± 0.004)	0.905	0.120	38	1
15	32.362 (± 0.439)	− 0.099 (± 0.025)	/	0.024 (± 0.004)	0.908	0.116	39	1
16	32.318 (± 0.371)	− 0.083 (± 0.021)	/	0.023 (± 0.003)	0.918	0.098	41	1, 3
17	31.664 (± 0.350)	− 0.059 (± 0.020)	/	0.023 (± 0.003)	0.910	0.092	40	1
18	32.928 (± 0.410)	− 0.094 (± 0.023)	/	0.020 (± 0.003)	0.907	0.103	36	1, 2

The values in parentheses represent the determination error; 1, diethyl-ether; 2, EtAc; 3, THF; 4, *i*-butanol; 5, water; 6, DCM

substituted compounds. They are excluded from these correlations because of the steric interferences.

By correlating these values with absorption frequencies of mTCHs, linear dependencies are obtained such as dependency given in Fig. 7. For all other solvents used, similar results were recorded.

As it can be seen, two separate dependencies are obtained. The first, with a positive slope, belongs to electron-donor substituents (negative values of the *Hammett's* constants), while the second, with a negative slope, describes the electron-acceptor substituents (positive values of the *Hammett's* constants) with deviation for compounds **9** (3-NO_2), **14** (3-Cl), and **16** (3-Br). Results of correlations for all solvents used are given in Table 4.

The effect of substituent present is reflected through the absolute value of proportionality constant ρ—the higher the values, the bigger the influence on the change of electronic density in the molecule. From Table 4, it can be seen that greater impacts on spectral behavior of mTCHs have electron-acceptor substituents. Negative sign in front of all values of ρ for electron-acceptor substituents indicates a

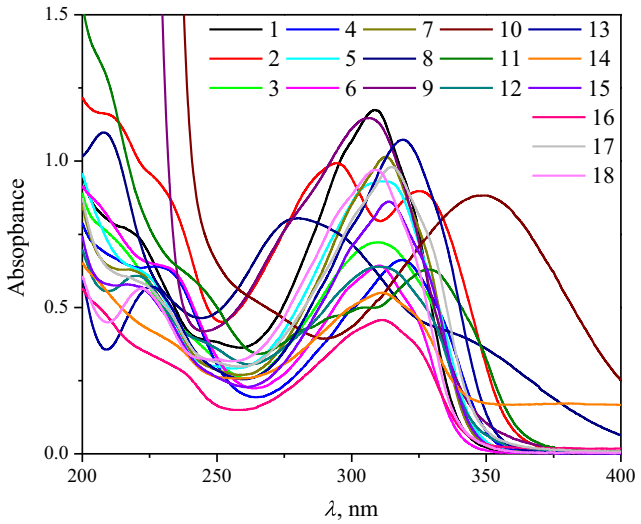


Fig. 6 UV–Vis Absorption spectra of all monothiocarbohydrazones recorded in water

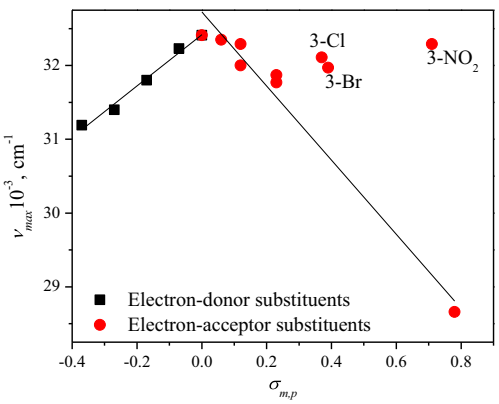


Fig. 7 Correlations of absorption frequencies of mTCHs in water with *Hammett's* constants

Table 4 Regression coefficients of *Hammett's* equation

Solvent/ parameter	$\nu_0 \cdot 10^{-3}$. cm^{-1}	$\rho \cdot 10^{-3}$. cm^{-1}	r	sd
Electron-donors				
Water	32.418 (± 0.050)	3.482 (± 0.226)	0.983	0.040
Methanol	32.080 (± 0.073)	3.385 (± 0.331)	0.986	0.098
Ethanol	31.960 (± 0.045)	3.339 (± 0.203)	0.994	0.061
n-Propanol	31.969 (± 0.071)	3.220 (± 0.320)	0.985	0.095
n-Butanol	31.904 (± 0.068)	3.204 (± 0.309)	0.986	0.092
n-Pentanol	31.848 (± 0.072)	3.305 (± 0.328)	0.986	0.098
i-Butanol	31.864 (± 0.054)	3.308 (± 0.247)	0.992	0.073
i-Propanol	31.844 (± 0.041)	3.262 (± 0.187)	0.995	0.056
t-Butanol	31.730 (± 0.095)	3.242 (± 0.431)	0.974	0.128
Acetic acid	32.055 (± 0.065)	3.290 (± 0.294)	0.988	0.088
2-ClEtOH	32.210 (± 0.046)	3.761 (± 0.207)	0.995	0.062
ACN	31.821 (± 0.069)	3.267 (± 0.311)	0.987	0.093
DMSO	31.714 (± 0.060)	3.230 (± 0.272)	0.990	0.081
DMF	31.655 (± 0.069)	2.996 (± 0.313)	0.984	0.093
DMA	31.626 (± 0.057)	3.071 (± 0.258)	0.990	0.077
DCM	31.623 (± 0.028)	3.085 (± 0.126)	0.998	0.038
Chloroform	31.594 (± 0.040)	3.206 (± 0.183)	0.995	0.054
EtAc	31.591 (± 0.048)	3.253 (± 0.216)	0.993	0.064
THF	31.565 (± 0.057)	3.120 (± 0.258)	0.990	0.077
1,4-dioxan	31.557 (± 0.064)	3.166 (± 0.283)	0.988	0.086
Diethyl-ether	31.458 (± 0.025)	3.137 (± 0.114)	0.998	0.034
Electron-acceptors				
Water	32.727 (± 0.125)	− 5.025 (± 0.383)	− 0.966	0.245
Methanol	32.352 (± 0.134)	− 5.140 (± 0.410)	− 0.985	0.262
Ethanol	32.192 (± 0.127)	− 5.284 (± 0.388)	− 0.987	0.248
n-Propanol	32.094 (± 0.113)	− 5.039 (± 0.344)	− 0.989	0.220
n-Butanol	32.073 (± 0.125)	− 5.259 (± 0.384)	− 0.987	0.245
n-Pentanol	31.999 (± 0.124)	− 5.204 (± 0.380)	− 0.987	0.243
i-Butanol	32.147 (± 0.144)	− 5.339 (± 0.442)	− 0.983	0.282
i-Propanol	32.178 (± 0.156)	− 5.479 (± 0.477)	− 0.982	0.305
t-Butanol	31.898 (± 0.132)	− 5.318 (± 0.404)	− 0.986	0.258
Acetic acid	32.244 (± 0.137)	− 5.109 (± 0.420)	− 0.983	0.268
2-ClEtOH	32.393 (± 0.134)	− 5.129 (± 0.412)	− 0.984	0.263
ACN	32.022 (± 0.134)	− 5.322 (± 0.410)	− 0.986	0.262
DMSO	31.882 (± 0.116)	− 5.425 (± 0.356)	− 0.989	0.228
DMF	31.843 (± 0.121)	− 5.392 (± 0.372)	− 0.988	0.238
DMA	31.771 (± 0.106)	− 5.349 (± 0.326)	− 0.991	0.208
DCM	31.827 (± 0.129)	− 5.426 (± 0.396)	− 0.987	0.253
Chloroform	31.768 (± 0.130)	− 5.422 (± 0.398)	− 0.987	0.254
EtAc	31.703 (± 0.128)	− 5.293 (± 0.391)	− 0.987	0.250
THF	31.690 (± 0.137)	− 5.521 (± 0.420)	− 0.986	0.268
1,4-dioxan	31.649 (± 0.129)	− 5.432 (± 0.394)	− 0.987	0.252
Diethyl-ether	31.580 (± 0.127)	− 5.480 (± 0.388)	− 0.988	0.248

reduced electron density in the excited state related to the ground. On the other hand, when proportionality constant has a positive sign there will be an increased electron density in the excited state in relation to the basic. In the end, observing values only within one type of substituents, it can be concluded that properties of the solvents used have no significant

effect on the absorption changes caused by the nature of the substituent (values of the proportionality constants for all solvents used are very close).

The reason for the deviation of the three mentioned compounds (**9**, **14**, and **16**) can be explained using resonant structures of the tested compounds presented on Scheme 2. A negative charge is clearly observed in the *ortho* and *para* positions, while *meta* positions are regions with a lack of electron density. The nitro group, as the strongest electron-acceptor, stabilizes *ortho* and *para* positions very well. For the same reason, this group in the *meta* position cannot express its electronic effects at full capacity. This behavior is characteristic for other *meta*-substituted derivatives with electron-acceptor substituents (such as compound **14** and **16**).

Determination of acidity constants (pK_a) of monothiocarbohydrazones

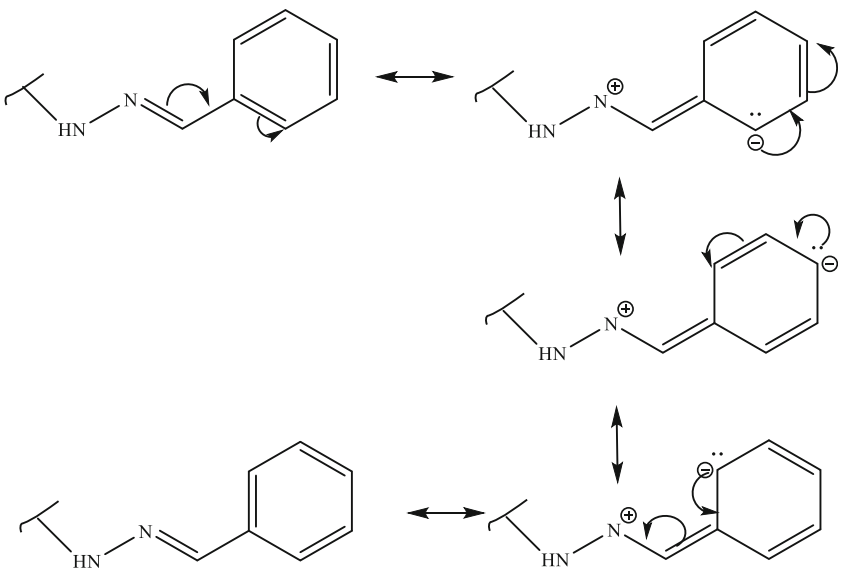
Determination of important physicochemical parameters such as acidity constant (pK_a value) is performed in early stage of testing new potential drugs due to easier determination of their further application. pK_a of mTCHs was theoretically calculated using the ADMET predictor [31] and experimentally determined by potentiometric titration. Compounds **9**, **10**, and **16** were not sufficiently soluble in methanol: water mixture, so their acidity constants were not determined. For all other compounds determinations were performed within the pH range 2.5–12.0. Possible protolytic equilibria present in studied solutions is shown on Scheme 3, exemplified by compound 4. pK_a Value of terminal amino group was determined for all compounds, while for compounds **2**–**4**, containing hydroxyl group as a substituent, pK_a value of phenolic group was also obtained. Obtained results are shown in Table 5.

Table 5 Theoretically calculated (p$K_{a\ calc}$) and experimentally determined (p$K_{a\ exp}$) pK_a values of mTCHs

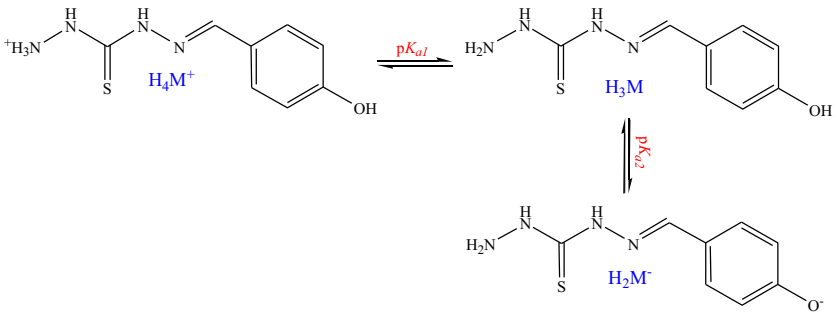
Compound	p$K_{a1\ calc}$	p$K_{a1\ exp}$	p$K_{a2\ calc}$	p$K_{a2\ exp}$
1	3.67	3.49 ± 0.05		
2	3.51	3.63 ± 0.07	8.94	9.18 ± 0.08
3	3.52	3.74 ± 0.09	9.11	9.86 ± 0.07
4	3.73	3.62 ± 0.07	9.00	10.37 ± 0.11
5	3.75	3.82 ± 0.04		
6	3.79	3.64 ± 0.03		
7	3.80	3.67 ± 0.06		
10	3.07	3.30 ± 0.27		
11	3.73	2.90 ± 0.09		
12	3.71	3.63 ± 0.03		
13	3.81	2.96 ± 0.10		
14	3.26	3.71 ± 0.02		
16	3.53	3.65 ± 0.01		
17	3.59	3.48 ± 0.04		
18	3.69	3.77 ± 0.03		

As can be seen from Table 5, values of the experimentally obtained acid constants of mTCHs showed good agreement with the predicted pK_a. For compounds **11** and **13** with -OCH_3 substituent in *ortho* and *para* position obtained pK_a have noticeable lower values that the predicted. Similarity between these two compounds is due to the same electronic effects of –OCH_3 group in mentioned positions. In general, by observing the results within Table 5, small differences between experimentally determined values of pK_{a1} (NH_3^+/NH_2) can be noted. This trend can be explained by the fact that due to the large distance of the substituent present on the benzene ring from the ionization center, its electronic effects cannot be manifested.

Scheme 2 Resonant structures of thiocarbohydrazone derivatives



Scheme 3 Possible equilibrium in solution for compound **4**



TD–DFT calculations

In order to further support experimental findings, theoretical UV–Vis absorption spectra of *E* and Z isomers of all synthesized monothiocarbohydrazones in DMSO were calculated from MP2 optimized structures by TD–DFT method using CAM–B3LYP functional and 6-311G(d,p) basis set. Obtained results of TD–DFT calculations, oscillator strength, vertical excitation energies, and orbital decomposition of electronic transitions are presented in Tables S6 and S7. A comparison of experimentally obtained and theoretically calculated spectra of the *E* isomer of compound **17** in DMSO is shown in Fig. 8.

The obtained results of quantum chemical calculations are in good qualitative agreement with the experimental data. Most of the compounds have a bathochromic shift relative to unsubstituted compound with the exception of compound **5** where small hypsochromic shifting was noted. TD–DFT calculations show that, due to its planar geometries, *E* isomers have first absorption maxima at lower energies than *Z* isomers. For most of the *E* isomers, the main contribution to the first excited state comes from HOMO–LUMO single particle excitation. On the other hand, in the case of *Z* isomers, for the first excited state, the transition from HOMO to LUMO is expressed in a significantly smaller percentage and is often coupled with other orbital transitions. On Fig. S2 some orbitals included in electron excitations for *E* isomers of mTCHs are shown. Photon absorption can induce a deformation in the molecular electronic cloud due to appropriate partial shift of electrons from one moiety of a molecule to another. In order to quantify this phenomenon known as intramolecular charge transfer (ICT), charge transfer distance (D_{CT}) was calculated using the TD–DFT method. The results of the calculations of the ICT index for *E* isomers of all investigated compounds are shown in Table 6. On Fig. 9 the difference between electronic densities in the ground and first excited state (left picture) and positions of charge loss and charge gain barycenters (right picture) are shown. In the *nitro*-substituted compounds **8**, **9**, and **10**, during excitations, the ICT process is noticed from the nitro group to thiocarbohydrazide moiety. In compound **10**, charge is transferred across the longer distance (4.051 Å) from nitro group in para position to the thiocarbohydrazide part of the molecule. As can be seen in Fig. 9, the positions of barycenters confirm the ICT character of *nitro*-substituted compounds (**8**, **9**, and **10**). In other compounds, the degree of CT character of an electronic transition is low.

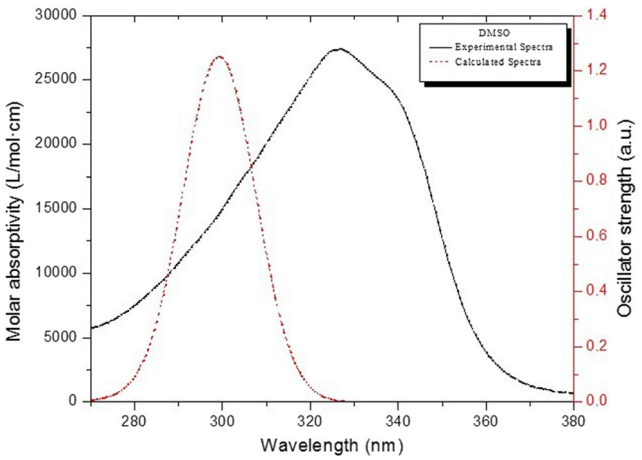


Fig. 8 Theoretically calculated and experimentally determined UV–Vis absorption spectra of the *E* isomer of compound **17** in DMSO

Conclusion

Within this paper, eighteen compounds of monothiocarbohydrazones were synthesized under controlled conditions in order to avoid the formation of bis-compounds.

Table 6 Calculated values of D_{CT} during electron excitation for *E* isomer

Compound	*es*	D_{CT} (Å)	Compound	*es*	D_{CT} (Å)
1	1	1.118	10	1	4.051
2	1	0.464	11	1	0.642
3	1	0.541	12	1	0.346
4	1	0.287	13	1	0.411
5	1	1.012	14	1	1.466
6	1	0.961	15	1	1.018
7	1	0.581	16	1	1.453
8	1	2.127	17	1	0.908
	2	1.133			
9	1	3.897	18	1	0.904

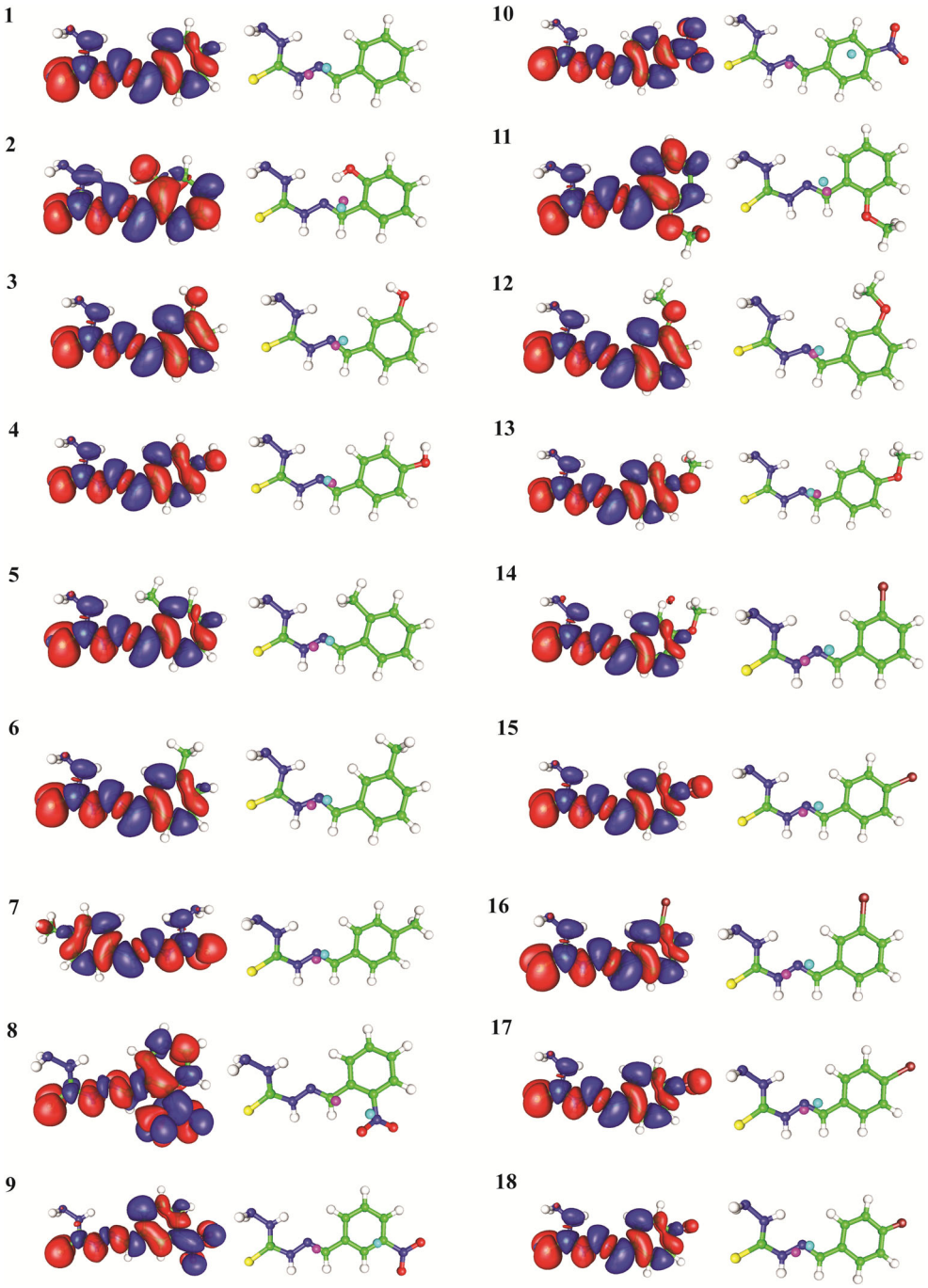


Fig. 9 ICT processes in *E* isomers of monothiocarbohydrazones (**1**–**18**). Left images, difference between densities in first excited and ground state (red and blue, density increase and decrease upon transition, respectively); right images, positions of barycenters for charge loss (cyan circle) and charge gain (violet circle) upon transition

Purity and structure of the synthesized compounds was confirmed by NMR and FT–IR spectroscopy and elemental analysis. A proof that all synthesized compounds belong to monoderivatives is given trough the existence of a signal in the region between 4.70 and 4.91 ppm (^{1}H NMR spectra) assigned to the NH_2 group, for all compounds. Optimized structures show that *E* isomer is more stable for all derivatives and that most of the synthesized compounds have planar structures (exceptions are compounds with –OH, $–NO_2$, and $–OCH_3$ groups in *ortho* positions). For compound **17** (4–Br), X-ray structural analysis was performed, and obtained results are in agreement with theoretical calculations. The effect of specific and non-specific solvent–solute interactions studied by *Catalan's* model showed that the greatest impact on spectral changes of the mTCHs has the acidity of the solvent used (exceptions are compounds **2** and **10**). Somewhat smaller effects on maxima shifting have polarizability and dipolarity of the solvent, while the basicity of the solvent has the slightest impact on spectral changes of the investigated derivatives. In addition to the solvent effect, results of the correlations of the absorption maxima with *Hansen's*

solubility parameters showed that the dispersion forces are the most dominant interactions between the examined mTCHs and the surrounding medium. They are followed by the influence of hydrogen bond construction and finally, with the smallest impact, dipolar forces. Results of the influence of the substituent present on the UV–Vis absorption spectra of mTCHs determined using *Hammett's* equation show that greater impact on spectral behavior of mTCHs has electron-acceptor than electron-donor substituents. Also, it has been concluded that properties of the solvents used have no significant effect on the absorption changes caused by the nature of the substituent. Experimentally obtained pK_a values of mTCHs showed good agreement with the theoretically calculated ones and for amino group were in the range from 2.90 to 3.77. For compounds **2**–**4**, pK_a of the phenol group were also determined (9.18, 9.86 and 10.37, respectively). Theoretically predicted UV–Vis absorption spectra calculated in DMSO showed good agreement with experimentally obtained spectra. TD–DFT calculations in DMSO showed that for *E* isomers of the mTCHs the main contribution to the first excited state comes from HOMO–LUMO single particle excitation. In *nitro*-substituted compounds (**8**, **9**, and **10)**, the ICT process was noticed and electron density was transferred from the nitro group to the thiocarbohydrazide part of the molecule.

The obtained results gave insight into physicochemical properties of monothiocarbohydrazones and opened the possibilities for the future examinations in the field of potential biological activities and application of these compounds.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11224-020-01700-y.

Author's contribution All authors contributed to the study conception and design. Material preparation, data collection, and synthesis of the compounds were performed by G. Mrdjan. Structural characterization, X-ray analysis, and interpretation of the specific and non-specific interactions were performed and analyzed by G. Mrdjan, D. Škorić, M. Radanović, Gy. Vastag, and B. Matijević. Determination of the pK_a was performed by T. Verbić, and O. Marković. TD–DFT calculations were carried out by M. Milčić, and I. Stojiljković. The first draft of the manuscript was written by G. Mrdjan, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding The authors acknowledge financial support of the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grants No. 451-03-68/2020-14/ 200125; 451-03-68/2020-14/ 200026; 451-03-68/2020-14/200168).

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Consent to participate This article does not contain any studies involving animals performed by any of the authors.

Consent to publish All the authors mentioned in the manuscript have given consent for submission and subsequent publication of the manuscript.

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