



Dedicated to the memory of Professor Margareta Avram  
on the remembrance of her 100<sup>th</sup> anniversary

## EXAMINATION OF STRUCTURE-ACTIVITY RELATIONSHIP OF NEW *N*-ACYLHYDRAZONES\*\*

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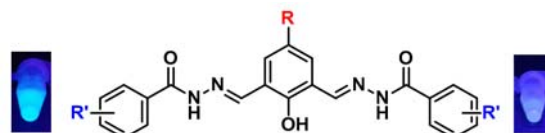
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In this study we describe synthesis and characterization of new substituted hydroxy-bis-*N*-acylhydrazones in order to investigate influence of their switching emission properties, according to the nature of the substituent. The fluorescence of the compounds depended on the solvent used (organic or aqueous). The different emission colors observed could be explained by conformation modifications.



New *N*-Acylhydrazones display different colour emissions

### INTRODUCTION

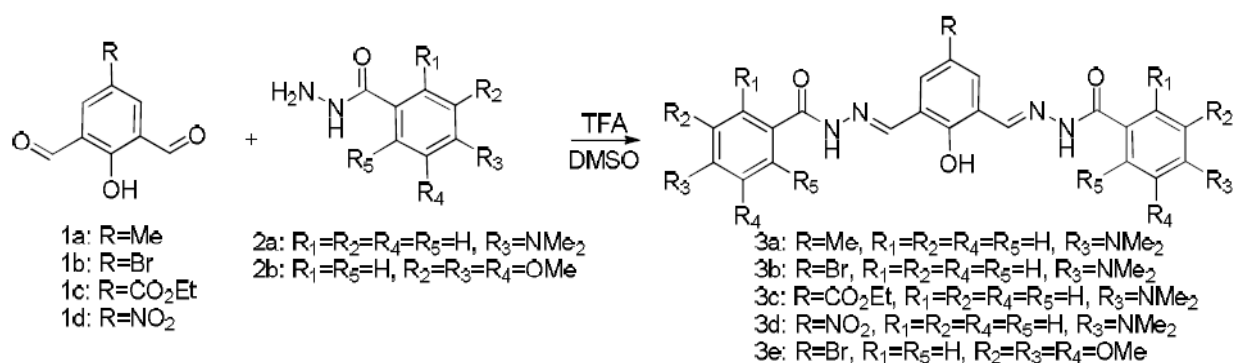
*N*-acylhydrazones are organic molecules that found numerous and useful applications in different fields of chemistry, from biological and medicinal chemistry<sup>1</sup> to supramolecular, dynamic and materials chemistry.<sup>2</sup> Addition of functionalities on the molecular core or increase in the number of the hydrazone moieties come along with new properties (*i.e.* luminescence) that allows expansion of their usefulness.<sup>3</sup> Moreover, the highly reactive electrophilic character of the hydrazone bond affords cyclisation to aromatic nitrogen-based heterocycles (*i.e.* 1,3,4-oxadiazoles) under the action of oxidizing reagents.<sup>4</sup> Hydroxy-bis-*N*-acylhydrazones were very

much encountered as ligands for metal-ions,<sup>5</sup> organogelators<sup>6</sup> or light emissive switching molecules.<sup>7</sup>

As a continuation of our work, corroborated with the structural simplicity and convenient preparation, we continued to scan behavior of such molecules. Thus, we performed a larger library of compounds (Scheme 1), by varying the substituents both on the aldehyde and hydrazide moiety. We chose a wide range of electron-donor or electron-withdrawing substituents, in an attempt to discover compounds with enhanced properties. We present here synthesis of compounds **3**, their characterization and investigation of the photophysical properties and responses to various stimuli.

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\*\* Supplementary information on <http://web.icf.ro/rrech/> or <http://revroum.lew.ro>

Scheme 1 – Synthesis of hydroxy-bis-*N*-acylhydrazones **3a–e**.

## RESULTS AND DISCUSSION

Considering our previous results<sup>7</sup> in which we preserved the substituent on the aldehyde moiety (*t*-butyl group) and varied the substituent on the hydrazide moiety, we performed the following structural changes: replacement of the *t*-butyl with methyl, bromine, ethyl ester and nitro groups and choose of the dimethylamine group on the hydrazide moiety (compounds **3a–d**). In addition, we synthesized compound **3e** in order to find the modification of the photophysical properties when the residue on the hydrazide moiety (trimethoxyphenyl) was preserved, in order to compare it with compound **3b**.

### Synthesis

Synthesis of compounds **3a–e** was achieved through condensation between the corresponding aldehyde and hydrazide, under acid catalysis of TFA (Scheme 1). The aldehydes **1b–d** were synthesized by Duff reaction of the *p*-substituted phenols, using a mixture of urotropine and trifluoroacetic acid, by a slightly modified previously described procedure.<sup>8</sup> The formylation reactions proceeded smoothly, in good yields and short reaction times (overnight), for **1b**<sup>9</sup> bearing electron-donor substituents, while dialdehydes **1c**<sup>10</sup> and **1d**<sup>11</sup> were obtained after prolonged times (several days). Dialdehyde **1a** was synthesized by oxidation of 2,6-bis(hydroxymethyl)-*p*-cresol with manganese dioxide, in very good yield (>90%).<sup>12</sup> Hydrazides **2a,b** were synthesized starting from the corresponding carboxylic acids in a two step sequence (esterification and reaction with hydrazine hydrate of the ester). Solubility tests indicated good solubility in polar solvents such as

DMSO, DMF or THF, unlike most hydrazone-based compounds, which have a well-known poor solubility.

### Absorption and emission properties

Absorption spectroscopy of compounds **3a–c** (Fig. 1) indicated two maxima at approximately  $\lambda_{\text{max}}=340$  and  $\lambda_{\text{max}}=370$  nm. Compound **3d** also displayed a band with a maximum at  $\lambda_{\text{max}}=438$  nm, while compound **3e** lacks the band at  $\lambda_{\text{max}}=340$  nm. The spectra of compounds **3c** and **3d** slightly differ from the spectra of compounds **3a,b**, which may be correlated to the presence of the electron-withdrawing substituents (ethyl ester and nitro residues).

The electronic properties are, thus, considerably affected by variation of the substituent nature. The molar extinction coefficients were calculated from the UV-Vis spectra at the indicated excitation wavelength and have great values, above  $30.000 \text{ M}^{-1}\text{cm}^{-1}$  (Table 1). Compound **3c** has the highest value of the molar absorptivity, which can be correlated with the extended conjugation between the phenol and the ester group. Measurements were performed on different dilutions in DMSO from stock solutions of compounds dissolved in DMSO  $10^{-2}$  M and the extinction coefficients were calculated as an average of the individual values resulted for each sample.

The fluorescence spectra (Fig. 2) generally displayed large emission bands, with maxima between  $\lambda_{\text{em}}=550\text{--}590$  nm, when excited at  $\lambda_{\text{exc}}=370$  nm, and blue shifted maxima, around  $\lambda_{\text{em}}=500$  nm, when excited between  $\lambda_{\text{exc}}=420\text{--}460$  nm (wavelengths chosen after excitation and emission scans).

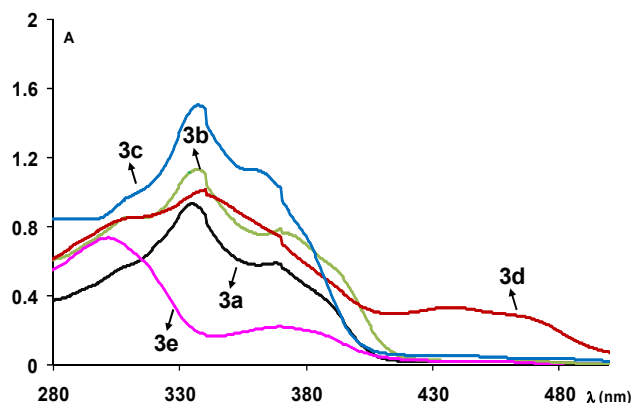
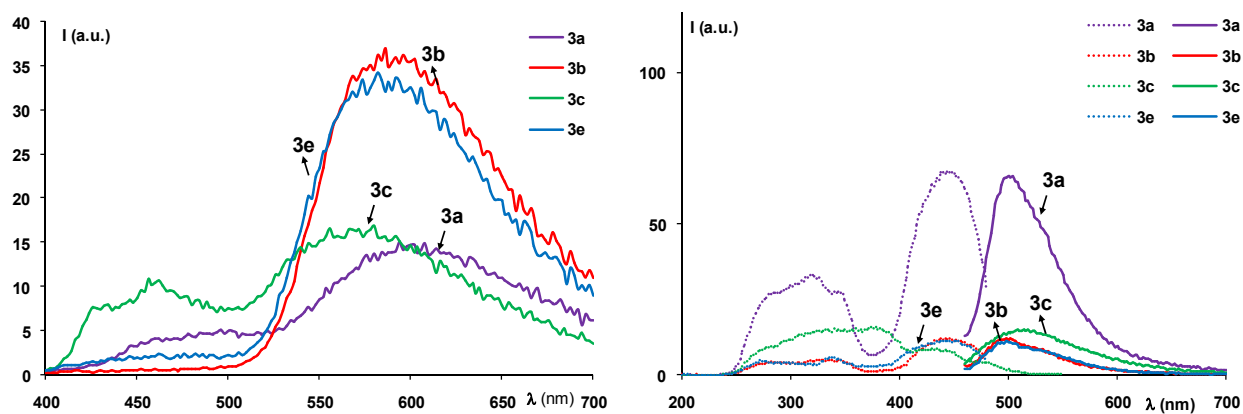
Fig. 1 – UV-Vis spectra of compounds **3a-e** recorded in DMSO.

Table 1

Photophysical properties of compounds **3a-e** in DMSO

Cmpn.	$\lambda_{\max}$	$\varepsilon$ ( $M^{-1}cm^{-1}$ ) $\times 10^{-4}$	$\lambda_{exc}$	$\lambda_{em}$	Stokes shift (nm, $cm^{-1} \times 10^{-4}$ )
<b>3a</b>	335	4.34	370	606	238, 10.53
	368	2.80	440	500	60, 2.72
<b>3b</b>	337	5.55	370	592	222, 10.18
	370	3.87	444	494	50, 2.28
<b>3c</b>	337	7.04	370	590	220, 10.08
	363	5.16	440	510	70, 3.13
<b>3d</b>	340	3.39	-*	-*	-*
	438	1.79			
<b>3e</b>	300	3.1	370	590	220, 10.08
	370	0.84	444	494	50, 2.28

\* luminescence intensity very low

Fig. 2 – Left: Emission spectra of compounds **3a-c** and **3e**, recorded in DMSO  $10^{-4}$  solutions ( $\lambda_{exc}=370$  nm). Right: Excitation and emission spectra of compounds **3a-c** and **3e**, recorded in DMSO  $10^{-4}$  solutions.

Differences in the absorption and excitation spectra, as well as the very large Stokes shift (almost 200 nm) and variation of the emission wavelength according to excitation confirmed the ESIPT process,<sup>13</sup> which occurs in molecules that are able to intramolecularly transfer a proton from a donor group (*i.e.* OH) to an acceptor group (*i.e.* C=N) when irradiated with light. The transfer of the proton (tautomerization) takes place in the

excited state and relaxation to the ground state occurs with emission of light. We have previously proved that the occurrence of this process in similar molecules<sup>7</sup> led to conformation modification and made these compounds behave as switchable light emissive molecules. However, the absorption and excitation spectra indicated a complex mechanism of light emission, which involves conformation and configurational

changes. All spectra of the newly synthesized compounds display a rather low light intensity, suggesting that the *tert*-butyl group is very important for the optical properties. Compound **3d**, bearing a nitro group, displays, as expected, almost no fluorescence, while compound **3e** behaves similarly to previously described ones,<sup>7</sup> as well as to **3b**.

Addition of water to DMSO solutions of the synthesized *N*-acylhydrazones led to a change of colour and red-shift of the emission maxima to yellow region, behaving similarly to our previous results,<sup>7</sup> however, with much smaller intensities of the light emission.

### Solid state structure of compound **3b**

Crystals suitable for X-ray diffraction were obtained compound **3b** from DMSO. Compound **3b** crystallizes together with DMSO solvent molecules in the monoclinic  $P2_1/c$  space group and its molecular structure is shown in Fig. 3 along with the atoms labelling scheme. The two C=N bonds of this bis-*N*-acylhydrazone are in the *E* configurations, but the two *N*-acylhydrazone arms are unsymmetrical due to different conformations around the C-N bonds. The solid state conformation is sustained by intra- and intermolecular hydrogen bonding. One *N*-acylhydrazone arm involves intramolecular hydrogen interaction between OH phenol group and N3 atom ( $O2-H2O\cdots N3=1.77$  Å), while the other arm exhibits intermolecular hydrogen bonds between N-H and DMSO molecules. ( $N5-H5\cdots O4=2.02$  Å). The four nitrogen atoms of the two hydrazone groups are almost coplanar with the

central benzene ring. The mean plans of the external benzene rings form with the mean plan of the central  $\pi$  system (including the benzene ring and the two imino groups) angles of  $2.0^\circ$  and  $3.4^\circ$  respectively. Selected bond lengths in the bis-*N*-acylhydrazone molecule are gathered in Table S1 in Supporting Information.

## EXPERIMENTAL

**Organic synthesis. General experimental information.** All commercial reactants and reagents were used without further purification. Thin layer chromatography (TLC) was performed on silica gel 60 coated aluminium F254 plates with visualization by UV irradiation at 254 and 365 nm. The NMR spectra were recorded on Bruker Advance Ultrashield Plus spectrometer operating at 500 MHz for  $^1H$  and 125 MHz for  $^{13}C$  or Bruker Fourier spectrometer operating at 300 MHz for  $^1H$  and 75 MHz for  $^{13}C$  and the numbering scheme of the atoms for which the spectra description is given is provided in Supporting Information. High resolution mass spectrum was recorded on Thermo Scientific (LTQ XL Orbitrap) spectrometer, in positive ion mode, using APCI technique. Melting points were determined in open capillary tubes using a STUART SMP3 electric melting point apparatus and are uncorrected. Hydrazides **2a,b** were synthesized from the corresponding carboxylic acids through esterification and subsequent reactions with hydrazine hydrate. Aldehydes **1b-d** were synthesized according to previously reported procedure<sup>8</sup> and their spectral characterisation is described in Supporting Information. All synthesized compounds matched the literature data.<sup>8-12</sup>

**General experimental procedure for the synthesis of compounds **3**.** A mixture of the corresponding dialdehyde (1 eq.) and the corresponding hydrazide (2 eq.) were dissolved in DMSO (up to a 0.1-0.01 M concentration) and a few drops of trifluoroacetic acid were added. The reaction mixture was heated at  $100^\circ C$  for 4 hours and left at room temperature overnight (12 h). To the reaction mixture water was added (90% v/v) and the resulting precipitate was filtered, washed with water and dried to afford pure product.

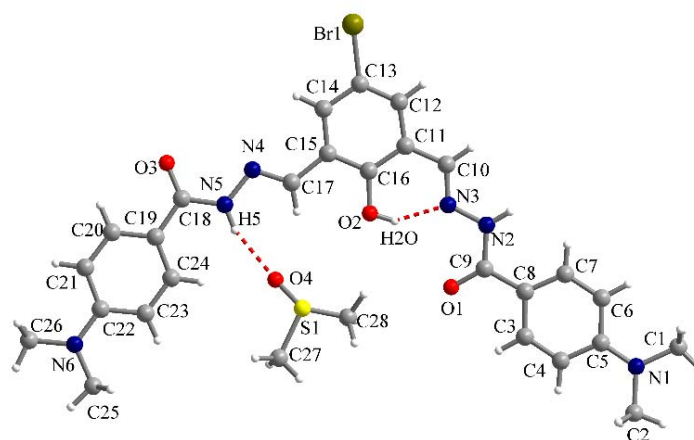


Fig. 3 – View of the asymmetric unit in the crystal structure of compound **3b**-DMSO along with the atoms labelling scheme (for clarity only the hydrogen atoms involved in hydrogen interactions were labelled).

**(*N',N'''E,N',N'''E*)-*N',N'''*-(2-hydroxy-5-methyl-1,3-phenylene)bis(methanylylidene)bis(4-(dimethylamino)benzohydrazide) 3a.** Yellow solid. Yield 81% (0.445 g). *m.p.* 209-212 °C. *R<sub>f</sub>*=0.29 (silica, DCM:MeOH=9:1). <sup>1</sup>H NMR (500.13 MHz, DMSO-*d*<sub>6</sub>): δ= 12.42 (s, 1H, -OH), 11.81 (s, 2H, -NH), 8.67 (s, 2H, H<sub>5</sub>), 7.84 (d, 4H, <sup>3</sup>*J* = 8.9 Hz, H<sub>7</sub>/H<sub>11</sub>), 7.50 (s, 2H, H<sub>3</sub>), 6.77 (s, 4H, <sup>3</sup>*J* = 8.9 Hz, H<sub>8</sub>/H<sub>10</sub>), 3.01 (s, 12H, -N(CH<sub>3</sub>)<sub>2</sub>), 2.31 (s, 3H, -CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (125.77 MHz, DMSO-*d*<sub>6</sub>): 162.7 (C=O), 154.4 (C-1), 152.6 (C-9), 144.5 (C-5), 129.7 (C-3), 129.2 (C-7/C-11), 128.1 (C-4), 120.2 (C-2), 118.9 (C-6), 110.9 (C<sub>8</sub>/C<sub>10</sub>), 39.6 (-N(CH<sub>3</sub>)<sub>2</sub> overlapped with DMSO), 20.0 (-CH<sub>3</sub>) ppm. HRMS (APCI, +) *m/z*: calc. for C<sub>27</sub>H<sub>31</sub>N<sub>6</sub>O<sub>3</sub> [M+H]<sup>+</sup> 487.2458; found 487.2447.

**(*N',N'''E,N',N'''E*)-*N',N'''*-(5-bromo-2-hydroxy-1,3-phenylene)bis(methanylylidene)bis(4-(dimethylamino)benzohydrazide) 3b.** Light-yellow solid. Yield 81% (0.446 g). *m.p.* 284-287 °C. *R<sub>f</sub>*=0.87 (silica, DCM:MeOH=9:1). <sup>1</sup>H NMR (500.13 MHz, DMSO-*d*<sub>6</sub>): δ= 12.88 (s, 1H, -OH), 11.98 (s, 2H, -NH), 8.65 (s, 2H, H<sub>5</sub>), 7.85-7.83 (m, 6H, H<sub>3</sub> and H<sub>7</sub>/H<sub>11</sub>), 6.77 (d, 4H, <sup>3</sup>*J* = 8.8 Hz, H<sub>8</sub>/H<sub>10</sub>), 3.01 (s, 12H, -N(CH<sub>3</sub>)<sub>2</sub>), ppm. <sup>13</sup>C NMR (125.77 MHz, DMSO-*d*<sub>6</sub>): 162.8 (C=O), 155.2 (C-1), 152.7 (C-9), 142.9(C-5), 130.8 (C-3), 129.3 (C-7/C-11), 122.7 (C-2), 118.6 (C-6), 110.9 (C<sub>8</sub>/C<sub>10</sub>), 110.7 (C-4), 39.5 (-N(CH<sub>3</sub>)<sub>2</sub> overlapped with DMSO) ppm. HRMS (APCI, +) *m/z*: calc. for C<sub>26</sub>H<sub>28</sub>BrN<sub>6</sub>O<sub>3</sub> [M+H]<sup>+</sup> 551.1406, 553.1386; found 553.1374.

**Ethyl 3,5-bis((*E*)-(2-(4-(dimethylamino)benzoyl)hydrazono)methyl)-4-hydroxybenzoate 3c.** Light-yellow solid. Yield 82% (0.446 g). *m.p.* 284-296 °C. *R<sub>f</sub>*=0.43 (silica, DCM:MeOH=9:1). <sup>1</sup>H NMR (500.13 MHz, DMSO-*d*<sub>6</sub>): δ= 13.50 (s, 1H, -OH), 11.98 (s, 2H, -NH), 8.74 (s, 2H, H<sub>5</sub>), 8.28 (s, 2H, H<sub>3</sub>), 7.85 (d, 4H, <sup>3</sup>*J* = 8.9 Hz, H<sub>7</sub>/H<sub>11</sub>), 6.78 (d, 4H, <sup>3</sup>*J* = 8.9 Hz, H<sub>8</sub>/H<sub>10</sub>), 4.36 (q, 2H, <sup>3</sup>*J* = 7.1 Hz, CH<sub>2</sub> (Et)), 3.01 (s, 12H, -N(CH<sub>3</sub>)<sub>2</sub>), 1.36 (t, 3H, <sup>3</sup>*J* = 7.1 Hz, CH<sub>3</sub> (Et)) ppm. <sup>13</sup>C NMR (125.77 MHz, DMSO-*d*<sub>6</sub>): 165.0 (COOEt), 162.8 (C-1), 160.0 (C=O), 152.7 (C-9), 143.6 (C-5), 130.0 (C-3), 129.3 (C-7/C-11), 121.2 (C-4), 120.6 (C-2), 118.6 (C-6), 110.9 (C<sub>8</sub>/C<sub>10</sub>), 60.8 (CH<sub>2</sub> (Et)), 39.5 (-N(CH<sub>3</sub>)<sub>2</sub> overlapped with DMSO), 14.4 (CH<sub>3</sub> (Et)) ppm. HRMS (APCI, +) *m/z*: calc. for C<sub>29</sub>H<sub>33</sub>N<sub>6</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 545.2512, found: 545.2499.

**(*N',N'''E,N',N'''E*)-*N',N'''*-(2-hydroxy-5-nitro-1,3-phenylene)bis(methanylylidene)bis(4-(dimethylamino)benzohydrazide) 3d.** Orange solid. Yield 94% (0.487 g). *m.p.* 269-271 °C. *R<sub>f</sub>*=0.40 (silica, DCM:MeOH=9:1). <sup>1</sup>H NMR (500.13 MHz, DMSO-*d*<sub>6</sub>): δ= 14.03 (s, 1H, -OH), 12.1 (s, 2H, -NH), 8.76 (s, 2H, H<sub>5</sub>), 8.56 (s, 2H, H<sub>3</sub>), 7.86 (d, 4H, <sup>3</sup>*J* = 9.0 Hz, H<sub>7</sub>/H<sub>11</sub>), 6.68 (s, 4H, <sup>3</sup>*J* = 8.8 Hz, H<sub>8</sub>/H<sub>10</sub>), 3.01 (s, 12H, -N(CH<sub>3</sub>)<sub>2</sub>) ppm. <sup>13</sup>C NMR (125.77 MHz, DMSO-*d*<sub>6</sub>): 162.9 (C=O), 161.3 (C-1), 152.7 (C-9), 142.5(C-5), 139.9 (C-4), 129.3 (C-7/C-11), 123.8 (C-3), 121.2 (C-2), 118.4 (C-6), 110.8 (C<sub>8</sub>/C<sub>10</sub>), 39.5 (-N(CH<sub>3</sub>)<sub>2</sub> overlapped with DMSO) ppm. HRMS (APCI, +) *m/z*: calc. for C<sub>26</sub>H<sub>28</sub>N<sub>7</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 518.2152, found: 518.2143.

**(*N',N'''E,N',N'''E*)-*N',N'''*-(5-bromo-2-hydroxy-1,3-phenylene)bis(methanylylidene)bis(3,4,5-trimethoxybenzohydrazide) 3e.** Light-yellow solid. Yield 83% (0.535 g). *m.p.* 283-285 °C. *R<sub>f</sub>*=0.50 (silica, DCM:MeOH=9:1). <sup>1</sup>H NMR (300.18 MHz, DMSO-*d*<sub>6</sub>): δ= 12.77 (s, 1H, -OH), 12.17 (s, 2H, -NH), 8.70 (s, 2H, H<sub>5</sub>), 7.91 (s, 2H, H<sub>3</sub>), 7.27 (s, 4H, H<sub>7</sub>/H<sub>11</sub>), 3.87 (s, 12H, -OCH<sub>3</sub> near C-8 and C-10), 3.74 (s, 6H, -OCH<sub>3</sub> near C-9) ppm. <sup>13</sup>C NMR (75.48 MHz, DMSO-*d*<sub>6</sub>): 165.0 (C=O), 155.6 (C-1), 152.9 (C-6 or C-9), 144.5 (C-5), 140.5 (C-8/C-10), 131.6 (C-3), 127.7 (C-6 or C-9), 122.5 (C-2), 111.1 (C-4), 105.4 (C-7/C-11), 60.3 (-OCH<sub>3</sub> near C<sub>9</sub>), 56.2 (-OCH<sub>3</sub> near C-8 and C-10) ppm.

HRMS (APCI, +) *m/z*: calc. for C<sub>28</sub>H<sub>30</sub>BrN<sub>4</sub>O<sub>9</sub> [M+H]<sup>+</sup>: 645.1196, 647.1176, found: 647.1166.

**Absorption and emission spectroscopy.** UV- VIS spectroscopy. Absorption spectra were recorded with a Jasco V-630 spectrophotometer, using 10 mm quartz cell. Stock solutions of compound were prepared in DMSO (10<sup>-2</sup> mol L<sup>-1</sup>), diluted to 2 × 10<sup>-5</sup> mol L<sup>-1</sup>.

**Fluorescence spectroscopy.** Fluorescence spectra were recorded with a Thermo Scientific Varioskan Flash spectral scanning multimode reader. The spectra were recorded in suitable plates using 5 nm excitation and emission slits for all measurements. Stock solutions of compound were prepared in DMSO (10<sup>-2</sup> mol L<sup>-1</sup>), diluted to 10<sup>-4</sup> mol L<sup>-1</sup>.

**X-ray structure determination.** X-ray diffraction measurements were performed on a STOE IPDS II diffractometer, operating with Mo-Kα (λ = 0.71073 Å) X-ray tube with graphite monochromator. The structure was solved by direct methods and refined by full-matrix least squares techniques based on *F*<sup>2</sup>. The non-H atoms were refined with anisotropic displacement parameters. Calculations were performed using SHELX-2014 crystallographic software package. A summary of the crystallographic data and the structure refinement for crystal **3b** are given in Table S2. CCDC reference number: 1914206.

## CONCLUSIONS

In conclusion, we described synthesis of new bis-*N*-acylhydrazones that bear various electron donor and withdrawing substituents, in order to study their influence on the photophysical properties. In general, the compounds display a weak fluorescence in organic solvent (DMSO) and modifications of the emission does not vary significantly. However, few differences in the electronic and optical properties may be correlated to the structural variation and the donor or withdrawing character of the substituents.

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