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New N-aryloxy-phthalimide derivatives. Synthesis, physico-chemical properties, and QSPR studies

Research Article

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Abstract: Starting from N-hydroxyphthalimide **1** and the reactive fluoro- or chloro-nitroaryl derivatives **2**, **3** and **4a–e** (2-chloro-3,5-dinitropyridine; **3**, NBD-chloride; **4a**, 1-fluoro-2,4-dinitrobenzene; **4b**, picryl chloride; **4c**, 4-chloro-3,5-dinitrobenzotrifluoride; **4d**, 2-chloro-3,5-dinitrobenzotrifluoride; **4e**, 4-chloro-3,5-dinitrobenzoic acid) the corresponding N-(2-nitroaryloxy)-phthalimide derivatives **5a–e**, or **6** and **7** were obtained and characterized by IR, UV-Vis ^{1}H-NMR and ^{13}C-NMR spectroscopy. The TLC behavior and the hydrophobicity of these derivatives have been experimentally evaluated by R_{M0} parameters (using RP-TLC). The experimental R_{M0} parameters were compared with the calculated partition coefficient, log P. A QSPR study was also performed to establish possible correlations between the structure and physical properties (λ_{max} and R_{M0}) of compounds **5a–e**, **6**, and **7**.

Keywords: *N-aryloxy-phthalimide derivatives • UV-Vis • TLC • RP-TLC • QSPR*

1. Introduction

N-Hydroxy-phthalimide **1** (known also as NHPI), is a commercially available compound that is easily synthesized from phthalic anhydride and hydroxylamine [1] (obtained for the first time by Cohn [2] in 1880). This compound is a weak acid (pK_a = 6.1) [3,4] and has a variety of practical uses. Recently, it has been used as a catalyst in oxidation processes, *via* the phthalimide *N*-oxyl radical [5] (known as PINO). The PINO radical can be obtained in several ways [5-7], and has an important role in the oxidation of a large variety of compounds, including aliphatic hydrocarbons [7,8], alkylbenzenes [9,10], alcohols and aliphatic amines [11,12], benzylamines [13], N-alkylamides [14], *etc*. *O*-Substituted hydroxylamines have found applications in medicinal chemistry, having antihistaminic and bactericidal properties, as well as being used as prophylactic chemicals in protecting animals against ionizing radiations [15,16]. Such types of compounds are not easily synthesized, because direct alkylations of the hydroxyl group of the hydroxylamine usually leads to *N*-substituted derivatives. Thus, for obtaining the *O*-substituted derivatives, the first step consists in protecting the amino group. The current way to obtain such derivatives starts from **1**, which is derivatized with a reactive reagent (*i.e.*, an activated haloderivative), and the resulting compound is treated with acid, hydrazine or hydroxylamine to prepare the expected *O*-substituted hydroxylamine, possibly followed by deprotection [15,19].

Starting from compounds **1**, **2**, **3** and **4a-e**, we report the synthesis of seven nitro-substituted N-(2-nitroaryloxy)-phthalimide derivatives **5a–e**, or **6** and **7** (Fig.1), where compounds **5a,b** were known [15,19]. All the synthesized compounds were characterized by IR, NMR, UV-Vis and TLC to confirm their structure.

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Because such compounds may have some biological activity, we studied their hydrophobicity (lipophilicity) using different chromatographic systems. We also used QSPR (quantitative structure-property relationships) for studying these synthesized compounds **5a–e**, **6** and **7** (Fig. 1).

2. Experimental Procedure

All the starting chemicals (*N*-hydroxyphthalimide **1**, 2-chloro-3,5-dinitropyridine **2**, NBD-chloride **3**, 1-fluoro-2,4-dinitrobenzene **4a**, 4-chloro-3,5-dinitrobenzotrifluoride **4c**, 2,4-dinitro-6-trifluoromethyl-chlorobenzene **4d**, and 4-chloro-3,5-dinitrobenzoic acid **4e**) were purchased from Sigma-Aldrich and used as received. Picryl chloride **4b** was synthesized as we described previously [20]. Preparative and analytical silica gel TLC plates were purchased from Sigma-Aldrich and Merck. Solvents were purchased from Chimopar or Sigma-Aldrich and used without further purification.

UV-Vis spectra were recorded in methanol at room temperature (22°C) using a UVD-3500 spectrophotometer. IR spectra were recorded in solid state (ATR) on a Bruker Vertex 70 spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker BB300 instrument, using deuterated chloroform or deuterated dimethylsulfoxide as solvent.

2.1. Computational details.

The values of octanol-water partition coefficient (*log P*) for compounds **1**, **5a–e**, **6**, and **7** were calculated by means of the Hyperchem program (trial version [21]); values of net atomic charges and dipole moments for these compounds were calculated with the MOPAC program (a semiempirical molecular orbital package developed by J. J. P. Stewart [21]). For the geometry optimization we used the semiempirical PM3 (parametric method number 3) method [21,22] implemented in the program ArgusLab [23], because the MM+ [24] force field and the AM1 [25] method did not lead to satisfactory results. The geometry optimizations were performed without symmetry constraints applying the geometry-optimizing routine EF (eigenvector following [26]) and were completed after reaching a gradient norm of 0.01 kcal mol^{-1} Å^{-1}. To obtain the energies displayed in Table 4 we used the Gamess program and hybrid QM/MM force field [27].

2.2. Synthesis of compounds 5a–e, 6, and 7.

The synthesis of these compounds has been performed according to literature data (available for compounds **5a,b**) [15,19]. The general procedure involves the reaction of the reactive chloro- or fluoro-derivatives **2**, **3**, and **4a-e** with N-hydroxyphthalimide **1** in dry acetone as solvent and in the presence of triethylamine. The ratio between these reagents was 1 : 1.1 : 1.2 (halogen-derivative : *N*-hydroxyphthalimide : triethylamine), exception being made for the synthesis of compound **5e**, when a twofold excess of triethylamine has been used to neutralize the COOH group. The reaction mixture was stirred at room temperature for at least 2 h, then the mixture was poured into icy water, and allowed to stand overnight at 4°C. Then the precipitate was filtered off, washed with hexane and dried in a dessicator. If the purity of the final product (as checked by TLC) was not satisfactory, the product was purified by preparative TLC on silica gel using methylene chloride as eluent.

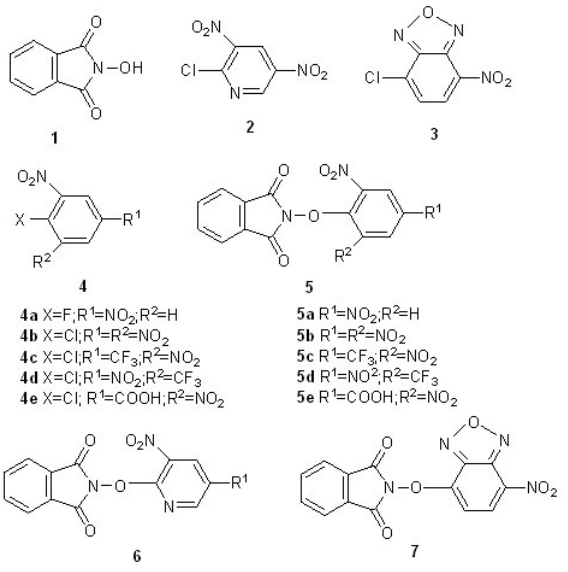

Figure 1. Compounds **1**-**7**.

5a (*N-(2,4-Dinitrophenyl)oxyphthalimide*), yield 88%, mp. 180-183°C, ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 8.97 (d, 1H, H-11, 2.7); 8.44 (dd, 1H, H-13, 2.7, 9.2); 7.99 (m, 2H, H-1, H-4); 7.91 (m, 2H, H-2, H-3); 7.46 (d, 1H, H-14, 9.2).

^{13}C-NMR ($CDCl_3$, δ ppm): 162.07 (C-5, C-6); 156.50 (C-9); 143.22 (C-12); 137.31 (C-10); 135.83 (C-2, C-3); 129.50 (C-13); 128.70 (C-5, C-6); 124.74 (C-1, C-4); 122.65 (C-11); 115.82 (C-14).

Elemental analysis: calculated for $C_{14}H_7N_3O_7$: M = 329, C, 51.08%, H, 2.14%, N, 12.76; found: C, 51.17%, H, 2.14%, N, 12.55%.

IR (ATR, cm^{-1}): 3101, 1798, 1732, 1603, 1526, 1476, 1418, 1347, 1266, 1227, 1184, 1112, 1069, 967, 913, 870, 831, 784, 737, 690, 586, 509.

5b (*N-(2,4,6-Trinitrophenyl)oxyphthalimide*), yield 50%, mp. 185-188°C, ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 8.89 (s, 2H, H-11, H-13); 7.96÷7.81 (m, 4H, H1, H-2, H-3, H-4).

^{13}C-NMR ($CDCl_3$, δ ppm): 161.99 (C-7, C-8); 144.33 (C-9); 134.38 (C-12); 131.26 (C-10, C-14); 134.97 (C-1, C-4); 128.95 (C-5, C-6); 124.15 (C-2, C-3); 124.00 (C-11, C-13).

Elemental analysis: calculated for $C_{14}H_6N_4O_9$: M = 374, C, 44.93%, H, 1.62%, N, 14.97; found: C, 45.05%, H, 1.68%, N, 14.67%.

IR (ATR, cm^{-1}): 3436, 3323, 3084, 2922, 2853, 1795, 1740, 1534, 1340, 1279, 1225, 1178, 1077, 931, 872, 693, 516.

5c (*N-(2,6-Dinitro-4-trifluoromethylphenyl) oxyphthalimide*), yield 40%, mp. 155-160°C, ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 8.30 (s, 2H, H-11, H-13); 7.92÷7.86 (m, 4H, H-1, H-2, H-3, H-4).

^{13}C-NMR ($CDCl_3$, δ ppm): 161.89 (C-7, C-8); 152.87 (C-9); 142.74 (C-10, C-14); 135.93 (C-1, C-4); 128.58 (q, C-12, *J*(F-C)= 35.7 Hz); 128.35 (C-5, C-6); 126.14 (q, C-11, C-13, ^3J(F-C)=3.7 Hz); 124.79 (C-2, C-3); 120.61 (q, CF_3, *J*(F-C)=272.8 Hz).

Elemental analysis: calculated for $C_{15}H_6F_3N_3O_7$: M = 397, C, 45.36%, H, 1.52%, N, 14.35; found: C, 45.35%, H, 1.55%, N, 14.14%.

IR (ATR, cm^{-1}): 3081, 2922, 1801, 1745, 1624, 1544, 1347, 1318, 1133, 1057, 918, 869, 787, 699, 663, 589, 515.

5d (*N-2,4-Dinitro-6-trifluoromethylphenyl) oxyphthalimide*), yield 40%,mp.165-170°C,^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 8.78 (d, 1H, H-11, 2.5); 8.72 (d, 1H, H-13, 2.5); 7.93÷7.86 (m, 4H, H-1, H-2, H-3, H-4).

^{13}C-NMR ($CDCl_3$, δ ppm): 161.48 (C-7, C-8); 152.54 (C-9); 143.12 (Cq); 140.62 (Cq); 135.93 (C-1, C-4); 128.25 (C-5, C-6); 126.10 (q, C-13, ^3J(F-C)=5.1 Hz); 124.82(C-2, C-3); 124.54(C-11); 124.07 (q, C-14, ^3J(F-C)=34.4 Hz); 120.85 (q, CF_3, *J*(F-C)=273.2 Hz).

Elemental analysis: calculated for $C_{15}H_6F_3N_3O_7$: M = 397, C, 45.36%, H, 1.52%, N, 14.35%; found: C, 45.50%, H, 1.59%, N, 14.23%.

IR (ATR, cm^{-1}): 3083, 2854, 1802, 1746, 1545, 1470, 1319, 1134, 1058, 939, 918, 871, 817, 700, 665, 590, 516.

5e (*N-(4-Carboxy-2,6-dinitrophenyl)oxyphthalimide*), yield 50%, mp. 155-160°C, ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 8.87 (s, 2H, H-11, H-13); 7.93 (m, 2H, H-1, H-4); 7.83 (m, 2H, H-2, H-3).

^{13}C-NMR ($CDCl_3$, δ ppm): 161.95 (C-7, C-8); 160.49 (COOH); 149.63 (C-9); 141.22 (C-10, C-14); 134.98 (C-1, C-4); 132.92 (C-11, C-13); 128.94 (C-5, C-6); 125.73 (C-12); 124.19 (C-2, C-3).

Elemental analysis: calculated for $C_{15}H_7N_3O_9$: M = 373, C, 48.27%, H, 1.89%, N, 11.26%; found:C ,48.29%, H, 1.79%, N, 11.04%.

IR (ATR, cm^{-1}): 3215, 3083, 2524, 1779, 1735, 1705, 1538, 1420, 1356, 1246, 1185, 1116, 1013, 974, 917, 873, 693, 517.

6 (*N-(2,4-Dinitropyridine)oxyphthalimide*), yield 60%, mp. 185-190°C, ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 9.31(d, 1H, H-13, 2.4); 9.15 (d, 1H, H-11, 2.4); 7.97 (m, 2H, H-1, H-4); 7.88 (m, 2H, H-2, H-3).

^{13}C-NMR ($CDCl_3$, δ ppm): 161.29 (C-7, C-8); 157.10 (C-9); 147.34 (C-13); 141.62 (C-12q); 135.29 (C-1, C-4); 132.52 (C-11); 131.71 (C-10); 128.66 (C-5, C-6); 124.45 (C-2, C-3).

Elemental analysis: calculated for $C_{13}H_6N_4O_7$: M = 330, C, 47.29%, H, 1.83%, N, 16.97; found: C,47.15 %, H, 1.88%, N,14.71 %.

IR (ATR, cm^{-1}): 3094, 3059, 1828, 1737, 1527, 1465, 1334, 1243, 1183, 1080, 994, 948, 895, 871, 694, 594, 516.

7 (*N-[4-(7-Nitrobenzofurazan)]oxyphthalimide*), yield 54%, mp.195-198°C, ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 8.52 (d, 1H, H-13, 8.4); 8.01 (m, 2H, H-1, H-4); 7.91 (m, 2H, H-2, H-3); 7.16 (d, 1H, H-14, 8.4).

^{13}C-NMR ($CDCl_3$, δ ppm): 161.69 (C-7, C-8); 154.83 (Cq); 152.85 (C-9); 145. 31 (Cq); 144.14 (Cq); 142.67 (Cq); 135.74 (C-1, C-4); 132.16 (C-13); 128.64 (C-5, C-6); 108.14 (C-14).

Elemental analysis: calculated for $C_{14}H_6N_4O_6$: M = 326, C, 51.55%, H, 1.85%, N, 17.17%; found:C, 51.76%, H, 1.89%, N, 16.94%.

IR (ATR, cm^{-1}): 3081, 1796, 1740, 1600, 1547, 1340, 1221, 1182, 1132, 1077, 969, 942, 872, 828, 692, 537, 512.

3. Results and Discussion

3.1. Synthesis of compounds 5a–e, 6, and 7.

Compounds **5a–e**, **6**, and **7** (Fig. 1), are easily obtained starting from **1** and the fluoro- or chloro-nitroaryl derivatives, namely 2-chloro-3,5-dinitropyridine **2**; 4-chloro-7-nitrobenzofurazan (or 4-chloro-7-nitrobenz-2-oxa-1,3-diazole, NBD chloride) **3**; 1-fluoro-2,4-dinitrobenzene **4a**; picryl chloride (or 1-chloro-2,4,6-trinitrobenzene) **4b**; 4-chloro-3,5-dinitrobenzotrifluoride **4c**; 2-chloro-3,5-dinitro-benzotrifluoride **4d**; and 4-chloro-3,5-dinitrobenzoic acid **4e**.

The reaction was conducted in dry acetone, in the presence of a slight excess of triethylamine as base, to obtain in the first step the corresponding anion from **1** and in the next step an S_NAr process *via* Meisenheimer σ-anion complexes [28,29]. The expected products were obtained with yields varying from 40% to 95%, depending on the structure and reactivity of the nitroaryl derivatives **2**, **3** and **4a-e**. The reaction conditions were similar to those described in the literature [15,19] (acetone as solvent, triethylamine as base, room temperature), due to the fact that other conditions [16-18,30] (*i.e.*, potassium hydroxide as base, DMF as solvent, or ultrasound condition) do not work properly.

3.2. Spectral data

The IR spectra of all compounds **5a–e**, **6** and **7** confirm the presence of carbonyl groups, with a very intense peak around 1700-1750 cm^{-1}; the aromatic hydrogen stretching bands appear around 3100 cm^{-1}. For compounds **5a–e**, **6**, and **7**, which contain nitro group(s), two characteristic IR bands are noticed at around 1550 cm^{-1} and 1350 cm^{-1}. The *N*-aryloxy bond is characterized by a band at around 900 cm^{-1}.

^{1}H-NMR and ^{13}C-NMR spectra confirm the structure the compounds **5a–e**, **6** and **7**; thus, in ^{1}H-NMR the aromatic phthalimide hydrogens appear at around 8 ppm as a multiplet; hydrogens from the nitroaryl group come out as singlets or doublets, depending on the structure, around 8.5-9 ppm. For the fluoro-derivatives **5c,d** supplementary splittings are noticed in ^{13}C-NMR (due to the ^{19}F atoms).

In solid state, compounds **1**, **5a–e**, **6** and **7** have different colors, from almost white to yellow or red. The UV-Vis spectra recorded in methanol (Table 1) showed that with two exceptions (**5a** and **5d**), the synthesized compounds have two absorption maxima, one of which appears at 350–410 nm. Table 1 presents also calculated [21,31] values (see Experimental Procedure) for log *P*, net atomic charges and dipole moments of compounds **1**, **5a–e**, **6**, and **7.** Compound **7** is not fluorescent in solution or solid state (at 366 nm) although it contains the NBD moiety. This behavior is analogous to other NBD-OAr derivatives [32].

3.3. TLC investigations

Thin layer chromatography (TLC) is a fast and reliable method for checking compound purity, for the evaluation of hydrophobic/lipophilic properties, and also for the preparative isolation of pure compounds.

3.3.1 TLC behavior

The TLC behavior of compounds **5a–e**, **6** and **7** leads to the following observations (Table 1): (*i*) depending on the nitroaryl moiety, the R_f values decrease in the following order: **5c** = **5d** > **5a** > **6** > **7**> **5b** > **5e** > **1**; (*ii*) the supplementary NO_2 or CF_3 groups increase the R_f values through their hydrophobicity (compounds **5b–d**), while OH or COOH groups decrease the R_f values, due to the strong bonds formed with the stationary phase (compounds **1** and **5e**); (*iii*) R_f for **5a** and R_f for **6** are explained by the nitrogen atom present in the 2,4-dinitropyridine moiety of the compound **6**, which is less basic; (*iv*) the R_f value for the isomeric pair **5c**,d is the same; and (*v*) the comparative R_f values of **5a** and **7** (ΔR_f = 0.12) prove the lower interaction with stationary phase of 2,4-dinitrobenzene moiety, comparatively with the 4-nitrobenzofurazan moiety (NBD).

3.3.2 RP-TLC

Reversed phase thin layer chromatography (RP-TLC) is often used to evaluate the organic–water partitioning properties of solutes [33-36]. The correlation between structure and activity plays an important role in the study of biological interactions. Among the molecular properties the lipophilicity is important because the biological activity is correlated in QSAR (Quantitative Structure-Activity Relationship) studies with their capacity to cross the lipophilic cell membrane [37]. Along with classical methods of hydrophobicity (lipophilicity) determination by partitioning the compound between a polar and a non-polar solvent pair (usually, *n*-octanol and water [22,37]), RP-TLC is widely used owing to the simplicity and the rapidity of this method. For RP-TLC, this method uses the measurement of $R_f$values obtained using a non-polar stationary phase [18,33-36] (silica gel impregnated with paraffin oil, silanized silica gel, C_{18} derivatized silica gel, *etc.*) and two miscible solvents, one of which is water (*i.e.*, alcohol–water, acetone-water, acetonitrile-water, *etc.*). The R_M values necessary for the determination of the hydrophobicity/lipophilicity of the compounds are obtained as shown by Eq. 1 [18,33-36]. To measure the specific hydrophobic surface area, the

Table 1. Experimental (R_f and λ_{max} in nm) and calculated [21,31] values for log*P*, net atomic charges and dipole moments of compounds **1**, **5a–e**, **6**, and **7**.

Comp.	R_f[a]	λ_{max} (log ε)	log*P*	Net atomic charges			Dipole moment (Debyes)
				N	O	C	
1	0.11	294 (3.12)	1.23	-0.207	-0.197	–	1.47
5a	0.69	276 (4.05)	2.85	-0.233	-0.042	0.171	2.23
5b	0.76	313 (3.83), 403 (3.60)	2.80	-0.274	-0.239	0.215	1.40
5c	0.77	302 (3.55), 407 (3.27)	3.73	-0.244	-0.066	0.243	1.76
5d	0.76	351 (3.52)	3.73	-0.245	-0.227	0.207	0.74
5e	0	293 (4.09), 403 (3.49)	2.55	-0.246	-0.228	0.209	0.99
6	0.67	289 (3.96), 351 (3.50)	2.70	-0.242	-0.245	0.212	2.77
7	0.57	265 (4.08), 352 (3.85)	2.62	-0.232	-0.237	0.170	4.86

[a] R_f values on analytical TLC plates silica gel with fluorescent indicator (Sigma) stationary phase and dichloromethane mobile phase (detection at 254 nm).

linear correlation between the R_M values of compounds **1**, **5a–e**, **6**, and **7** and the concentration of the organic solvent in the eluent (*C*) were calculated by Eq. 2 [18,33-36]. The intercept R_{M0} (*molecular hydrophobic*ity) is the R_M value of a compound extrapolated to zero organic phase concentration in the eluent, and the slope *b* is the change of lipophilicity caused by unit concentration change of the organic phase. These values (R_{M0} and *b*) are the best indicators of the lipophilicity and the specific hydrophobic surface area of the compounds [18,33-36].

$$R_M = \log(1/R_f - 1) \quad (1)$$

$$R_M = R_{MO} + bC \quad (2)$$

We used two analytical systems to measure the hydrophobicity; in the first one, we used silanized silica gel as the stationary phase (Table 2).

In the second one, C_{18}-derivatized silica was used (Table 3).

For both systems (Table 2 and Table 3), the eluent was a mixture of acetone with water in different proportions (50–85% acetone).

From the data presented in Table 2 and Table 3, one can notice that the lowest R_{M0} values have been recorded in the case of compounds **1** and **5e** as expected, and the highest values for R_{M0} have been recorded in the case of the fluoro-derivatives **5c,d** (again as expected, it being well known that the trifluoromethyl group has a high hydrophobicity [37]) and the NBD-derivative **7**.

Satisfactory correlations of the calculated [31] log*P* (as in Table 1) with measured R_{M0} values are obtained: for Table 2, the coefficient of determination is $R^2 = 0.853$, the standard deviation is $SD = 0.751$, and cross-validated $R_{CV}^2 = 0.751$; for Table 3, the coefficient of determination is $R^2 = 0.867$, $SD = 0.667$, and cross-validated $R_{CV}^2 = 0.801$. Between the two sets of R_{M0} values, a better correlation exists, namely R_{M0} (Table 3) = 0.7945 × R_{M0} (Table 2) + 1.247, with $R^2 = 0.933$.

For the data presented in Table 2:

$$R_{M0} = 1.611 \times \log P - 2.108 \quad (3)$$

For the data presented in Table 2:

$$R_{M0} = 1.336 \times \log P - 0.583 \quad (4)$$

For the data presented in Table 3:

$$R_{M0,exp} = 1.029 R_{M0,calc} - 0.052 \quad (5)$$

For the data presented in Table 3:

$$R_{M0,exp} = R_{M0,calc} \quad (6)$$

Table 2. Experimental data for R_{M0} and *b* using silanized silica as the stationary phase [a]

Comp.	R_M				R_{MO}	b	R	SD
	A	B	C	D				
1	-0.41	-0.43	-0.57	-0.54	-0.13	-0.5619	0.88	0.05
5a	0.95	0.50	0	-0.19	2.88	-3.9461	0.99	0.11
5b	0.57	0.26	-0.12	-0.28	2.05	-2.9816	0.99	0.07
5c	1.38	0.72	0.12	-0.12	3.84	-5.1056	0.98	0.15
5d	1.38	0.72	0.15	-0.12	3.83	-5.0699	0.99	0.14
5e	-0.10	-0.41	-0.62	-0.78	0.99	-2.2704	0.99	0.05
6	0.90	0.50	0.01	-0.19	2.77	-3.7900	0.99	0.09
7	0.86	0.52	0.05	-0.19	2.68	-3.6512	0.99	0.07

[a] A, B, C, and D are the R_M values obtained for 50%, 60%, 70% and 80% acetone–water ratios in eluent, respectively.

Table 3. Experimental data for R_{M0} and *b* using a C_{18}-derivatized silica gel stationary phase [a]

Comp.	R_M				R_{MO}	b	R	SD
	A	B	C	D				
1	-0.45	-0.36	-0.66	-1.00	1.08	-0.0234	0.86	0.17
5a	0.82	0.68	0.09	-0.39	4.00	-0.0510	0.95	0.20
5b	0.55	0.048	-0.052	-0.347	2.60	-0.0352	0.98	0.08
5c	0.90	0.86	0.18	-0.39	4.36	-0.0548	0.93	0.27
5d	0.90	0.86	0.18	-0.39	4.36	-0.0548	0.93	0.27
5e	0	-0.47	-0.69	-1.00	2.37	-0.0401	0.99	0.05
6	0.70	0.147	0.05	-0.347	3.12	-0.0414	0.98	0.07
7	0.70	0.147	0	-0.347	3.11	-0.0409	0.98	0.07

[a] A, B, C, and D are the R_M values obtained for 50%, 60%, 70% and 80% acetone–water ratios in the eluents, respectively.

3.4. Theoretical studies

3.4.1. Geometries of the compounds 1, 5a–e, 6, and 7

For more information about the relationship between the structure of the compounds **1**, **5a–e**, **6**, and **7** and their physical-chemical properties, we performed computational studies. For geometry optimization we used programs [22,23,26,31] (see Experimental Procedure). As seen in Fig. 2, steric hindrance causes marked deviations from planarity in compounds **5b–e** and **7**.

Calculations using the GAMESS software package [27,38] were used for total energies of compounds **1**, **5a–e**, **6**, and **7** (Table 4).

The total energy calculated for the compounds **1**, **5a–e**, **6** and **7** decreases in the following order: **5b>6>7>5e>5c>5d>5a>1** (see the comment at the end of this paragraph justifying the comparison between non-isomeric compounds); these total energies are the sum of the seven types of energies displayed in Table 4. It is interesting to note that the planar structures (**1** and **5a**) with no steric strain have the lowest energies.

3.4.2. QSPR studies

Because in physical-chemical properties of compounds **1**, **5a–e**, **6** and **7** the bonds that play the main role involve phthalimidic heteroatoms and their adjacent carbon atoms (N–O for **1**, and N–O–C for **5a–e**, **6** and **7**), we have calculated the net atomic charges on these atoms (Table 1) [21]. Also we have calculated dipole moments of compounds **1**, **5a–e**, **6** and **7** (Table 1) using the MOPAC program [21].

The results presented in Table 1 lead to the following observations: (i) the most negative net atomic charges on the hydroxyphthalimidic (NHPI) nitrogen atom are recorded for compounds with three nitro groups (**5b**), trifluoromethyl group (**5c,d**) or carboxyl groups (**5e**); (ii) the most net negative atomic charges on the NHPI oxygen atom are recorded for 2,4-dinitropyridine (**6**), picryl (**5b**) and NBD (**7**) derivatives; (iii) the most positive net atomic charge on the N–O–C carbon atom are recorded for the trifluoromethyl derivative (**5c**); and (iv) the highest dipole moment is recorded for NBD-derivative (**7**). No satisfactory correlation for experimental λ_{max} (Table 1) *vs.* calculated λ_{max} was obtained using dipole moments plus net atomic charges (Table 1), but Eq. 7 allowed a fairly good correlation in terms of dipole moments *D* plus the average information content atomic index of order 0 (AIC_0) [39-42]; the average information content is defined on the basis of the Shannon information theory and is calculated as in formula I [41,42]. This is understandable because the dipole moment integrates information about the whole molecule, whereas net atomic charges on a single atom cannot provide such information.

$$\lambda_{max} = 72.67(\pm 28.23)AIC_0 - 13.41(\pm 3.966)D + 169.8 \quad (7)$$

$$^{k}\overline{IC} = -\sum_{i} \frac{n_i}{n} \log_2 \frac{n_i}{n} \qquad \text{Formula I}$$

where n_i is the number of atoms in the i-th class, and *n* is the total number of atoms in the molecule.

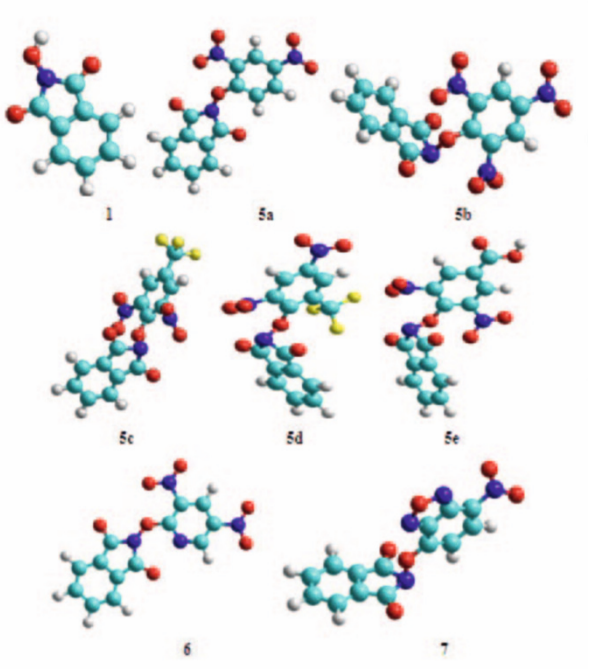

Figure 2. Optimized geometries of compounds **1**, **5a–e**, **6**, and **7**.

Table 4. Calculated energies [26,27] (kcal mol^{-1}) of compounds **1**, **5a–e**, **6**, and **7**

Comp.	Stretch energy	Bend energy	Stretch-Bend energy	Torsion energy	Non-1,4 VDW energy	1,4 VDW energy	Dipole-dipole Energy	Total energy
1	0.331	10.650	-0.117	-2.259	-3.344	5.985	7.661	18.907
5a	1.798	27.258	-0.521	-7.796	-10.882	15.880	14.375	40.112
5b	2.297	36.643	-0.654	-7.779	-5.496	14.615	12.977	52.603
5c	2.049	28.129	-0.485	-3.918	-4.992	15.109	11.394	47.286
5d	2.044	28.887	-0.291	-3.629	-2.991	14.721	3.075	41.816
5e	2.482	30.221	-0.517	-6.032	-9.210	17.029	15.341	49.314
6	1.649	28.161	-0.414	-2.105	-4.427	14.940	13.073	50.877
7	1.383	28.945	-0.329	-7.769	-4.096	14.112	17.555	49.801

A satisfactory correlation (Eq. 9) was found according to Eqs. 7 and 8:

$$\lambda_{max,\ exp} = \lambda_{max,\ calc} - 0.221 \quad (8)$$

$N = 8$; $R^2 = 0.800$; $SD = 12.56$; $R_{CV}^2 = 0.767$

A QSPR study has been conducted on the R_{M0} values of compounds **1**, **5a–e**, **6** and **7** in terms of the average nucleophilic reactivity index for carbon ($ANRI_C$) [39,43] and the molecular weight-adjusted hydrophilic-lipophilic balance (HLB) [44,45]; $ANRI_C$ is the extreme (maximum and minimum) or average value of the simplified nucleophilic (N'A) reactivity indices for a given atomic species in the molecule, defined by formula II [43].

$$N'_A = \sum_{i \in A} c_{iHOMO}^{\ 2} \qquad \text{Formula II}$$

where the summation is performed over all atomic orbitals at the given atom, and c_{iHOMO} denotes the i-th AO coefficient on the highest occupied molecular orbital (HOMO).

The hydrophilic/lipophilic balance HLB was calculated using formula III [44,45]:

$$HLB = 20\frac{Mh}{M} \qquad \text{Formula III}$$

where Mh is the molecular mass of the hydrophilic portion of the molecule, and M is the molecular mass of the whole molecule, giving a result on an arbitrary scale of 0 to 20.

Values for the calculated [39,40] R_{M0} in terms of $ANRI_C$ and HLB were obtained by Eq. 9:

$$R_{M0} = -632.29\ (\pm 128.98)\ ANRI_C - 0.557\ (\pm 0.118)HLB + 12.11 \quad (9)$$

$N = 8$; $R^2 = 0.889$; $SD = 0.536$; $R_{CV}^2 = 0.791$

Satisfactory correlations [39,40] (Eqs. 10 and 11) were found for R_{M0}:

for Table 5, $R_{M0,exp} = 1.029R_{M0,calc} - 0.052$ (10)

for Table 6, $R_{M0,exp} = R_{M0,calc}$ (11)

The correlations between experimental values and those calculated according to Eqs. 10 and 11 are as follows. For Table 5, the coefficient of determination is $R^2 = 0.927$, the standard deviation is $SD = 0.155$, and cross-validated $R_{CV}^2 = 0.907$; for Table 6 the coefficient of determination is $R^2 = 0.983$, $SD = 0.449$, and cross-validated $R_{CV}^2 = 0.874$.

Table 5. Values obtained for correlation between experimental and calculated R_{M0} for silanized silica as stationary phase.

Comp.	$ANRI_C$	HLB	R_{M0}		
			Experimental [a]	Calculated [b]	Residuals
1	9.003×10^{-3}	11.777	-0.13	-0.142	0.012
5a	4.523×10^{-3}	10.312	2.88	3.300	-0.420
5b	5.590×10^{-3}	11.980	2.05	1.902	0.148
5c	5.988×10^{-3}	8.798	3.84	3.423	0.417
5d	5.240×10^{-3}	8.837	3.83	3.874	-0.044
5e	5.229×10^{-3}	12.694	0.99	1.733	-0.743
6	3.861×10^{-3}	13.050	2.77	2.399	0.371
7	4.317×10^{-3}	12.749	2.68	2.279	0.401

[a] As in Table 2. [b] Calculations according to [27,28]

Table 6. Values obtained for correlation between experimental and calculated R_{M0} for C_{18}-derivatized silica gel stationary phase.

Comp.	$ANRI_C$	HLB	R_{M0}		
			Experimental [a]	Calculated [b]	Residuals
1	9.003×10^{-3}	11.777	1.08	1.064	0.016
5a	4.523×10^{-3}	10.312	4.00	4.102	-0.102
5b	5.590×10^{-3}	11.980	2.60	2.699	-0.099
5c	5.988×10^{-3}	8.798	4.36	4.135	0.225
5d	5.240×10^{-3}	8.837	4.36	4.497	-0.137
5e	5.229×10^{-3}	12.694	2.37	2.516	-0.146
6	3.861×10^{-3}	13.050	3.12	3.030	0.090
7	4.317×10^{-3}	12.749	3.11	2.952	0.158

[a] As in Table 3. [b] Calculations according to [27,28]

4. Conclusions

Starting from *N*-hydroxyphthalimide **1** and reactive nitroaryl derivatives **2**, **3** and **4a-e**, compounds **5a–e**, **6**, and **7** were obtained, from which five are new (namely compounds **5c–e**, **6**, and **7**). The IR, ^{1}H-NMR, ^{13}C-NMR, and UV-Vis spectra, TLC behavior and experimental hydrophobicity (lipophilicity) measurements were used to characterize all compounds, and computational calculations were performed to correlate them. The QSPR study correlated structures with electronic spectra and the hydrophilic/hydrophobic balance for compounds **1**, **5a–e**, **6** and **7**.

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