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LINEAR AND CYCLIC ETHYLENE-GLYCOLS LABELLED WITH NITROBENZOFURAZAN MOTIFS

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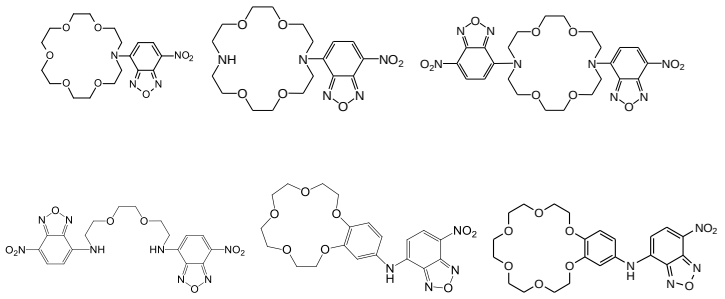
NBD-chloride was used as a chromogenic and fluorogenic label to obtain three new derivatives, starting from 1,8-diamino-3,6-dioxaoctane, 4-aminobenzo-15-crown-5-ether and 4-aminobenzo-18-crown-6-ether (compounds **D-F**, respectively). These compounds were compared with the corresponding derivatives obtained in a similar way, from NBD-chloride and 1-aza-18-crown-6-ether and 4,13-diaza-18-crown-6-ether (compounds **A-C**, respectively). UV-Vis, IR, NMR, fluorescence and MS spectra are discussed.



INTRODUCTION

Polyethylene-glycols are a class of organic compounds that have important applications, starting with common industrial processes and going further towards pharmaceuticals and medicine. For example, it is well known their ability to form gels, and their strong interaction with cations is also well-established.[1–3]

Cyclic polyethylene-glycols, many of them known as crown-ethers, have significant capabilities to form host-guest complexes with positively charged species, like inorganic or organic cations.[4] The discovery and development of this special property of such compounds led to the Nobel Prize in 1987, establishing the supramolecular chemistry as a new domain.[5]

Crown ethers or just linear polyethylene-glycols functionalized with chromophores or fluorophores can easily work as chemo-sensors, due to their chromogenic or fluorogenic behaviour, which is often greatly affected by the presence of a cation.[6] Because of their strong binding affinities to various cations, many crown ethers were widely used in the design of smart fluorescence-based sensor systems. The fluorescence technique is quite useful for molecular recognition due to its high sensitivity and the facile mode of operation.[7]

Although the literature data is abundant in information about chromogenic and fluorogenic crown-ethers,[8] there is still a high interest in the synthesis and characterization of crown-ether derivatives with such properties that might induce strong changes upon metal complexation.[9]

Usually, a chemo- or a fluoro-sensor has two main components, a receptor and a signalling unit, linked through a spacer. For example, compounds **A-C** from Fig. 1 have a crown-ether moiety as a

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receptor and the NBD (nitro-1,2,3-benzoxadiazole or nitrobenzofurazan) moiety as a chromophore or fluorophore. In this work we synthesised and characterized by different structural analyses three new derivatives, denoted as compounds **D-F**.

RESULTS AND DISCUSSION

Synthesis

Compounds **A-C** are known in literature, and they were obtained using the same procedure, with some slight changes.[10–12] Mainly, these compounds can be easily obtained by reacting NBD-chloride with the corresponding aza- or diaza-crown-ether, in the presence of a base. Compounds **D-F** were obtained in a similar way, starting from 1,8-diamino-3,6-dioxaoctane, 4-aminobenzo-15-crown-5-ether, and 4-aminobenzo-18-crown-6-ether; the reactions work well in acetonitrile as a solvent and in the presence of sodium hydrogen carbonate as a base (see Experimental part for details). It is worth mentioning that 4-aminobenzo-15-crown-5-ether and 4-aminobenzo-18-crown-6-ether can also be obtained easily starting from the plain benzo-15-crown-5-ether and benzo-18-crown-6-ether, in two steps, the first one being the nitration process, followed in the second step by the reduction of the nitro group to the corresponding amino-derivative; both reactions occur with high yields.

The structure of the new compounds **D-F** was confirmed by UV-Vis, IR, ^{1}H- and ^{13}C-NMR, and ESI-MS (see Experimental for more details). Thus, as any compounds containing the NBD moiety (like **A-C**), these are red to red-brown solids, showing a maximum absorption visible band between 450–490 nm (more details follow in the chromogenic and fluorogenic properties discussion). In the IR spectra can be easily noticed the NH group at about 3200 cm^{-1}, NO_2 group at 1569 cm^{-1}, the furazan moiety between 1250–1320 cm^{-1}, while the ether group from the ethylene glycol moiety appears at about 1130 cm^{-1}. NMR spectra supply more details that fit the structure, the most important being the presence of the doublets of doublets from the NBD structure, located at about 8.40-8.50 ppm and 6.40-6.50 ppm, respectively. The mass spectra of compounds **D-F** complete the structural characterization; for all compounds, including the known ones (**A-C**) and the new ones (**D-F**), the corresponding peak of the molecular ion was noticed, and also the peaks corresponding to the ions with Na and K were often noticed (Table 1).

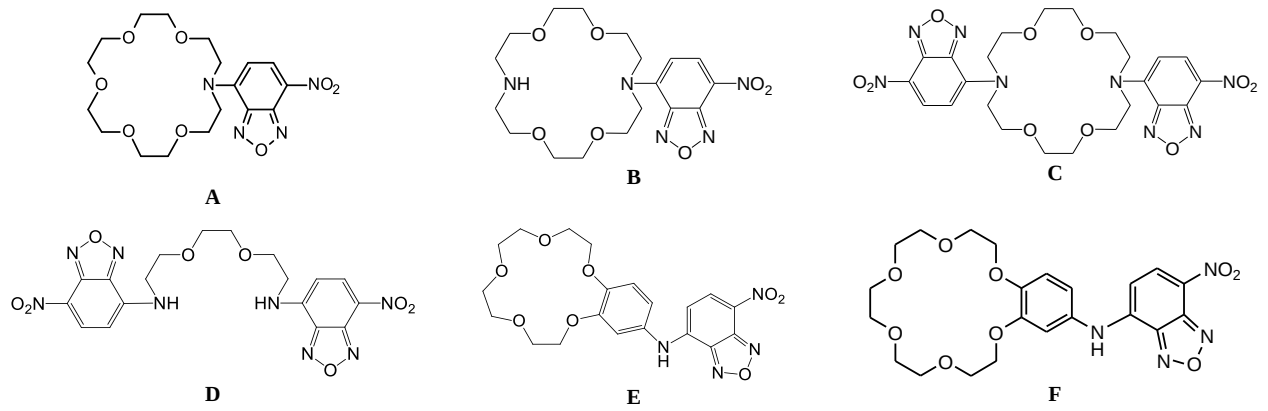


Fig. 1 – Chemical structure of compounds **A-F**.

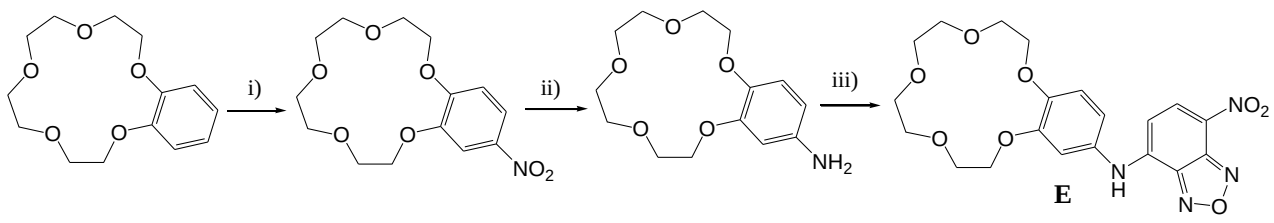


Fig. 2 – Synthesis of **E**: i) HNO_3 30%, 2h; ii) Zn/ CH_3COOH, 1h; iii) NBD-Cl/$NaHCO_3$, 24h.

Table 1

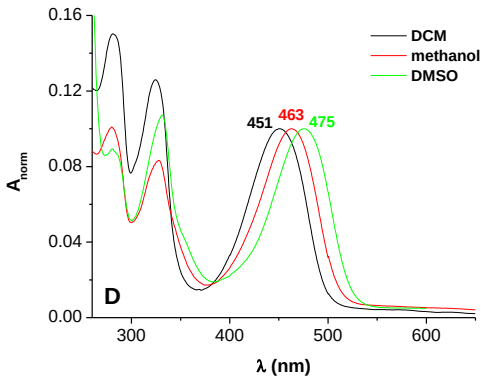
Physico-chemical values for compounds **A-D**

	MW	R_f [i]	Log *P* [ii]	$\lambda_{a\ max}$ [iii]	$\lambda_{f\ max}$	ESI-MS	
A	426	0.37	0.74	341, 482	530 [iv]	427 (100%, $M+H^+$)	444 (65%, $M+NH_4^+$) 449 (50%, $M+Na^+$) 465 (23%, $M+K^+$)
B	425	0.46	-0.07	339, 478	550 [iv]	426 (45%, $M+H^+$)	
C	588	0	2.29	331, 547	528 [iv]	589 (28%, $M+H^+$)	611 (100%, $M+Na^+$) 627 (65%, $M+K^+$)
D	474	0.57	1.94	332, 463	534	473 (100%, $M-H^+$)	
E	446	0.19	1.91	334, 480	-	445 (100%, $M-H^+$)	469 (100%, $M+Na^+$)
F	490	0.07	2.05	335, 477	-	489 (100%, $M-H^+$)	513 (100%, $M+Na^+$) 529 (70%, $M+K^+$)

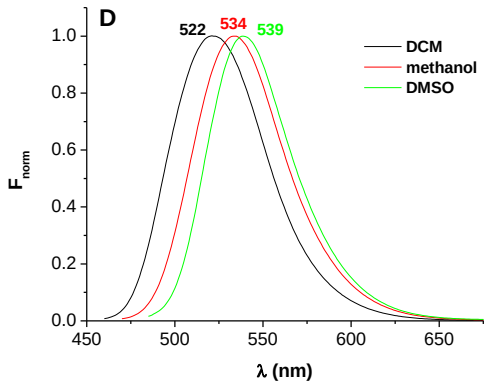
i) silicagel/ ethyl acetate; ii) calculated; iii) in methanol; iv) literature data.

Chromogenic and fluorogenic properties

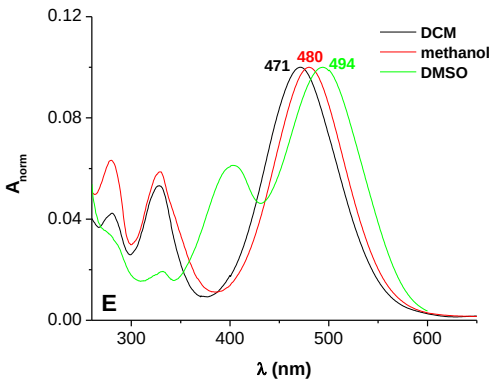
For the newly synthesised compounds **D-F** we recorded the UV-Vis spectra in different solvents, to check the presence of a solvatochromic effect, being known that such kind of compounds containing NBD moieties are strongly coloured derivatives that have this behaviour. Thus, for compound **D**, UV-Vis spectra recorded in dichloromethane (DCM), methanol and DMSO showed the $\lambda_{a\ max}$ values of 451, 463 and 475 nm, as is pictured in Fig. 3. The same behaviour is presented for the compounds **E** and **F**, the UV-Vis spectra being in the same three solvents showing the corresponding values of 471, 480, 494 nm, and 472, 477, 490 nm, respectively (Fig. 3). Thus, between DCM and DMSO a bathochromic shift of about 20 nm is noticed.



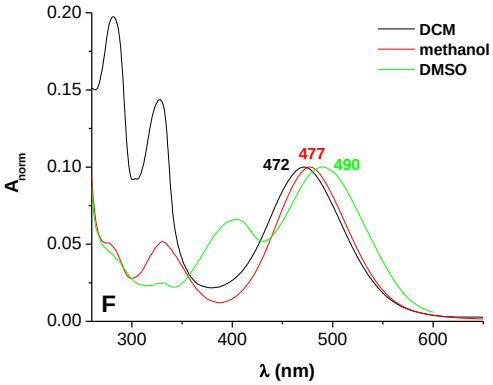
UV-Vis spectra of **D**



Fluorescence spectra of **D**



UV-Vis spectra of **E**



UV-Vis spectra of **F**

Fig. 3 – UV-Vis spectra for compounds **D-F** and fluorescence spectra of **D**.

Regarding the fluorescence of the new compounds **D-F**, only compound **D** showed a strong fluorescence, while for **E** and **F** a Rayleigh scattering of the excitation light was noticed, and this behaviour was correlated with the presence of the aromatic ring directly linked to the amino group, which extinguishes the fluorescence, otherwise observed for NBD derivatives (including **A-C**). Similarly with the case of the UV-Vis longest wavelength absorption band, the fluorescence emission of **D** displays a bathochromic shift with increasing solvent polarity: the $\lambda_{f\ max}$ values in DCM, methanol, and DMSO are 522, 534 and 539 nm (again, about 20 nm bathochromic shift).

As all these linear or cyclic ethylene glycol derivatives have the capacity of cations complexation, this behaviour is well reflected in the MS recorded in different conditions. Table 1 shows that all compounds, except **D**, led to the formation of ammonium, sodium or potassium positively charges complexes that were spotted in the MS spectra, as peaks with high intensities, up to 100%. The exception of **D** is explained by its linear ethylene glycol structure, leading to a lower supramolecular interaction with cations. Such interactions of crown-ethers or pseudo-crown-ethers with different ions is well documented,[13] these compounds being able to transport through membranes different cationic species.[14,15]

Membrane transport is highly dependent on the partition coefficient values (P or log P) of the complexing agent (linear or cyclic ethylene glycol derivative), therefore the evaluation of these is necessary. Log *P* is the common value taken into consideration, and its measuring can be done either experimentally (as distribution of the compounds in a biphasic system, usually *n*-octanol-water), or theoretically, using incremental fragment calculus. In this work log *P* values were calculated using a computational program supplied by *ACDLabs* and they are compiled in Table 1. Compounds **C-F** have the log *P* values around 2, the highest being recorded for compound **C**; it can be also noticed that the experimental R_f value for this compound is the smallest (Table 1).

EXPERIMENTAL

Chemicals and apparatus. All chemicals, solvents and materials (TLC plates, silica gel, etc.) were purchased from Merck, Sigma-Aldrich or Chimopar and used as received. UV-Vis spectra were recorded on a V-560 Jasco or an UVD-3500 double beam spectrophotometer, using 1 cm path length quartz cells and ethanol as solvent, while steady-state fluorescence on a FP-6500 Jasco spectrofluorometer at room temperature. The fluorescence of compound **D** was recorded using λ_{ex} = 450 nm for DCM, 463 nm for methanol, and 475 nm for DMSO. IR spectra (4000–400 cm^{-1}) were recorded on a Jasco FTIR 4700 spectrophotometer using KBr disk technique. ^{1}H- and ^{13}C-NMR were recorded in $CDCl_3$ or DMSO-d6 at room temperature, using a Bruker Advance spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. The residual solvent peaks were taken as the internal reference and the chemical shifts d are reported as ppm values. For MS a Varian 310-MS LC/MS/MS triple quadrupole mass spectrometer fitted with an electrospray ionization interface (ESI) was used. The fragmentation conditions are the following: Compounds **A-F** have been solubilized in DMSO and diluted with methanol. The solutions thus obtained were injected directly into the interface using a syringe pump, with a 0.01 mL/min flow. In this way, the protonated or deprotonated molecular ion obtained was selected by the first quadrupole. Into the second quadrupole, the protonated or deprotonated molecular ion was fragmented by collision with an inert gas (argon) to 1.5 mTorr pressure. Fragments were analysed by the third quadrupole. Prior to these experiments, the tuning of the mass spectrometer was performed using PPG both for positive and negative. Air was used as drying gas at a pressure of 19 psi and temperature according to the experiment. The nebulizing gas was nitrogen to 40 psi for positive ionization and air to 55 psi for negative ionization. The needle voltage had been established to the potential 5000 V for positive ionization and -4500 V for negative ionization. Log P values were calculated using ACD/ChemSketch free software from *AcdLabs* (version 12.01).[16]

Synthesis. Nitro-crown ethers and the corresponding amines were obtained following the literature data, with small changes.[17] Their purity was checked by NMR. Thus, as a general procedure of nitration, 1 g crown ether (benzo-15-crown-5 or benzo-18-crown-6) was dissolved in 50 mL of nitric acid (30–35%) and the mixture was stirred for 2–3 h. An equal amount of water was added and the solution extracted three times with 100 mL DCM. The collected DCM solution was washed with water, separated and dried over anhydrous sodium sulphate. After filtration and removal of the solvent, the corresponding nitro-derivatives were obtained in over 90% yield. Reduction to the amines was performed dissolving the nitro-derivative in 100 mL methanol, adding 10 g of powdered zinc and 5 mL of acetic acid (added dropwise in about 30 min), with energic stirring for 1–2 h. Finally, after the addition of 100 mL DCM, the mixture was extracted with diluted sodium hydrogen carbonate solution to remove the excess acetic acid, and the separated DCM solution was filtered, dried over sodium anhydrous sulphate and the solvent removed using a rotavap.

***4-Nitrobenzo-15-crown*-5.** ^{1}H-NMR ($CDCl_3$): 7.88 (dd, 1H, 8.9 Hz, 2.5 Hz, arom); 7.71 (d, 1H, 2.5 Hz, arom); 6.86 (d, 1H, arom); 4.18–4.21 (m, 4H, CH_2); 3.91–3.94 (m, 4H, CH_2); 3.74–3.75 (m, 8H, CH_2). ^{13}C-NMR ($CDCl_3$): 154.6; 148.6; 141.4; 118;111.2; 108.3; 71.1; 70.2; 70.1; 69; 68.9; 68.8.

***4-Aminobenzo-15-crown-5*.** ^{1}H-NMR ($CDCl_3$): 6.72 (d, 1H, 8.4 Hz, arom); 6.26 (3, 1H, 2.5 Hz, arom); 6.20 (dd, 1H, 8.4 Hz, 2.5 Hz, arom); 4.04–4.07 (m, 4H, CH_2); 3.85–3.89 (m, 4H, CH_2); 3.74 (m, 8H, CH_2). ^{13}C-NMR ($CDCl_3$): 150.4; 141.4; 141.9; 117.3; 107.2; 102.5; 70.9; 70.8; 70.7; 70.4; 69.9; 69.5; 68.6.

***4-Nitrobenzo-18-crown-6*.** ^{1}H-NMR ($CDCl_3$): 7.87 (dd, 1H, 8.9 Hz, 2.6 Hz, arom); 7.72 (d, 1H, 2.6 Hz, arom); 6.87 (d,

1H, 8.9 Hz, arom); 4.20–4.25 (m, 4H, CH_2); 3.92–3.96 (m, 4H, CH_2); 3.70–3.78 (m, 12H, CH_2). ^{13}C-NMR ($CDCl_3$): 154.4; 148.4; 141.4; 117.9;111.2; 108.1; 70.9; 70.7; 70.5; 69.2; 69.1; 69.

4-Aminobenzo-18-crown-6. ^{1}H-NMR ($CDCl_3$): 6.69 (d, 1H, 8.4 Hz, arom); 6.25 (s, 1H, 2.6 Hz, arom); 6.19 (dd, 1H, 8.4 Hz, 2.6 Hz, arom); 4.04–4.09 (m, 4H, CH_2); 3.83–3.90 (m, 4H, CH_2); 3.66–3.74 (m, 12H, CH_2). ^{13}C-NMR ($CDCl_3$): 145; 141.6; 141.3; 116.6; 107.1; 102.5; 70.6; 70.5; 70.0; 69.8; 69.5; 69.5.

Compounds **A-C** were obtained following the general literature procedure.[10-12]

A. $C_{18}H_{26}N_4O_8$. Exact Mass: 426.175. ^{1}H-NMR ($CDCl_3$): 8.30 (d, 1H, 9.1 Hz, NBD); 6.30 (d, 1H, 9.1 Hz, NBD); 4.24 (s, 4H, N-CH_2); 3.83 (t, 4H, 5.4 Hz, O-CH_2); 3.60 (m, 16H, O-CH_2). ^{13}C-NMR (CDCl3): 145.5; 144.8;144.4; 135.3; 121.6; 101.9; 70.7; 70.5; 68.6; 54.4.

B. $C_{18}H_{27}N_5O_7$. Exact Mass: 425.191. ^{1}H-NMR (DMSO-d6): 8.46 (d, 1H, 9.2 Hz, NBD); 6.54 (d, 1H, 9.2 Hz, NBD); 3.6–3.7 (m, 16H, O-CH_2), 3.0 (m, 4H, O-CH_2). ^{13}C-NMR (DMSO-d6): 145.6; 144.9; 144.6; 136.3; 120.4; 102.6; 69.6; 69.4; 69.2; 66.7; 53.6; 48.5.

C. $C_{24}H_{28}N_8O_{10}$. Exact Mass: 588.1928. ^{1}H-NMR (DMSO-d6): 8.44 (d, 2H, 9.2 Hz, NBD); 6.52 (d, 2H, 9.3 Hz, NBD); 3.81 (t, 8H, 5.4 Hz, N-CH_2); 3.30–3.65 (m, 16H, O-CH_2). ^{13}C-NMR (DMSO-d6): 145.6; 144.8;144.6; 125.9; 120.7;102.7; 75.6; 74.9; 70.1; 67.7; 66.5; 30.7.

Synthesis of the new compounds **D-F** was performed in acetonitrile at room temperature, following these general steps. For each amino-groups an equivalent of NBD-chloride and five equivalents of solid sodium hydrogen carbonate should be considered; the volume of acetonitrile corresponding to 1 mmol of NBD-chloride should be around 50 mL. The reaction time is 24 h, with stirring. After that, the solution is filtered off, the filter is washed with small portions of DCM, and to the collected organic mixture DCM and water is added. The biphasic system is poured into a separatory funnel, extracted, and the DCM phase is collected, dried over anhydrous sodium sulphate, filtered off and the solvent removed. The residue is chromatographed on silica gel using ethyl acetate or DCM/methanol 9/1 as eluent. The yields vary from 30% for **D** to about 75% for **E** and **F**.

D. $C_{18}H_{18}N_8O_8$. Exact Mass: 474.1248. ^{1}H-NMR (DMSO-d6): 9.38 (s, 2H, NH); 8.46 (d, 2H, 8.5 Hz, NBD); 6.41 (d, 2H, 8.5 Hz, NBD); 3.69–3.57 (m, 12H, CH_2). ^{13}C-NMR (DMSO-d6): 145.2; 144.3; 143.9; 137.7; 121.8; 120.8; 99.3; 72.8; 69.8; 67.9; 60.2; 43.3.

E. $C_{20}H_{22}N_4O_8$. Exact Mass: 446.1438. ^{1}H-NMR ($CDCl_3$): 8.42 (d, 1H, 8.6 Hz, NBD); 6.94 (m, 2H, arom); 6.88 (m, 1H, arom); 6.54 (d, 1H, 8.6 Hz, NBD); 4.18–4.14 (m, 4H, CH_2); 3.94 (m, 4H, CH_2); 3.78-3.77 (m, 8H, CH_2). ^{13}C-NMR ($CDCl_3$): 149.9; 148.4; 144.5; 143.9; 141.9; 136; 129.7; 125.2; 117.3; 114.3; 110.4; 100.7; 70.9; 70.2; 69.1; 69. IR: 3434, 3203, 2938, 2870, 1569, 1516, 1488, 1440, 1308, 1250, 1237, 1129, 1098, 1062, 1038, 986, 943, 906, 852, 594.

F. $C_{22}H_{26}N_4O_9$. Exact Mass: 490.17. ^{1}H-NMR ($CDCl_3$): 8.39 (d, 1H, 8.7 Hz, NBD); 8.08 (s, 1H, NH); 6.92 (m, 2H, arom); 6.88 (m, 1H, arom); 6.53 (d, 1H, 8.7 Hz, NBD); 4.20-4.13 (m, 4H, CH_2); 3.96–3.92 (m, 4H, CH_2); 3.78–3.69 (m, 12H, CH_2). ^{13}C-NMR ($CDCl_3$): 149.7; 148.1; 144.5; 143.9; 142.1; 136.2; 129.7; 124.9; 117.1; 113.9; 110.1; 100.7; 70.7; 70.5; 69.3; 68.9. IR: 3590, 3236, 3159, 3091, 3051, 2920, 2863, 1723, 1610, 1569, 1508, 1444, 1402, 1314, 1242, 1120, 1097, 1032, 937, 899, 737, 677, 596.

CONCLUSIONS

The new derivatives **D-F** synthesised and characterized are potential benzofurazan ethylene glycol derivatives designed for their possibility of qualitative and quantitative measurements with interacting cations, using either a UV-Vis or fluorescence approach. Such chemo- or fluoro-sensors can be widely used in many other areas of chemistry and biology, for analytical purposes. Further developments can be achieved in medicine and environmental sciences.

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