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Synthesis of fluorescent 3-benzoxazol-2-yl-coumarins

XH Luan, NMFSA Cerqueira, AMAG Oliveira, MMM Raposo, LM Rodrigues, P Coelho* and AMF Oliveira-Campos#

Centro de Química, IBQF, Universidade do Minho, 4710-057 Braga, Portugal

** Departamento de Química, Universidade de Trás-os-Montes e Alto Douro, Quinta dos Prados, 5000-Vila Real, Portugal*

 # Author for correspondence

Twelve 3-benzoxazol-2-yl-coumarins were synthesised by reacting various *ortho*-aminophenols with three coumarin-3-carboxylic acids either directly or by formation of the intermediate amide. The cyclodehydrating agent was polyphosphoric acid (PPA). The compounds were characterised by spectroscopic methods. Absorption and fluorescence spectra of the compounds were also recorded.

Keywords: fluorescence, coumarins, benzoxaloyl coumarins

INTRODUCTION

Coumarin derivatives constitute an important class of organic fluorescent dyes with considerable interest for various applications [1] as mentioned below.

Recent developments on long wavelength fluorescent compounds have been reviewed [2].

Heterocyclic compounds containing benzoxazole and coumarin moieties have gained commercial interest as optical brighteners for polyester, polyamide and polyvinyl chloride. Derivatives of coumarin are quite stable to light, which is rather unusual among fluorescent dyes [3].

A considerable number of natural or synthetic coumarin derivatives display pharmaceutical properties with a wide range of activity [4] and others are useful for optical applications. Derivatives of 7-hydroxycoumarins are efficient photo stable laser dyes and the lasing range covered is extended when there is a heterocyclic moiety in position 3 of the coumarin [5].

Due to their potential as light emitters in organic light emitting devices (LEDs), studies on coumarin molecules covalently linked to sol-gel matrices were conducted by Kärkkäinen [6].

Following our interest on synthesising fluorescent 1,3-benzothiazoles [7] it was now decided to prepare compounds of the coumarin type containing a benzoxazole moiety.

Several synthetic routes to benzoxazoles have been reported. Carpignano [8] heated together carboxylic acids and *ortho*-aminophenol in the presence of PPA. Other authors have synthesised similar compounds also starting from *ortho*-aminophenols with S-methylisothioamide hydroiodides under microwave heating [9].

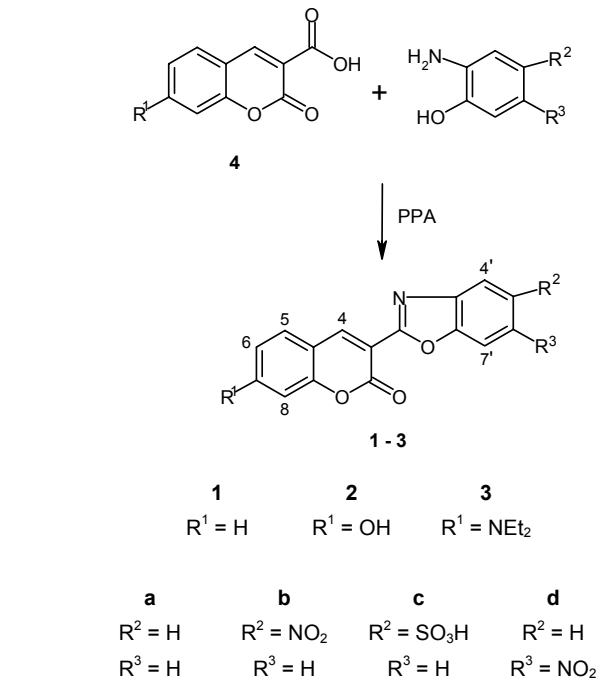
In this work coumarin derivatives containing electron withdrawing groups in the benzoxazoloyl moiety, such as nitro and sulphonic, were prepared and the resulting changes in their absorption and emission spectra observed.

Two methods were used for the preparation of the final products. The method described by Carpignano [8] (Scheme 1) was the most extensively used.

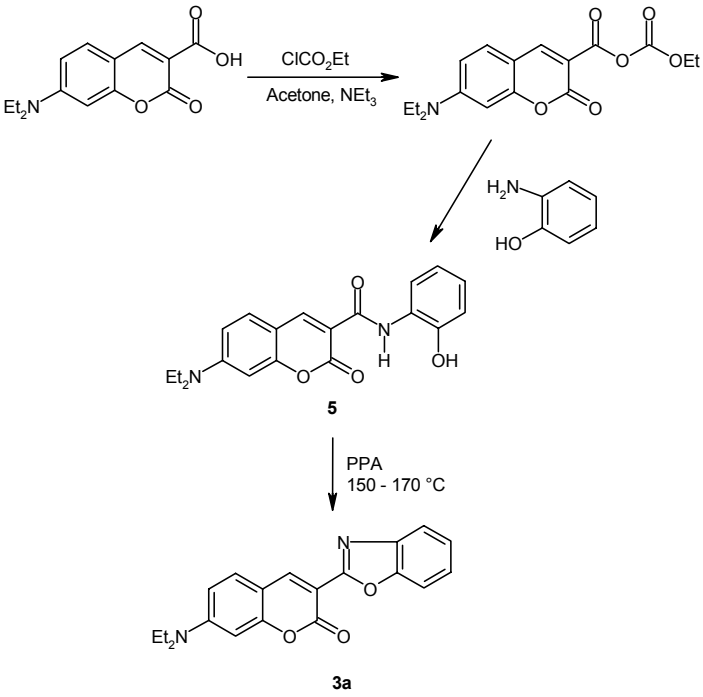
The high polarity of some of the compounds led to difficulties in the purification of the final product and low yields resulted. It was then decided to apply another method of preparation starting with the carboxylated coumarin activated as a mixed anhydride [10]. After filtration of the triethylamine hydrochloride the intermediate was at once reacted with the *ortho*-aminophenol. The amide that was obtained (**5**) was separated and then cyclised by heating with PPA. This method, which is exemplified for the preparation of **3a** (Scheme 2), improved the yield significantly for this compound. In the case of compound **1d** the yield was slightly lower but the product was obtained directly in a pure state.

It is our intention to test, in the future, this method for the preparation of synthetically difficult compounds.

Scheme 1

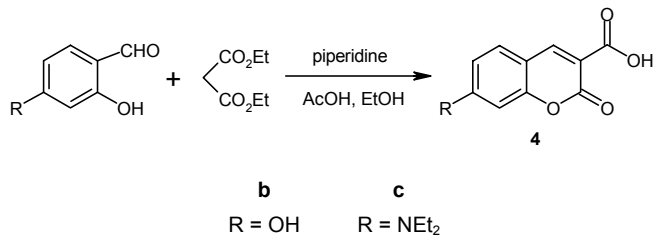


Scheme 2



The starting coumarins (**4b**, **4c**) were made from the corresponding *ortho*-hydroxybenzaldehydes by Knoevenagel condensation [11] followed by basic hydrolysis (Scheme 3).

Scheme 3



To obtain a sample which was suitable for elemental analysis, UV-Vis absorption and emission spectra, in some cases, with method A, it was necessary to submit the product mixture to chromatography before crystallisation.

EXPERIMENTAL

Equipment

The infrared and visible absorption spectra were recorded on Perkin Elmer FTIR-1600 and on Hitachi U-2000 spectrometers. A Varian Unity Plus Spectrometer at 300 MHz was used to obtain the ^{1}H NMR spectra. Electron impact mass spectra were recorded on a Unicam GC/MS 120 by direct insertion. FAB and high resolution mass spectra were run on a VG Ultima HRMS or an Auto Spec E spectrometer. Fluorescence spectra were determined on a SPEX FLUOLOG-2 analyser, with double monochromator and an emission Xenon lamp of 4450 watts. Elemental analyses were carried out on a Leco CHNS 932 instrument.

Synthesis of the starting coumarins [11]

A mixture of the corresponding *ortho*-hydroxybenzaldehyde (3.6 mmol), diethyl malonate (1.1 ml, 7.2 mmol), ethanol (10 ml), piperidine (0.2 ml) and glacial acetic acid (3 drops) was refluxed for 3 hours. After cooling the ethanol was removed by evaporation at reduced pressure, then a solution of 10 % KOH (25 ml) was added and the mixture was refluxed for one hour. After cooling, water (40 ml) was added. The solution was taken to pH 3 (or to pH 6 for compound **4c**) with 10% HCl. The precipitate formed was collected by filtration and the product was recrystallised from methanol. A white solid for 7-hydroxycoumarin-3-carboxylic acid, **4b**, was obtained (57 %, m.p. 268 - 270 ºC, lit. 264 – 265 ºC [12]). For the compound 7-*N,N*-diethylamino-coumarin-3-carboxylic acid, **4c**, orange plates were obtained (44 %), m.p. 230 - 233 ºC (lit. no m. p. quoted [4b]).

Synthesis of the final fluorescent compounds (Method A)

A mixture of coumarin (0.5 mmol), the suitable *ortho*-aminophenol (2.5 mmol) and polyphosphoric acid (10 g) were heated at 160 °C for 1.5 – 2 hours. After cooling, water (40 ml) was added and then a 5N NaOH solution (20 ml). The solid that precipitated out was filtered, washed with water and dried at 60 °C. After testing its purity by tlc (thin layer chromatography) it was purified by crystallisation.

Synthesis of coumarin 3a (Method B)

To an ice cold suspension of *N,N*-diethylamino-coumarin-3-carboxylic acid (0.28 g, 1 mmol) in acetone (10 ml) ethyl chloroformate (0.15 ml, 1.2 mmol) and triethylamine (0.164 ml, 1.2 mmol) were added. The initially orange suspension turned light yellow and a white solid precipitated out in 10 minutes. The triethylamine hydrochloride was filtered off and to the filtrate, ortho-aminophenol (0.11 g, 1 mmol) was added and the mixture was stirred at room temperature overnight. The yellow suspension was evaporated to dryness and a yellow solid was obtained which was pure by tlc. A small portion of this solid (50 mg) was kept aside and proved to be the amide 3-*N*-(2-hydroxyphenyl)-7-*N,N*-diethylamino-coumarin-3-carboxamide, **5**, (m.p. 258-262 °C; IR (Nujol mull) 1688, 1639 cm^{-1}).

To the amide PPA (c.a. 5 g) was added and the mixture was heated at 150 – 170 °C for 4 hours. After cooling, water was added (a reddish-orange solution was formed) and then 5N NaOH solution to pH 7. A yellow oil separated that solidified overnight and showed to be the impure product **3a** (0.27 g) m.p. 150-169°C. This solid was washed with ether and gave the pure compound **3a** as a dark yellow solid, 0.15 g (44 %) m.p. 176-178 ºC (lit. m.p. 184.5-185.5 ºC [13]).

RESULTS AND DISCUSSION

For compounds **1**-**3** the synthetic data are shown in Table 1. The nitro compounds (**b**, **d**) gave the lowest yields and the sulphonated (**c**) derivatives the highest.

All the compounds synthesised were characterised by ^{1}H NMR spectroscopy and sets of selected data for some final compounds and precursors are presented (Table 2). In the coumarin ring the expected pattern was observed, always showing the proton 4 on the coumarin system as a singlet at 8.7-9.13 ppm.

The characterisation of the final products also included elemental analysis and/or mass spectra as shown in Table 3.

It was possible to rationalise the cleavages that might originate the charged fragments observed in the mass spectra. For example for nitro compound **1d** M^+ could lose NO giving fragment *m/z* 278 (27%), followed by loss of CO (250, 14%). Loss of NO_2 (262, 4%) then CO (234, 66%) from M^+ was also observed.

In Table 4 the absorption (UV-Vis and IR) and emission characteristics for compounds **1** – **4** are described. Although the fluorescence properties are not discussed in detail, values obtained by our group or described in the literature are given as an indication. It is also possible to draw a few general observations, as follows.

An electron-donating group in position 7 of the coumarin ring induces a bathochromic shift in the absorption spectra, this shift being larger for a NEt_2 group as compared to an OH group. This effect is already apparent on the spectra of the starting coumarins carboxylated in position 3 (**4b** and **4c**) and it is observed in the final compounds where those containing the *N,N*-diethylamino group absorb and fluoresce at longer wavelengths (compare compounds **3** with the corresponding **1** and **2**). The presence of a nitro group in the second moiety reinforces this effect mainly when it is located in position *para* to the O atom of the benzoxazole ring (compare **3a**, **3b** and **3d**).

When the CO_2H group is replaced by a benzoxazolyl moiety the fluorescence maxima are shifted towards higher wavelengths. This shift is about 40 nm for R=OH and varies between 9 nm (**3c**) and 47 nm (**3b**) for R= NEt_2.

A detailed investigation of the spectral properties of coumarins **1a** and **3a** is under progress [18] and results on compound **2a** have already been published [17].

Table 1: Yields, purification details and physical properties of fluorescent compounds **1-3**

	% yield after purification	Purification solvent	Appearance	m.p. (ºC)	Literature m.p. (ºC)
1a	58	–	Light yellow crystals	186 – 189	186 [14]
1b	19	DMF – MeOH	Light brown solid	278 – 279	
1c	21	MeOH	Off white solid	c	
1d	9	DMF – MeOH	Light brown solid	285 – 289	298 – 300 [15]
	7[a]	CH_3CN[b]	Light brown solid	304 – 306[a]	
2a	20	MeOH	Golden yellow crystals	314 – 315	280 [6]; >300 [16]
2b	10	DMF – MeOH	Dark yellow solid	Sublimes at t>210	
2c	87	DMF – MeOH	Light brown solid	c	
2d	17	DMF – MeOH	Brown solid	210	
3a	19	acetone	Dark yellow solid	170 – 175	184.5 – 185.5 [13]
	44[a]		Dark yellow solid	176 – 178[a]	
3b	18	DMF – acetone	Brick coloured solid	328 – 335	
3c	60	MeOH	Dark yellow solid	234 – 238	
3d	14	DMF – acetone	Light brown solid	c	

[a] Synthesised by Method B

[b] Extraction with CH_3CN and evaporation to dry

c Did not melt up to 350 ºC

Table 2: ^{1}H NMR data for selected fluorescent compounds and their precursors

	Solvent	δ (ppm, 300 MHz)
1a	$CDCl_3$	7.35-7.46 (4H,m), 7.62-7.71 (3H, m), 7.86-7.90 (1H, m, 5-H), 8.79 (1H, s, 4-H)
1b	$CDCl_3$	7.40-7.50 (2H, m, 5-H and 8-H), 7.70-7.77 (2H, m, 6-H and 7-H), 7.77 (1H, d J 8.9 Hz, 7´-H), 8.04 (1H, dd J 8.9 and 2.5 Hz, 6´-H) , 8.75 (1H, d J 2.5 Hz, 4´-H), 8.88 (1H, s, 4-H)
1c	DMSO-d_6	7.45 (1H, dt J 8.0 and 1.7 Hz, 6-H), 7.50 (1H, br d J 8.0 Hz, 8-H), 7.71-7.79 (3H, m, 7-H, 7´-H and 6´-H), 7.97 (1H, tap J 1.0 Hz, 4´-H), 8.01 (1H, dd J 8.0 and 1.7 Hz, 5-H) , 9.13 (1H, s, 4-H)
1d	$CDCl_3$	7.40-7.55 (2H, m), 7.60-7.80 (2H, m), 7.98 (1H, d J 8.0 Hz, 4´-H), 8.38 (1H, dd J 8.0 and 2.0 Hz, 5´-H), 8.56 (1H, d J 2.0 Hz, 7´-H), 8.91 (1H, s, 4-H)
2a	DMSO-d_6	6.79 (1H, d J 2.0 Hz, 8-H), 6.88 (1H, dd J 8.5 and 2.0 Hz, 6-H), 7.40-7.46 (2H, m), 7.4-7.82 (2H, m), 7.82 (1H, d J 8.5 Hz, 5-H), 8.95 (1H, s, 4-H). OH was not observed.
2b	Acetone-d_6	6.89 (1H, br s, OH), 6.91 (1H, d J 2.4 Hz, 8-H), 7.04 (1H, dd J 9.0 and 2 Hz, 6-H), 7.92 (1H, d J 9 Hz, 5-H), 8.01 (1H, d J 9.0 Hz, 7´-H), 8.44 (1H, dd J 9.0 and 2.0 Hz, 6´-H), 8.67 (1H, d J 2.0 Hz, 4´-H), 9.02 (1H, s, 4-H)
2c	CD_3OD	6.83 (1H, d J 2.0 Hz, 8-H), 6.94 (1H, dd J 8.4 and 2.0 Hz, 6-H), 7.76 (1H, d J 8.4 Hz, 5-H), 7.77 (1H, dap J 8.4Hz, 7´-H), 7.99 (1H, dd J 8.4 and 2.1 Hz, 6´-H), 8.30 (1H, dap J 1.5 Hz, 4´-H), 8.95 (1H, s, 4-H). OH was not observed.
3a	$CDCl_3$	1.27 (6H, t J 7.5 Hz, 2x $CH_2\mathit{CH_3}$), 3.48 (4H, q J 7.5 Hz, 2x $\mathit{CH_2}CH_3$), 6.57 (1H, d J 2.3 Hz, 8-H), 6.70 (1H, dd J 9.0 and 2.3 Hz, 6-H), 7.32-7.40 (2H, m, 5´-H and 6´-H), 7.46 (1H, d J 9.0 Hz, 5-H), 7.56-7.64 (1H, m, 4´-H), 7.78-7.86 (1H, m, 7´-H), 8.62 (1H, s, 4-H)
3c	CD_3OD	1.28 (6H, t J 7.5 Hz, 2x $CH_2\mathit{CH_3}$), 3.55 (4H, q J 7.5 Hz, 2x $\mathit{CH_2}CH_3$), 6.62 (1H, dt J 2.4 Hz, 8-H), 6.86 (1H, dd J 8.5 and 2.4 Hz, 6-H), 7.63 (1H, d J 8.5 Hz, 5-H), 7.72 (1H, d J 8.0 Hz, 7´-H), 7.94 (1H, dd J 8.0 and 1.5 Hz, 6´-H), 8.26 (1H, d J 1.5 Hz, 4´-H), 8.78 (1H, s, 4-H)
3d	$CDCl_3$	0.9 (6H, t J 7.0 Hz, 2x $CH_2\mathit{CH_3}$), 3.50 (4H, q 7.0 Hz, 2x $\mathit{CH_2}CH_3$), 6.69 (1H, d J 2.4 Hz, 8-H), 6.76 (1H, dd J 8.5 and 2 Hz, 6-H), 7.50 (1H, d J 8.5 Hz, 5-H), 7.90 (1H, d J 8.0 Hz, 4´-H), 8.34 (1H, dd J 8.0 and 2.0 Hz, 5´-H), 8.50 (1H, d J 2. Hz, 7´-H), 8.7 (1H, s, 4-H)
4b	Acetone-d_6	6.97 (1H, d J 2.1 Hz, 8-H), 7.09 (1H, dd J 8.7 and 2.4 Hz, 6-H), 7.94 (1H, d J 8.7 Hz, 5-H), 8.92 (1H, s, 4-H), 11.50 (1H, br s, OH), the other OH was not observed.
4c	$CDCl_3$	1.27 (6H, t J 7.5 Hz, 2x $CH_2\mathit{CH_3}$), 3.50 (4H, q 7.5 Hz, 2x $\mathit{CH_2}CH_3$), 6.53 (1H, d J 2.7 Hz, 8-H), 6.71 (1H, dd J 9.3 and 2.4 Hz, 6-H), 7.46 (1H, d J 9.2 Hz, 5-H), 8.66 (1H, s, 4-H), 12.40 (1H, br s, OH)
5	$CDCl_3$	1.28 (3H, t J 7.0 Hz, $CH_2\mathit{CH_3}$), 3.50 (2H, q J 7.0 Hz, $\mathit{CH_2}CH_3$), 6.55 (1H, d J 2.7 Hz, 8-H), 6.70 (1H, dd J 8.7 and 2.4 Hz, 6-H), 6.90 (1H, dt J 8.0 and 1.5 Hz, 5´-H), 7.04-7.20 (3H, m), 7.48 (1H, d J 9.0 Hz, 5-H), 8.80 (1H, s, 4-H), 9.80 (1H, br s, OH), 11.20 (1H, br s, NH)

dap = pseudo doublet, tap = pseudo triplet

Table 3: Mass spectra and elemental analysis data for selected fluorescent compounds and their precursors

	Mass Spectra	Elemental Analysis (%)	
	m/z (%) (EI)	Found	Theory
1a	264(M^++1, 20) 263((M^+, 100) 236(12) 235(66)	C(72.88), H(3.46), N(5.38)	C(73.00), H(3.42), N(5.32), $C_{16}H_9NO_3$
1b	308(M^+, 24) 262(2) 250(4) 234(13) 206(4) 91(34) 63(100)	C(62.40), H(2.92), N(8.98)	C(62.38),H(2.62), N(9.09), $C_{16}H_8N_2O_5$
1c	366(M^++1+Na, 18) FAB^+	C(47.88), H(3.10), N(3.59), S(7.95) 366.004037 (HRMS, FAB^+)	C(47.84),H(3.24), N(3.49), S(7.97) $C_{16}H_8NO_6SNa.2\ H_2O$ 366.004829 $C_{16}H_9NO_6SNa$
1d	309(M^++1, 19) 308(M^+, 100) 278(27) 262(14) 250(14) 234(66) 206(27) 8418) 80(16) 63(57)	C(60.91), H(3.02), N(8.53)	C(60.60),H(2.84), N(8.83) $C_{16}H_8N_2O_5.½\ H_2O$
2a	279(93) 251(100) 222(18)	-----	-----
2b	325(M^++1, 19) 324(M^+, 100) 308(5) 296(7) 278(7) 250(19) 91(17)	324.037947 (HRMS)	324.038236 $C_{16}H_8N_2O_6$
2d	325(M^++1, 17) 324(M^+, 100) 294(8) 267(6) 250(27) 222(14) 189(34) 162(11) 69(37)	324.038577 (HRMS)	324.038236 $C_{16}H_8N_2O_6$
3a	334((M^+, 80) 319(100) 291(20) 262(18) 72(16)	C(71.75), H(5.97), N(7.86)	C(71.87), H(5.39), N(8.38) $C_{20}H_{18}N_2O_3$
3b	380(M^++1, 16) 379(M^+, 73) 365(22) 364(100) 336(8) 318(6) 290(8) 246(8) 244(18)	379.117165 (HRMS)	379.116821 $C_{20}H_{17}N_3O_5$
3c	--------	415.095330 (HRMS, FAB^+)	415.096383 (M^++1) $C_{20}H_{19}N_2SO_6$
3d	379(3) 364(6) 246(24) 236(13) 206(10) 164(14) 91(60)	379.116757 (HRMS)	379.116821 $C_{20}H_{17}N_3O_5$
4b	207(M^++1, 22)	-----	-----
4c	262(M^++1, 8) 261(M^+, 42) 246(100) 202(12) 174(20) 89(15) 78(12) 63(10)	C(63.57), H(5.63), N(5.40)	C(63.26), H(5.78), N(5.27) $C_{14}H_{15}N_3O_4.¼H_2O$

Table 4: Spectroscopic data for fluorescent compounds and their precursors

	UV - Visible		Fluorescence λ_{max} / nm		IR
	λ_{max} / nm	ε / $mol^{-1}.dm^3.cm^{-1}$	Excitation	Emission	ν / cm^{-1}
1a	348	27324	354	422	1742, 1611
	349 [14] (aq.EtOH)	17783		445 [14]	
1b	366 (DMF)	28400	366	487	1745, 1609
1c	272, 350	55794, 20028	356	435	3429, 1740, 1606
1d	274, 341	48670, 20213	312	352	1756
2a	380 (MeOH) [17]	25704	381	447 [17]	3401, 1739, 1721, 1599
2b	383 449 (EtOH: H_2O, 45:5)	29688, 8854	383	451	3260, 1730, 1614
2c	377.5 (MeOH)	14250	377	446	3493, 1736, 1615
2d	367, 414, 459	-----	414	444	3351, 1745, 1699, 1614
3a	441 [18]	50119	441	489 [18]	1738, 1612
3b	299, 466.5	2900, 11074	466	513	1737, 1665, 1615
3c	269 432 (EtOH: H_2O, 45:5)	23878, 28980	430	475	1738, 1712, 1633, 1607
3d	268, 465	44845, 50041	467	500	1709 (KBr)
4b	352, 413	21125, 3417	352	402	3470, 1731, 1681 (KBr)
4c	423	27417	423	466	3447, 1738, 1666 (KBr)

UV-vis and fluorescence spectra run in ethanol except when stated otherwise

IR spectra run in Nujol except when stated otherwise

CONCLUSIONS

It is necessary to study the emission properties and light stability of the new compounds that are described here, to conclude if any of them will be promising for practical applications.

One may envisage that those characteristics can be improved by using convenient substituents in both moieties. Work will proceed in this direction.

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