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Synthesis and NMR Spectroscopic Characterization of Some Fluoro-2*H*-1-Benzopyran Derivatives

Yannick Teral,[A] *Gabriel Roubaud*,[B] *Claude Aubert*,[C] *Robert Faure*,[B] *and Mylène Campredon*[A,D]

[A] JE 2421 TRACES, Université de la Méditerranée, Faculté des Sciences de Luminy, 13298 Marseille Cedex 9, France.

[B] UMR-CNRS-6178, Faculté des Sciences de St Jérome, Université Paul Cézanne, 13397 Marseille Cedex 13, France.

[C] UPRES EA 3286, Faculté de Pharmacie de la Timone, Université de la Méditerranée, 13385 Marseille Cedex 5, France.

[D] Corresponding author. Email: Mylene.Campredon@luminy.univ-mrs.fr

The synthesis of some new fluoro-2*H*-1-benzopyran derivatives utilizing a reaction between titanium phenolates and β-phenylcinnamaldehydes in toluene is reported. These compounds were characterized by NMR and UV/visible spectroscopy as well as mass spectrometry. In solution all the compounds are photochromic. Complete assignment of the ^{1}H and ^{13}C resonances was achieved by concerted application of homonuclear (*gs*-COSY), proton-detected (C, H) one-bond (*gs*-HMQC), and long-range (*gs*-HMBC) heteronuclear two-dimensional chemical shift correlation experiments using a 500 MHz NMR spectrometer equipped with a cryoplatform and a 5 mm cryoprobe. The mass spectra of the different compounds were characterized by intense molecular and high fragment ions. The introduction of an atom of fluorine as a molecular probe is of interest in determining the mechanistic aspects of the photochemical process.

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Introduction

2*H*-Pyran compounds are present in nature as a key unit of natural products[1] and the benzopyran ring system is the active constituent of natural pigments.[2] Even though Becker et al.[3] reported on the photochromism of several naturally occurring 2*H*-1-benzopyrans for the first time in 1970, only a few articles dealt with these derivatives until the 1990s. However, interest in these photochromic molecules has since grown as a result of their commercial use in the field of variable optical materials. Photochromic compounds are of great interest to industry, but 2*H*-1-benzopyrans are less photochromic than 2*H*-naphtho[1,2-*b*]pyrans and 3*H*-naphtho[2,1-*b*]pyrans,[1] and the lack of interest in these compounds arises as a result of their poor colour.[4] The photochromic activity of these molecules is a well known phenomenon based on UV absorption of the uncoloured form, which can undergo isomerization after the scission of the C─O bond of the pyran moiety. This reaction is reversible and the back isomerization to the uncoloured form takes place by thermal or photochemical processes. Several groups interested in the commercialization of photochromic plastic ophthalmic lenses have modified the parent compound in an attempt to provide molecules with appropriate properties and have patented[5,6] 2*H*-1-benzopyrans with heteroaromatic groups in order to enhance the photochromic properties of this series. From our perspective, the introduction of a fluorine atom may be useful in providing a molecular probe. Moreover, these fluoro compounds are of interest in determining the mechanistic aspects of the photochemical process.[7,8] In this paper, seven fluorobenzopyrans were synthesized and characterized using NMR and UV/visible spectroscopy as well as mass spectrometry.

Results

We have synthesized 2,2-diphenyl-6-fluoro-, 2,2-di(4-fluorophenyl)-6-fluoro-, 2,2-di(4-fluorophenyl)-6-methyl-, 2,2-di(4-fluorophenyl)-6-methoxy-, 2,2-di(4-fluorophenyl)-5,7-dimethyl-, 2,2-di(4-fluorophenyl)-7,8-dimethoxy-, and 2,2-di(3-trifluoromethylphenyl)-7,8-dimethoxy-2*H*-benzopyran **1**–**7**. These compounds have the general structure shown in Scheme 1.

These fluoro-2*H*-1-benzopyran derivatives have been synthesized in three steps from readily available starting materials. We have followed the most convenient synthetic route towards benzopyrans, namely one that involves a reaction between titanium phenolates and β-phenylcinnamaldehydes in toluene. The overall synthetic route to compounds **1**–**7** is outlined in Scheme 2.

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Propargyl alcohols **A**–**C** were prepared as outlined in Scheme 2. To a solution of sodium acetylide (solution in xylenes, 30 mL, 10 equiv.) in freshly distilled tetrahydrofuran (THF) (250 mL) at −10°C was added dropwise a solution of the ketone (11.0 mmol) in THF (100 mL). Upon complete addition, the mixture was allowed to warm to room temperature, the reaction mixture was poured into ice/water, and the two phases were separated. The organic phase was washed with saturated aqueous ammonium chloride solution (100 mL), while the aqueous phase was further extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum. The xylenes were then removed by azeotropic distillation of a methanol/xylene mixture. Chromatography (0–5% diethyl ether in pentane) afforded the alcohol **A** as a white powder (88% yield), mp 78°C. Compounds **B** and **C** were obtained as yellow oils in 75 and 79% yields, respectively, as reported in Table 1.

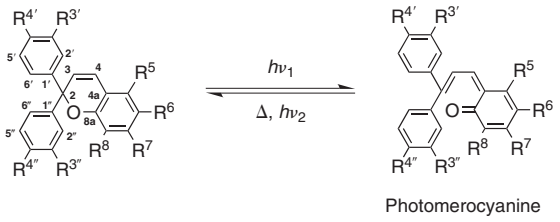
Precursors **A**, **B**, and **C** then gave rise to aldehydes **D**, **E**, and **F** upon Meyer–Schuster rearrangement[10] (1,3-migration) under acidic catalysis (H_2SO_4). To a solution of propargyl alcohol in dioxan was added a solution of sulfuric acid (2.5 mL H_2SO_4/2.5 mL H_2O). The mixture was then heated at reflux for five minutes. The yields (see Table 2) for this step were generally high and the crude products were often sufficiently pure as to be used directly in the formation of the benzopyran.

The benzopyran derivatives were subsequently synthesized as follows. A solution of tetraethylorthotitanate (10 mmol in 10 mL) in toluene (10 mL) was gently added under an atmosphere of nitrogen to the phenolic compound (10 mmol) in anhydrous toluene (50 mL) at room temperature and the ethanol was removed by azeotropic distillation of a toluene/ethanol mixture. The mixture was then allowed to cool to room temperature. The α,β-ethylenic compound (10 mmol) in anhydrous toluene (80 mL) was added to the mixture, which was subsequently heated at reflux for three hours while the reaction was monitored by thin-layer chromatography (TLC). The reaction mixture was subsequently hydrolyzed using a KOH solution (2 M) and filtered. The aqueous phase was further extracted with diethyl ether. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum. The resultant yellow oil was purified by chromatography (0–5% diethyl ether in pentane) to afford, after evaporation of the eluent and pentane recrystallization, compounds **1**–**5** as white powders and compounds **6** and **7** as yellow powders. The results are summarized in Table 3 along with the wavelength maxima of the coloured forms in toluene at 20°C.

The yields obtained were in accordance with previous work.[11] Formation of compound **8** was not achieved because the *C*-alkylation step was probably inhibited as a result of the (–I) effect on the aromatic ring of the trifluoromethyl group (Scheme 3).[12]

As a follow-on to these results, unsuccessful attempts were made to synthesize trifluoromethylpyrans using a bromoaromatic ring and trifluoromethylcopper reagents, as reported by Carr et al.[13] and Urata and Fuchikami.[14] This latter approach may be successful if iodopyran derivatives, which are known to be more reactive than their bromo analogues, are used.

For compounds **1**–**7** (Scheme 2), assignment of the ^1H and ^{13}C chemical shifts of the phenyl ring protons and carbons on the basis of $^nJ_{C,F}$ and $^nJ_{F,F}$ coupling constants and signal intensities was found to be trivial. However, even in the 500 MHz ^1H NMR spectra, on the basis of the multiplet pattern and the magnitude of the splitting, the proton resonances of the benzo[2,1-*b*]pyran skeleton were characteristic first-order spin systems which were no longer able



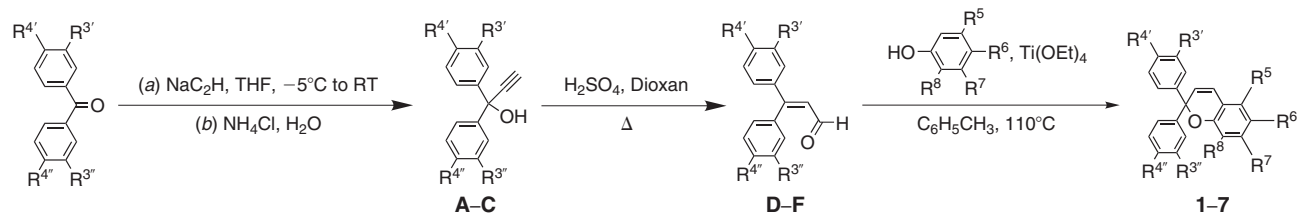
Scheme 1. Photochromic equilibrium and numbering system for 2*H*-benzopyran compounds **1**–**7**.

Table 1. Propargyl alcohol yields

Product	R^3	$R^{3'}$	R^4	$R^{4'}$	Yield [%]
A	H	H	H	H	88[9]
B	H	H	F	F	75
C	CF_3	CF_3	H	H	79

Table 2. Aldehyde yields

Product	R^3	$R^{3'}$	R^4	$R^{4'}$	Yield [%]
D	H	H	H	H	100
E	H	H	F	F	100
F	CF_3	CF_3	H	H	85



Scheme 2.

to be assigned. Therefore, complete assignment of the ^{1}H and ^{13}C resonances was achieved by concerted application of homonuclear (*gs*-COSY), proton-detected (C, H) one-bond (*gs*-HMQC), and long-range (*gs*-HMBC) heteronuclear two-dimensional chemical shift correlation experiments. All the CH_n groups were unambiguously characterized from the analysis of long-range correlation responses over two and three bonds (^{2}J and ^{3}J couplings) using the *gs*-HMBC sequence. To illustrate this strategy, significant long-range ^{1}H–^{13}C connectivities observed in the *gs*-HMBC spectrum for compound **3** are shown in Scheme 4 (the arrows always link a proton to a carbon).

There are few papers reported in the literature on mass spectrometric studies of chromene derivatives.[15,16] In our study, mass spectra of the different compounds were always characterized by intense molecular ions. Fragmentation pathways, such as the loss of a radical (77 Da) or neutral (78 Da) phenyl group in compound **1**, the loss of a fluorophenyl group (95 or 96 Da) in compounds **2**–**6**, and the loss of a trifluoromethylphenyl group (149 or 150 Da) in compound **7**, are common. This leads to the detection of the following high fragment ions: $[M - \varphi)]^{+\bullet}$, compound **1**; $[M - \varphi F]^{+\bullet}$, compounds **2**–**6**; and $[M - \varphi CF_3]^{+\bullet}$, compound **7**. In benzopyrans **1** and **2**, in which $R^6 = F$, loss of 19 Da is the result of a loss of the fluorine atom on the pyranic ring by homolytic cleavage. In benzopyrans **3**–**7**, the loss of 15 Da is due to the loss of a methyl group by homolytic cleavage. In benzopyrans **4**, **6**, and **7**, the loss of 31 Da results from methoxy loss.

The spectroscopic data presented in Table 3 lists the wavelength maxima of the coloured forms in toluene at 20°C. It is noteworthy that only the photomerocyanine of compound **4** shows a strong absorption at 485 nm. These observations indicate that substituents on the phenyl groups can have substantial effects on colour, but the introduction of two *para*-fluorine atoms causes no appreciable shift in λ_{max},[17] while the presence of two CF_3 groups in the *meta*-position leaves λ_{max} unchanged. As would be expected from previous reports, the presence of an electron-donating group in the six-position induced a red shift ($\Delta\lambda$ 76 nm).[4] On the other hand, electron-donating groups such as methoxy at the R^7- and R^8-positions had little effect.

The photochromic properties of compound **4** are promising and very similar to those of the 8′-methoxyspiro (fluorenenaphtho[2,1-*b*]pyran)[16] and spiro(3*H*-naphtho [2,1-*b*]pyran-3,9′-[9*H*]-thioxanthene),[18] which are included for comparison in Table 4.

A preliminary study has already been conducted[19,20] on compound **4**, while some fatigue resistance tests will be the subject of a following investigation.

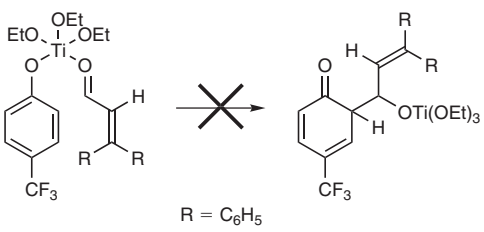
Conclusions

A series of new photochromic compounds of the benzopyran family that contain fluoro substituents have been prepared. Total ^{1}H and ^{13}C NMR assignments were elaborated by concerted application of homonuclear (*gs*-COSY), proton-detected (C, H) one-bond (*gs*-HMQC), and long-range (*gs*-HMBC) heteronuclear two-dimensional chemical shift correlation experiments. The mass spectra of the different compounds were characterized by intense molecular and high fragment ions. The photochromic properties were sensitive to substituents on the pyranic ring, but the introduction of two *para*-fluorine atoms caused little shift in λ_{max}, while the presence of two CF_3 groups in the *meta*-position left λ_{max} unchanged.

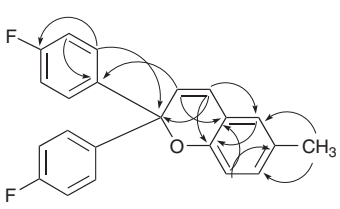
Kinetic studies under UV irradiation are in progress in order to determine the mechanistic aspects of the photochemical process.

Table 3. Yields and spectroscopic data for benzopyran derivatives

Compound	$R^{3'} = R^{3'}$	$R^{4'} = R^{4'}$	R^5	R^6	R^7	R^8	Yield [%]	λ_{max} [nm]
1	H	H	H	F	H	H	30	414
2	H	F	H	F	H	H	22	411–456w
3	H	F	H	CH_3	H	H	34	413
4	H	F	H	OCH_3	H	H	31	489s
5	H	F	CH_3	H	CH_3	H	37	400
6	H	F	H	H	OCH_3	OCH_3	20	400–497w
7	CF_3	H	H	H	OCH_3	OCH_3	22	401–499w
8	H	H	H	CF_3	H	H	0	–

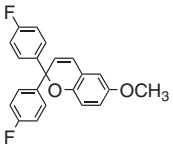
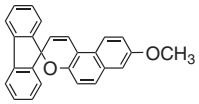
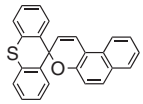


Scheme 3. Inhibition of *C*-alkylation.



Scheme 4. Significant HMBC correlations observed for compound **3**.

Table 4. Comparative spectroscopic data for benzopyrans and spiropyrans

Compound	2,2-Di(4-fluorophenyl)-6-methoxy-2*H*-benzopyran **4**	8′-Methoxyspiro(fluorene-naphtho[2,1-*b*]pyran)	Spiro(3*H*-naphtho[2,1-*b*]pyran-3,9′-[9*H*]-thioxanthene)
Structure			
λ_{max} [nm] in toluene	489	485	490

Experimental

Materials

Compounds were synthesized in accordance with Scheme 2. All reagents were obtained from Aldrich and were used as supplied. Reaction solvents were predried and distilled immediately before use. Dichloromethane was distilled from phosphorous pentoxide, while THF was predried over potassium hydroxide and distilled from sodium benzophenone. Flash column chromatography was carried out using Merck 60 silica gel (0.063–0.200 nm) using solvents as supplied.

Instrumentation

The compounds were characterized by NMR and UV/visible spectroscopy, as well as mass spectrometry.

NMR spectra were recorded in $CDCl_3$ solutions at 300 K using a Bruker Avance DRX 500 spectrometer equipped with a Bruker CryoPlatform and a 5 mm cryo TXI probe. The temperature of the probe and preamplifier was 30 K. Chemical shifts were referenced to $CDCl_3$: δ_H 7.25 ppm, δ_C 77.1 ppm.[21] For two-dimensional experiments Bruker microprograms using gradient selection (*gs*) were applied. The *gs*-COSY spectra[22] were obtained with an F_2 spectral width of 10 ppm in 2 K data points for 256 t_1 increments and sine-bell windows in both dimensions. The *gs*-HMQC spectra[23] resulted from a 256 × 1024 data matrix size with 2–16 scans per t_1, depending on the sample concentration, an inter-pulse delay of 3.2 ms, and a 5 : 3 : 4 gradient combination. The *gs*-HMBC spectra[24] were measured using a pulse sequence optimized on ^3J aromatic couplings (inter-pulse delay for the evolution of long-range couplings: 50 ms) and the same gradient ratio as described for the HMQC experiments. In this way, direct responses (^1J couplings) were not completely removed.

The visible absorption spectra of photomerocyanines were recorded for 10^{-4} M photochromic solutions in spectroscopic grade toluene in 10 mm quartz cells using a Beckman DU 7500 diode array spectrometer.[25] Samples were irradiated with a Xe lamp at 20°C and 400 W m^2.

Mass spectrometry was performed with a Hewlett Packard 5987 mass spectrometer operating in electron impact (70 eV) mode using a direct insertion probe interface. The direct probe temperature for analysis was programmed from 50 to 200°C at 30°C min^{-1} and the ion source was held at 200°C.

Melting points were measured using an Electrothermal 9100 apparatus.

General Synthesis Procedure

A solution of tetraethylorthotitanate (10 mmol in 10 mL) in toluene was added under an atmosphere of nitrogen to the phenolic compound (10 mmol in 50 mL) in anhydrous toluene at room temperature. The ethanol was then removed by azeotropic distillation of a toluene/ethanol mixture, and the reaction was allowed to cool to room temperature. The cinnamaldehyde compound (10 mmol in 80 mL) in anhydrous toluene was added to the mixture, which was subsequently heated at reflux for 3 h, while the reaction was monitored by TLC. The reaction mixture was hydrolyzed using a KOH solution (2 M) and filtered. The aqueous phase was further extracted with diethyl ether. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum. The resultant yellow oil was obtained and purified by column chromatography (silica, 0–5% diethyl ether in pentane).

*2,2-Diphenyl-6-fluoro-2*H*-benzopyran* ***1***

Compound **1**[26] was obtained as a white powder. The solid was recrystallized from pentane, mp 115–116°C. δ_H ($CDCl_3$) 6.27 (1H, d, *J* 9.8, H3), 6.60 (1H, d, *J* 9.8, H4), 6.75 (1H, dd, *J* 8.4 and 2.9, H5), 6.83 (1H, dd, *J* 8.6 and 2.9, H7), 6.89 (1H, dd, *J* 8.7 and 4.7, H8), 7.30 (2H, t, *J* 8.0, H4′), 7.36 (4H, t, *J* 7.9, H3′), 7.45 (4H, d, *J* 7.9, H2′). δ_C ($CDCl_3$) 82.4 (C2), 112.6 (d, *J* 23.8, C5), 115.6 (d, *J* 23.1, C7), 117.4 (d, *J* 8.0, C8), 122.1 (d, *J* 8.0, C4a), 122.8 (C4), 126.9 (C2′), 127.6 (C4′), 128.1 (C3′), 130.4 (C3), 144.4 (C1′), 148.3 (C1a), 157.3 (d, *J* 238.5, C6). *m/z* (70 eV) 302 (61%, $M^{+\bullet}$), 283 (4), 225 (100).

*2,2-Di(4-fluorophenyl)-6-fluoro-2*H*-benzopyran* ***2***

Compound **2**[20] was obtained as a white powder. The solid was recrystallized from pentane, mp 122.5–124°C. δ_H ($CDCl_3$) 6.16 (1H, d, *J* 9.8, H3), 6.60 (1H, d, *J* 9.8, H4), 6.76 (1H, dd, *J* 8.9 and 2.0, H5), 6.83 (2H, m, H5 and H7), 7.03 (4H, t, *J* 8.8, H3′), 7.39 (4H, dd, *J* 8.8 and 5.5, H2′). δ_C ($CDCl_3$) 81.8 (C2), 112.7 (d, *J* 23.8, C5), 115.0 (d, *J* 21.4, C3′), 115.8 (d, *J* 23.3, C7), 117.4 (d, *J* 7.9, C8), 121.9 (d, *J* 8.2, C4a), 123.2 (C4), 128.7 (d, *J* 8.2, C2′), 129.9 (C3), 140.0 (C1′), 147.9 (C1a), 157.4 (d, *J* 238.6, C6), 162.1 (d, *J* 247.2, C4′). *m/z* (70 eV) 338 (51%, $M^{+\bullet}$), 319 (7), 243 (100).

*2,2-Di(4-fluorophenyl)-6-methyl-2*H*-benzopyran* ***3***

Compound **3** was obtained as a white powder. The solid was recrystallized from pentane, mp 136–137°C. δ_H ($CDCl_3$) 2.22 (3H, s, CH_3), 6.06 (1H, d, *J* 9.8, H3), 6.59 (1H, d, *J* 9.8, H4), 6.79 (1H, d, *J* 8.2, H8), 6.83 (1H, br s, H5), 6.93 (1H, dd, *J* 8.1 and 1.4, H7), 7.00 (4H, t, *J* 8.7, H3′), 7.37 (4H, dd, *J* 8.8 and 5.4, H2′). δ_C ($CDCl_3$) 20.6 (CH_3), 81.7 (C2), 115.1 (d, *J* 21.5, C3′), 116.3 (C8), 120.9 (C4a), 124.0 (C4), 127.2 (C5), 128.6 (C3), 128.9 (d, *J* 8.2, C2′), 130.3 (C7), 130.8 (C6), 140.7 (C1′), 150.0 (C1a), 162.2 (d, *J* 247.0, C4′). *m/z* (70 eV) 334 (46%, $M^{+\bullet}$), 319 (6), 239 (100).

*2,2-Di(4-fluorophenyl)-6-methoxy-2*H*-benzopyran* ***4***

Compound **4** was obtained as a white powder. The solid was recrystallized from pentane, mp 152–153.5°C. δ_H ($CDCl_3$) 3.73 (3H, s, OCH_3), 6.13 (1H, d, *J* 9.8, H3), 6.60 (1H, d, *J* 2.9, H5), 6.61 (1H, d, *J* 9.8, H4), 6.71 (1H, dd, *J* 8.8 and 2.9, H7), 6.85 (1H, d, *J* 8.8, H8), 7.01 (4H, t, *J* 8.7, H3′), 7.40 (4H, dd, *J* 8.8 and 5.4, H2′). δ_C ($CDCl_3$) 55.7 (OCH_3), 81.7 (C2), 111.7 (C5), 115.09 (C7), 115.14 (d, *J* 21.4, C3′), 117.3 (C8), 121.8 (C4a), 124.1 (C4), 128.9 (d, *J* 8.2, C2′), 129.6 (C3), 140.6 (C1′), 146.1 (C1a), 154.3 (C6), 162.2 (d, *J* 246.8, C4′). *m/z* (70 eV) 350 (100%, $M^{+\bullet}$), 335 (3), 319 (7), 255 (98).

*2,2-Di(4-fluorophenyl)-5,7-dimethyl-2*H*-benzopyran* ***5***

Compound **5** was obtained as a white powder. The solid was recrystallized from pentane, mp 140.5–141°C. δ_H ($CDCl_3$) 2.34 (3H, s,

7-CH_3), 2.37 (3H, s, 5-CH_3), 6.16 (1H, d, *J* 9.9, H3), 6.65 (1H, br s, H6), 6.75 (1H, br s, H8), 6.90 (1H, d, *J* 9.9, H4), 7.10 (4H, t, *J* 8.6, H3′), 7.51 (4H, dd, *J* 8.5 and 5.4, H2′). δ_C ($CDCl_3$) 18.2 (5-CH_3), 21.4 (7-CH_3), 81.1 (C2), 115.0 (d, *J* 21.3, C3′), 115.1 (C8), 117.0 (C4a), 120.9 (C4), 124.2 (C6), 127.1 (C3), 128.8 (d, *J* 8.1, C2′), 134.2 (C5), 139.5 (C7), 140.9 (d, *J* 2.6, C1′), 152.3 (C1a), 162.1 (d, *J* 246.6, C4′). *m/z* (70 eV) 348 (42%, $M^{+\bullet}$), 333 (8), 253 (100).

*2,2-Di(4-fluorophenyl)-7,8-dimethoxy-2*H*-benzopyran* ***6***

Compound **6** was obtained as a yellow powder. The solid was recrystallized from pentane, mp 117–117.5°C. δ_H ($CDCl_3$) 3.83 (3H, s, 8-OCH_3), 3.84 (3H, s, 7-OCH_3), 6.01 (1H, d, *J* 9.7, H3), 6.46 (1H, d, *J* 8.3, H6), 6.61 (1H, d, *J* 9.7, H4), 6.75 (1H, d, *J* 8.3, H5), 7.02 (4H, t, *J* 8.5, H3′), 7.45 (4H, dd, *J* 8.5 and 5.4, H2′). δ_C ($CDCl_3$) 55.9 (7-OCH_3), 61.1 (8-OCH_3), 81.8 (C2), 104.6 (C6), 114.9 (d, *J* 21.4, C3′), 116.0 (C4a), 121.1 (C5), 123.7 (C4), 126.4 (C3), 128.7 (d, *J* 13.1, C2′), 137.5 (C8), 140.4 (d, *J* 3.1, C1′), 145.3 (C1a), 154.0 (C7), 162.1 (d, *J* 246.7, C4′). *m/z* (70 eV) 380 (100%, $M^{+\bullet}$), 365 (15), 349 (12), 285 (78).

*2,2-Di(3-trifluoromethylphenyl)-7,8-dimethoxy-2*H*-benzopyran* ***7***

Compound **7** was obtained as a yellow powder. The solid was recrystallized from pentane, mp 100–101°C. δ_H ($CDCl_3$) 3.84 (3H, s, 7-OCH_3), 3.87 (3H, s, 8-OCH_3), 6.05 (1H, d, *J* 9.7, H3), 6.48 (1H, d, *J* 8.4, H6), 6.69 (1H, d, *J* 9.7, H4), 6.78 (1H, d, *J* 8.4, H5), 7.47 (1H, t, *J* 7.7, H5′), 7.56 (1H, br d, *J* 7.6, H4′), 7.66 (1H, br d, *J* 7.7, H6′), 7.80 (1H, br s, H2′). δ_C ($CDCl_3$) 55.9 (7-OCH_3), 61.2 (8-OCH_3), 81.8 (C2), 104.8 (C6), 115.7 (C4a), 121.4 (C5), 123.6 (q, *J* 3.9, C2′), 123.9 (q, *J* 272.7, CF_3), 124.69 (q, *J* 7.6, C4′), 124.71 (C4), 125.0 (C3), 128.9 (C5′), 130.3 (C6′), 130.6 (q, *J* 32.4, C3′), 137.6 (C8), 145.1 (C1′), 145.3 (C1a), 154.3 (C7). *m/z* (70 eV) 480 (71%, $M^{+\bullet}$), 465 (8), 449 (8), 335 (100).

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