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Reaction of 2-(trifluoromethyl)chromones with pyridoxal: Formation of 1-benzopyranooxepino- and 1-benzopyranopyranopyridines

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ABSTRACT

Pyridoxal undergoes oxa-Michael initiated ring closure with 2-(trifluoromethyl)chromones giving 11a,13-dihydro-6*H*-1-benzopyrano[3′,2′:6,7]oxepino[3,4-*c*]pyridin-6-ones and 6*H*,11a*H*-1-benzopyrano[3′,2′:5,6]pyrano[2,3-*c*]pyridin-6-ones. Participation of alcoholic hydroxy group of pyridoxal in the initial oxa-Michael addition leads to the former product and that of the phenyl hydroxy group to the later one.

1. Introduction

Chromones (4*H*-1-benzopyran-4-ones, 4*H*-chromen-4-ones) are an important class of oxygenated heterocycles that have attracted much synthetic interest because of their reactivity and the biological activity of naturally occurring representatives [1]. Many natural and synthetic chromone derivatives exhibit various types of biological activity (antiviral, antiallergic, neuroleptic, anti-inflammatory, and antitumor) [2] and find use as valuable synthetic intermediates in the preparation of pharmacologically relevant products and new heterocyclic systems [3]. These compounds possess two strong electrophilic centers (carbon atoms C-2 and C-4 of the chromone system) and their reactions with dinucleophiles start predominantly with attack of the C-2 atom (1,4-addition) and are accompanied by pyrone ring-opening to form an intermediate capable of undergoing intramolecular cyclizations [4].

It is known that the introduction of electron-withdrawing R^F groups at the 2-position of the chromone system significantly changes the reactivity of the pyrone ring with respect to nucleophiles, and provides broad synthetic potential for 2-(polyfluoroalkyl)chromones [5]. In recent years, these compounds have attracted considerable attention as highly reactive substrates, which can serve as the starting materials in the synthesis of various partially fluorinated heterocycles due to the enhanced electrophilicity of the C-2 atom [6].

2-(Polyfluoroalkyl)chromones and oxacyclic 2-(polyfluoroalkyl)-2-en-4-ones condense with salicylaldehydes giving respectively the chromene derivatives **1** and **2** [7]. Similar reactions of the above mentioned substrates with pyridoxal are anticipated to form respectively the azachromenes **3** and **4** with fused acetal moiety (Fig. 1), which is an important structural subunit of a variety of biologically active natural products [8]. The observed biological activity of relatively simple fused acetals emphasizes the importance of their synthesis. Several catalytic methods, including reactions of manganic acetate [9] or silver carbonate [10] with β-diketones and β-ketoesters, have been developed for the preparation of such compounds.

Pyridoxal hydrochloride **5** in alkaline medium is likely to behave as salicylaldehyde towards the 2-(trifluoromethyl)chromones **6** in forming the fused azachromenes **8** whereas the initial oxa-Michael addition involving the alcoholic hydroxy group of **5** followed by ring closure leading to the fused oxepines **7** is also a possibility (Scheme 1). Both these contentions were found to be correct.

2. Results and discussion

Treatment of the chromones **6** with pyridoxal hydrochloride **5** in the presence of sodium hydroxide (2.6 equiv.) in aqueous methanol for several hours at 50 → 20 °C gave the fused oxepines **7** with no or a little azachromenes **8**, which are insoluble in water

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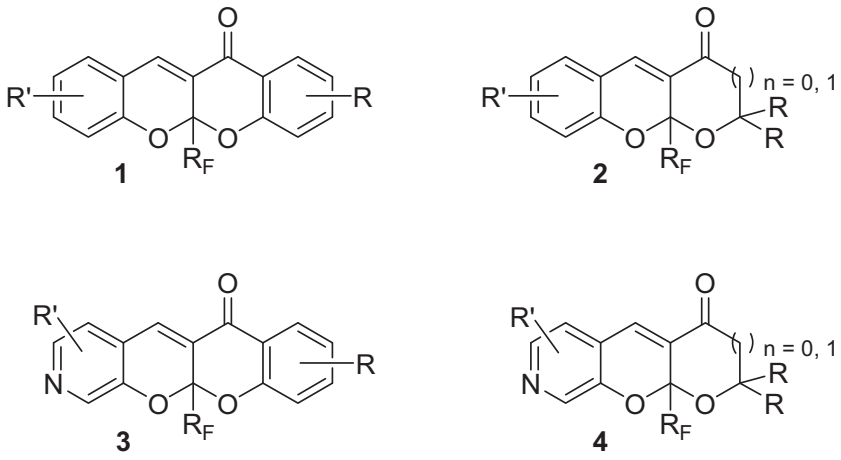
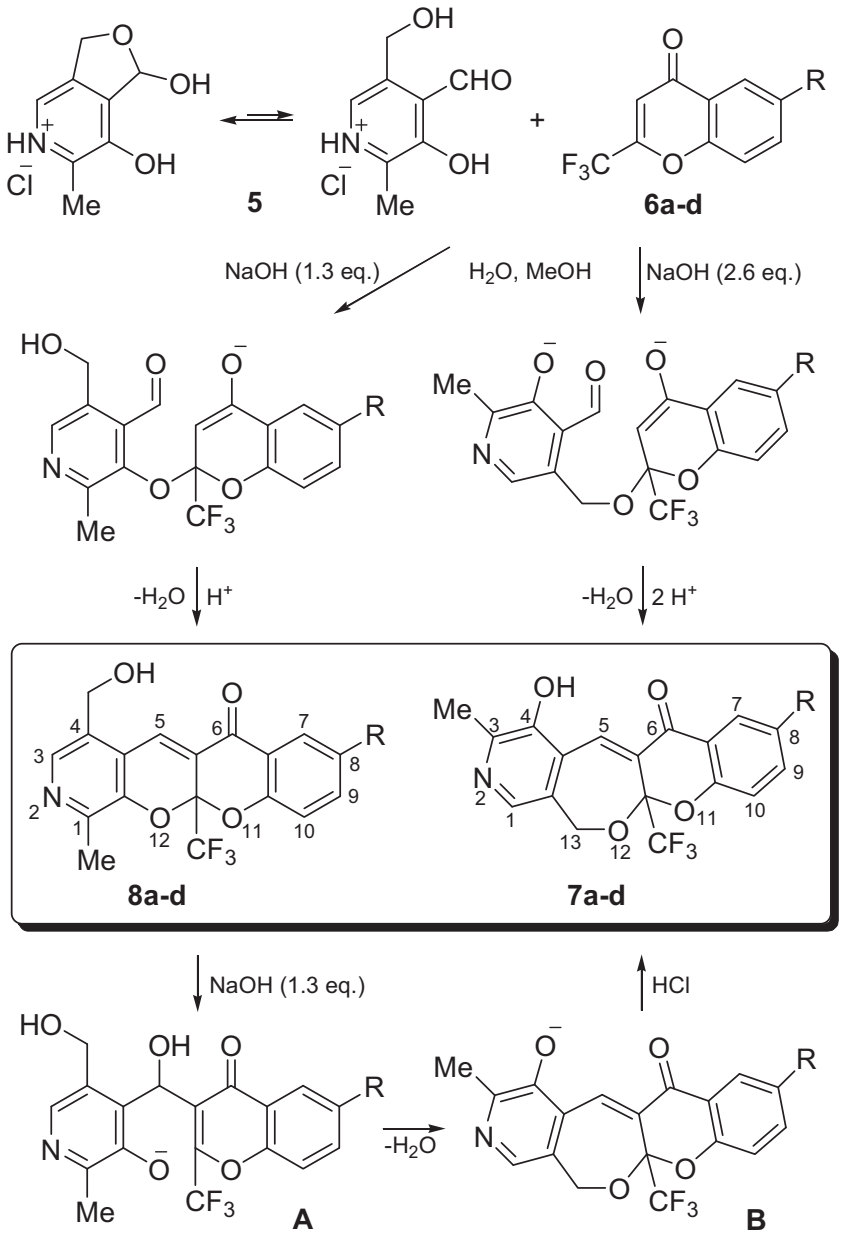


Fig. 1. Fused 2*H*-chromenes **1**–**4**.



Scheme 1. Synthesis of tetracyclic compounds **7** and **8**.

Table 1
Reactions of pyridoxal with 2-(trifluoromethyl)chromones.[a]

R	Product **7**	Yield[b] (%)	Product **8**	Yield[c] (%)
H	**7a**	56	**8a**	19 (13)[d]
Me	**7b**	51	**8b**	17
Cl	**7c**	62	**8c**	54
NO_2	**7d**	20[e] (25)[f]	**8d**	59

[a] Yields of isolated products.
[b] In the presence of 2.6 equiv. NaOH.
[c] In the presence of 1.3 equiv. NaOH.
[d] Yield of **7a** according to the ^{1}H and ^{19}F NMR spectra.
[e] At room temperature.
[f] Isolated yield of **8d**.

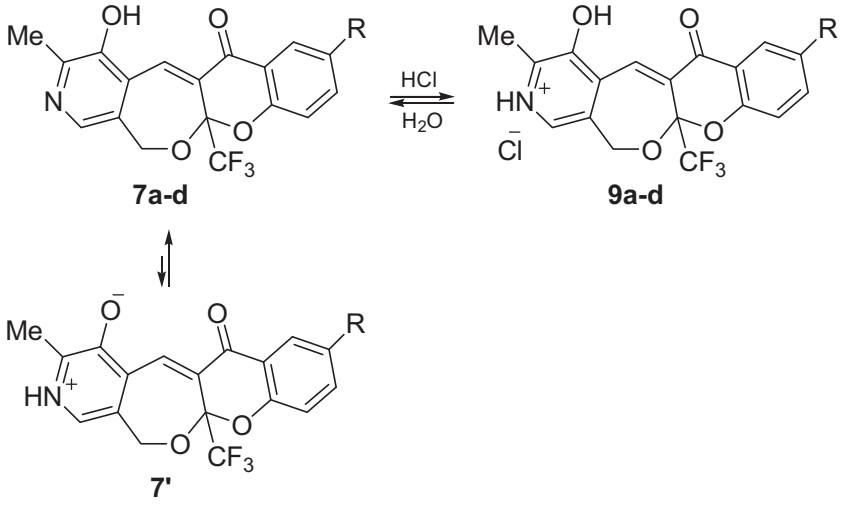
and thus can be easily separated from the target oxepines **7** before acidification of the reaction mixture (Scheme 1, Table 1).

To determine the regiochemistry of **7a**, and to verify the assignment in other compounds of this type, ^{13}C NMR and 2D ^{1}H–^{13}C HSQC and HMBC spectra of **7a** at 120 °C were obtained. The most informative cross-peak of the HMBC spectrum in DMSO-d_6 is a cross-peak between the protons of the CH_2 group and C-11a. This result clearly demonstrates that compound **7a** is a seven-membered ring. It is known that pyridoxal, and those of its analogs which possess an unsubstituted phenolic group, exist predominantly in the *N*-protonated zwitterionic form in neutral solution [11]. To answer the question whether the compounds obtained exist as a neutral 3-hydroxypyridine form **7** or they are formed as zwitterions **7′**, we prepared their hydrochlorides **9a**–**d** under usual conditions. Fortunately, being poorly soluble in water and in most organic solvents, the yellow salts **9** are soluble in DMSO-d_6. They are hygroscopic compounds and when treated with water they are easily hydrolyzed to **7** (Scheme 2).

It is apparent that the ability of the ring nitrogen to be protonated determines the shielding of the protons in its environment. Protonation of the nitrogen atom should increase the electron-withdrawing properties and hence should result in increased deshielding of protons. The H-1 proton can be expected to be especially sensitive to any changes in the electronic nature of the substituents in the ring, and to a lesser extent this should also be reflected in the shielding of the methyl protons. Indeed, the ^{1}H NMR spectra of **7a**–**d** and **9a**–**d** showed a singlet due to the H-1 proton at δ 8.07–8.11 for **7** and 8.26–8.42 ppm for **9**; the Me group appeared as a singlet at δ 2.48–2.49 for **7** and 2.59–2.68 ppm for **9**. Moreover, it is known that an increase in positive charge at the pyridine nitrogen results in low-frequency shifts of the α-carbon and in high-frequency shifts of the β- and γ-carbons resonances [11,12]. In the ^{13}C NMR spectrum of **9a** C-1 and C-3 signals are shifted by −5.7 and −2.6 ppm relative to **7a**, whereas C-4, C-4a and C-13a by 3.1, 3.9 and 6.1 ppm, respectively. These results provide evidence for the neutral structure of compounds **7**. In addition, a clear distinction between the neutral and zwitterionic forms **7** and **7′** should be possible using 2D ^{1}H–^{15}N HMBC spectra and indeed a signal was observed at 331.6 ppm from liquid NH_3 indicating that the N was present in a pyridine ring, and confirming the neutral structure for **7a** (for **9a**: δ 234.5 ppm) [13]. A characteristic feature of the ^{1}H and ^{13}C NMR spectra of compounds **7** is the broadening of the H-1 proton and C-1, C-4 carbon atoms in the pyridine ring, which may be attributed to substantial amounts of the zwitterion **7′** in equilibrium with the neutral tautomer **7** and can be overcome by heating to 120 °C or CD_3CO_2D addition.

Interestingly, using the same reaction conditions with 1.3 equiv. of NaOH, we were able to obtain 6*H*,11a*H*-1-benzopyrano[3′,2′:5,6]pyrano[2,3-*c*]pyridines **8a**–**d** in 17–59% yields (Table 1). In this case, the reaction proceeded not at the alcoholic hydroxyl of **5**, but at the phenolic functionality. We believe that this is due to the fact that the concentration of the base present is too small to promote deprotonation of alcoholic hydroxyl, but with the addition of 2.6 equiv. of NaOH this process becomes possible and the seven-membered cyclization might occur. These results indicate that the pH influences the course of the Michael addition: phenolic hydroxyl participates in the reaction at pH 8–9, while alcoholic hydroxyl works well at pH 10–11. It was also found that compounds **8** on prolonged (8–10 h) standing in an aqueous methanol solution of NaOH (1.3 equiv.) gradually dissolved to give after acidification oxepines **7** in almost quantitative yield. This can be taken as an indication of the opening of the six-membered product (intermediate A) and its recyclization into the soluble seven-membered sodium salt B (Scheme 1). Thus, the attractive feature of this reaction is the synthesis of two important bioactive heterocyclic frameworks, which integrate pyridine and chromone moieties and might possess properties of both, under the similar eco-friendly conditions.

The structure of compounds **8** agree well with the data from elemental analysis and with results of IR and NMR spectroscopy. A characteristic feature of the ^{1}H NMR spectra is the appearance of a singlet at δ 8.3–8.4 ppm for the olefinic H-5 proton in DMSO-d_6 (δ 8.5–8.6 ppm for **7** and **9**). In addition, an AB-system of the CH_2 group at δ 4.7–4.8 ppm with J_{AB} = 13.5 Hz due to the chiral center in these molecules is observed (δ 5.0–5.3 ppm for **7** and **9**). In compounds **8** and **7** the positions of the Me groups are very similar



Scheme 2. Preparation of salts **9**.

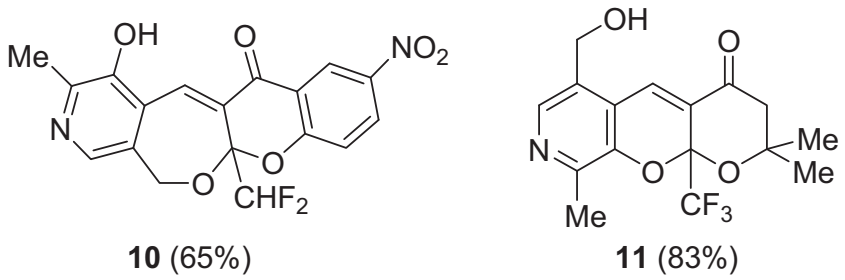


Fig. 2. Compounds **10** and **11**.

(δ ~2.5 ppm), as the changes in the electronic natures of the substituents are minor. In the IR spectra of compounds **7**–**9**, a highly characteristic carbonyl absorption at 1669–1686 (**7** and **9**) and 1687–1693 cm^{-1} (**8**), as well as C=C double bond at 1590–1629 cm^{-1} (**7**–**9**), were observed. Note that regioisomers **7** and **8** could be easily distinguished by the chemical shift of the CF_3 group. For oxepines **7** and **9**, this signal is observed as a singlet at δ 81.8–82.3 ppm, whereas for pyranes **8** it is more shielded (δ 77.2–77.6 ppm).

In attempting to ascertain if related cyclic enones can participate in this reaction, we found that 2-(difluoromethyl)-6-nitrochromone and 2,2-dimethyl-6-(trifluoromethyl)-2,3-dihydro-4*H*-pyran-4-one [14] also react with pyridoxal under the above experimental conditions to give compounds **10** and **11** in good yields (Fig. 2). These results show that the present methodology could be applicable to various types of cyclic polyfluoroalkyl-containing Michael acceptors, providing a simple and rapid route to the synthesis of a wide variety of fused 2*H*-pyrans and dihydrooxepines.

3. Conclusion

In conclusion, we have shown, for the first time, that the reaction of pyridoxal with chromones activated by tri(di)fluoromethyl groups provides a short, convenient, and eco-friendly approach to the synthesis of two novel heterocyclic systems: 11a,13-dihydro-6*H*-1-benzopyrano[3′,2′:6,7]oxepino[3,4-*c*]pyridin-6-ones and 6*H*,11a*H*-1-benzopyrano[3′,2′:5,6]pyrano[2,3-*c*]pyridin-6-ones. These one-pot transformations occurred through an oxa-Michael addition/aldol condensation pathway and are novel C–C bond forming reactions at the 3-position of the chromone system. The protocol avoids the use of expensive catalysts, toxic organic reagents/solvents, and anhydrous condition. The reuse of the aqueous medium makes this process inexpensive and highly environmentally friendly.

4. Experimental

NMR spectra were recorded on a Bruker DRX-400 (^{1}H-400 MHz, ^{13}C-100 MHz, and ^{19}F-376 MHz) and AVANCE-500 (^{1}H-500 MHz, ^{13}C-126 MHz, and ^{19}F-471 MHz) spectrometers in DMSO-d_6 and $CDCl_3$ with TMS and C_6F_6 as internal standards, respectively. IR spectra were recorded on a Perkin-Elmer Spectrum BX-II instrument as KBr discs. Mass spectra were obtained with the TurboMass (Perkin Elmer) mass spectrometer. Elemental analyses were performed at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences.

4.1. General procedure for the synthesis of compounds 7a–d

To a solution of pyridoxal hydrochloride **5** (2.0 mmol, 0.40 g) in water (1 mL) was added the corresponding chromone **6** (2.0 mmol) in methanol (2–10 mL) and NaOH (5.2 mmol, 0.21 g). The reaction mixture was stirred at 50 °C for 4–6 h, cooled to ~20 °C and allowed to stand at room temperature for 18–36 h (for **6d**: ~20 °C, 4 h). The resulting mixture was diluted with water (10 mL) and neutralized with HCl to pH 7. The solid that formed was filtered, washed with water, dried, and recrystallized from methanol to give product **7** as an orange powder.

4.1.1. 4-Hydroxy-3-methyl-11a-(trifluoromethyl)-11a,13-dihydro-6H-1-benzopyrano[3′,2′:6,7]oxepino[3,4-c]pyridin-6-one (7a)

Yield 0.41 g (56%), mp > 300 °C. IR (KBr) 1669, 1609, 1584, 1527, 1519, 1465 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.49 (s, 3H, Me), 4.95 (d, J = 13.5 Hz, 1H, H-13′), 5.04 (d, J = 13.5 Hz, 1H, H-13″), 7.23–7.29 (m, 2H, H-8, H-10), 7.74 (ddd, J = 8.6, 7.3, 1.6 Hz, 1H, H-9), 7.94 (dd, J = 7.8, 1.6 Hz, 1H, H-7), 8.09 (br s, 1H, H-1), 8.50 (s, 1H, H-5), 10.4 (br s, 1H, OH); ^{1}H NMR (500 MHz, DMSO-d_6, 393 K) δ 2.49 (s, 3H, Me), 4.88 (d, J = 13.6 Hz, 1H, H-13′), 4.98 (d, J = 13.6 Hz, 1H, H-13″), 7.19 (d, J = 8.3 Hz, 1H, H-10), 7.22 (dd, J = 7.8, 7.6 Hz, 1H, H-8), 7.68 (ddd, J = 8.3, 7.8, 1.6 Hz, 1H, H-9), 7.92 (dd, J = 7.6, 1.6 Hz, 1H, H-7), 8.06 (s, 1H, H-1), 8.55 (s, 1H, H-5); ^{13}C NMR (126 MHz, DMSO-d_6, 393 K) δ 18.6 (Me), 63.8 (C-13), 102.0 (q, ^2J = 32.1 Hz, C-11a), 116.7 (C-10), 119.0 (C-6a), 121.4 (q, ^1J = 291.8 Hz, CF_3), 122.4 (C-8), 125.6 (C-13a), 126.3 (C-7), 129.8 (C-5a), 131.3 (C-4a), 136.1 (br s, C-1), 136.4 (C-9), 138.1 (C-5), 148.6 (C-3), 150.6 (br s, C-4), 156.8 (C-10a), 179.6 (C-6); ^{19}F NMR (376 MHz, DMSO-d_6/C_6F_6) δ 82.1 (s, CF_3); ^{15}N NMR (50.7 MHz, DMSO-d_6/NH_3) δ 331.6. Anal. Calcd for $C_{18}H_{12}F_3NO_4$: C, 59.51; H, 3.33; N, 3.86. Found: C, 59.29; H, 3.31; N, 3.88.

4.1.2. 4-Hydroxy-3,8-dimethyl-11a-(trifluoromethyl)-11a,13-dihydro-6H-1-benzopyrano[3′,2′:6,7]oxepino[3,4-c]pyridin-6-one (7b)

Yield 0.38 g (51%), mp 210 °C (decomp.). IR (KBr) 1673, 1617, 1588, 1521, 1488 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.34 (s, 3H, Me-8), 2.48 (s, 3H, Me-3), 4.92 (d, J = 13.6 Hz, 1H, C-13′), 5.02 (d, J = 13.6 Hz, 1H, C13″), 7.17 (d, J = 8.4 Hz, 1H, H-10), 7.55 (dd, J = 8.4, 2.0 Hz, 1H, H-9), 7.72 (d, J = 2.0 Hz, 1H, H-7), 8.09 (br s, 1H, H-1), 8.49 (s, 1H, H-5), 10.4 (br s, 1H, OH); ^{1}H NMR (500 MHz, DMSO-d_6, 393 K) δ 2.33 (s, 3H, Me-8), 2.49 (s, 3H, Me-3), 4.85 (d, J = 13.7 Hz, 1H, H-13′), 4.96 (d, J = 13.7 Hz, 1H, H-13″), 7.08 (d, J = 8.4 Hz, 1H, H-10), 7.49 (dd, J = 8.4, 1.8 Hz, 1H, H-9), 7.71 (d, J = 1.8 Hz, 1H, H-7), 8.05 (s, 1H, H-1), 8.53 (s, 1H, H-5); ^{19}F NMR (376 MHz, DMSO-d_6/C_6F_6) δ 82.2 (s, CF_3); ^{13}C NMR (126 MHz, DMSO-d_6, 393 K) δ 18.6 (Me-3), 19.1 (Me-8), 63.8 (C-13), 101.4 (q, ^2J = 32.0 Hz, C-11a), 116.5, 118.6, 121.4 (q, ^1J = 292.2 Hz, CF_3), 125.6 (C-13a), 125.8, 130.0, 131.3, 131.8, 136.1 (br s, C-1), 137.2, 137.9, 148.6 (C-3), 150.6 (br s, C-4), 154.9, 179.6 (C-6). Anal. Calcd for $C_{19}H_{14}F_3NO_4 \cdot 0.5H_2O$: C, 59.07; H, 3.91; N, 3.63. Found: C, 59.05; H, 3.93; N, 3.51.

4.1.3. 8-Chloro-4-hydroxy-3-methyl-11a-(trifluoromethyl)-11a,13-dihydro-6H-1-benzopyrano[3′,2′:6,7]oxepino[3,4-c]pyridin-6-one (7c)

Yield 0.38 g (62%), mp 305 °C (decomp.). IR (KBr) 1680, 1604, 1593, 1555, 1474, 1423 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.48

(s, 3H, Me-3), 4.97 (d, J = 13.5 Hz, 1H, H-13′), 5.04 (d, J = 13.5 Hz, 1H, H-13″), 7.35 (d, J = 8.8 Hz, 1H, H-10), 7.78 (dd, J = 8.8, 2.7 Hz, 1H, H-9), 7.88 (d, J = 2.7 Hz, 1H, H-7), 8.07 (br s, 1H, H-1), 8.52 (s, 1H, H-5), 10.4 (br s, 1H, OH); ^{19}F NMR (376 MHz, DMSO-d_6/C_6F_6) δ 82.0 (s, CF_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 19.7, 64.4, 102.4 (q, ^2J = 32.4 Hz, C-11a), 119.8, 120.3, 121.7 (q, ^1J = 290.8 Hz, CF_3), 125.8, 127.3, 129.1 (br s), 131.9 (br s), 136.8, 139.8 (br s), 149.0, 155.9, 179.3 (C-6) (three C atoms were not observed due to their broadening). Anal. Calcd for $C_{18}H_{11}ClF_3NO_4{\cdot}2.5H_2O$: C, 48.83; H, 3.64; N, 3.16. Found: C, 48.67; H, 3.26; N, 3.06.

*4.1.4. 4-Hydroxy-3-methyl-8-nitro-11a-(trifluoromethyl)-11a,13-dihydro-6H-1-benzopyrano[3′,2′:6,7]oxepino[3,4-c]pyridin-6-one (**7d**)*

Yield 40 mg (20%) and 50 mg (25%) of **8d**, mp 310 °C (decomp.). IR (KBr) 1686, 1628, 1594, 1551, 1533, 1474, 1444, 1372, 1341 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.49 (s, 3H, Me), 5.05 (d, J = 13.5 Hz, 1H, H-13′), 5.09 (d, J = 13.5 Hz, 1H, H-13″), 7.56 (d, J = 9.1 Hz, 1H, H-10), 8.11 (br s, 1H, H-1), 8.54 (dd, J = 9.1, 2.8 Hz, 1H, H-9), 8.58 (s, 1H, H-5), 8.64 (d, J = 2.8 Hz, 1H, H-7), 10.5 (br s, 1H, OH); ^{1}H NMR (500 MHz, DMSO-d_6, 393 K) δ 2.50 (s, 3H, Me), 4.97 (d, J = 13.7 Hz, 1H, H-13′), 5.04 (d, J = 13.7 Hz, 1H, H-13″), 7.46 (d, J = 9.1 Hz, 1H, H-10), 8.07 (br s, 1H, H-1), 8.47 (dd, J = 9.1, 2.9 Hz, 1H, H-9), 8.63 (s, 1H, H-5), 8.64 (d, J = 2.9 Hz, 1H, H-7); ^{19}F NMR (376 MHz, DMSO-d_6/C_6F_6) δ 81.8 (s, CF_3); ^{13}C NMR (126 MHz, DMSO-d_6, 393 K) (18.5 (Me), 64.3 (C-13), 102.8 (q, ^2J = 32.4 Hz, C-11a), 118.7, 118.9, 121.1 (q, ^1J = 291.4 Hz, CF_3), 122.2, 125.1, 127.9, 130.5, 131.2 (C-4a), 135.5 (br s, C-1), 140.1, 142.7, 149.0 (C-3), 151.2 (br s, C-4), 160.6, 178.3 (C-6). Anal. Calcd for $C_{18}H_{11}F_3N_2O_6{\cdot}H_2O$: C, 50.71; H, 3.07; N, 6.56. Found: C, 50.88; H, 2.72; N, 6.40.

*4.2. General procedure for the synthesis of compounds **8a–d***

To a solution of pyridoxal hydrochloride **5** (2.0 mmol, 0.40 g) in water (1 mL) was added the corresponding chromone **6** (2.0 mmol) in methanol (2–10 mL) and NaOH (2.6 mmol, 0.10 g). The reaction mixture was stirred at 50 °C for 4–6 h, then cooled to ~20 °C and 10 mL of water was added. The resulting solid was filtered, washed with water, dried, and recrystallized from methanol to give pure product **8** as light-yellow or yellow crystals.

*4.2.1. 4-(Hydroxymethyl)-1-methyl-11a-(trifluoromethyl)-6H,11aH-1-benzopyrano[3′,2′:5,6]pyrano[2,3-c]pyridin-6-one (**8a**)*

Yield 0.14 g (19%), mp 169–170°C. IR (KBr) 3194, 1684, 1629, 1609, 1519, 1463 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.51 (s, 3H, Me-3), 4.71 (dd, J = 13.5, 5.4 Hz, 1H, C*H*H), 4.75 (dd, J = 13.5, 5.4 Hz, 1H, CH*H*), 5.58 (t, J = 5.4 Hz, 1H, OH), 7.34 (ddd, J = 7.8, 7.3, 0.8 Hz, 1H, H-8), 7.40 (br d, J = 8.4 Hz, 1H, H-10), 7.82 (ddd, J = 8.4, 7.3 1.7 Hz, 1H, H-9), 7.97 (dd, J = 7.8, 1.7 Hz, 1H, H-7), 8.29 (s, 1H, H-3), 8.32 (s, 1H, H-5); ^{19}F NMR (376 MHz, DMSO-d_6/C_6F_6) δ 77.5 (s, CF_3). Anal. Calcd for $C_{18}H_{12}F_3NO_4$: C, 59.51; H, 3.33; N, 3.86. Found: C, 59.40; H, 3.38; N, 3.91.

*4.2.2. 4-(Hydroxymethyl)-1,8-dimethyl-11a-(trifluoromethyl)-6H,11aH-1-benzopyrano[3′,2′:5,6]pyrano[2,3-c]pyridin-6-one (**8b**)*

Yield 0.13 g (17%), mp 158–159°C. IR (KBr) 3307, 1687, 1628, 1616, 1554, 1487 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.35 (s, 3H, Me-8), 2.50 (s, 3H, Me-3), 4.71 (dd, J = 12.9, 5.2 Hz, 1H, C*H*H), 4.75 (dd, J = 12.9, 5.2 Hz, 1H, CH*H*), 5.57 (t, J = 5.2 Hz, 1H, OH), 7.29 (d, J = 8.5 Hz, 1H, H-10), 7.62 (dd, J = 8.5, 2.2 Hz, 1H, H-9), 7.75 (d, J = 2.2 Hz, 1H, H-7), 8.28 (s, 1H, H-3), 8.30 (s, 1H, H-5); ^{19}F NMR (376 MHz, DMSO-d_6/C_6F_6) δ 77.6 (s, CF_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 18.3, 19.8, 58.0 (CH_2O), 98.0 (q, ^2J = 34.4 Hz, C-11a), 117.4, 118.8, 120.9, 121.3, 121.7 (q, ^1J = 295.2 Hz, CF_3), 126.3, 132.8 (2C), 133.7, 138.9, 142.9, 143.2, 145.3, 153.4, 177.0 (C-6). Anal. Calcd for $C_{19}H_{14}F_3NO_4$: C, 60.48; H, 3.74; N, 3.71. Found: C, 60.45; H, 3.86; N 3.68.

*4.2.3. 8-Chloro-4-(hydroxymethyl)-1-methyl-11a-(trifluoromethyl)-6H,11aH-1-benzopyrano[3′,2′:5,6]pyrano[2,3-c]pyridin-6-one (**8c**)*

Yield 0.21 g (54%), mp 196–197 °C. IR (KBr) 3368, 3184, 1690, 1629, 1604, 1553, 1470, 1423 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.51 (s, 3H, Me), 4.72 (dd, J = 12.9, 5.4 Hz, 1H, C*H*H), 4.75 (dd, J = 12.9, 5.4 Hz, 1H, CH*H*), 5.58 (t, J = 5.4 Hz, 1H, OH), 7.47 (d, J = 8.9 Hz, 1H, H-10), 7.85 (dd, J = 8.9, 2.7 Hz, 1H, H-9), 7.91 (d, J = 2.7 Hz, 1H, H-7), 8.30 (s, 1H, H-3), 8.35 (s, 1H, H-5); ^{19}F NMR (376 MHz, DMSO-d_6/C_6F_6) δ 77.4 (s, CF_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 18.4, 58.0, 98.2 (q, ^2J = 34.7 Hz, C-11a), 119.9, 120.1, 120.3, 121.1, 121.6 (q, ^1J = 294.9 Hz, CF_3), 125.8, 128.5, 133.0, 133.9, 137.7, 143.1, 143.2, 145.4, 154.0, 176.2. Anal. Calcd for $C_{18}H_{11}ClF_3NO_4$: C, 54.36; H, 2.79; N, 3.52. Found: C, 54.44; H, 2.62; N, 3.50.

*4.2.4. 4-(Hydroxymethyl)-1-methyl-8-nitro-11a-(trifluoromethyl)-6H,11aH-1-benzopyrano[3′,2′:5,6]pyrano[2,3-c]pyridin-6-one (**8d**)*

Yield 0.24 g (59%), mp 211–212 °C. IR (KBr) 3243, 1693, 1628, 1590, 1535, 1472, 1440, 1343 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.53 (s, 3H, Me), 4.74 (dd, J = 13.1, 5.4 Hz, 1H, C*H*H), 4.78 (dd, J = 13.1, 5.4 Hz, 1H, CH*H*), 5.62 (t, J = 5.4 Hz, 1H, OH), 7.70 (d, J = 9.0 Hz, 1H, H-10), 8.33 (s, 1H, H-3), 8.43 (s, 1H, H-5), 8.60 (dd, J = 9.0, 2.9 Hz, 1H, H-9), 8.64 (d, J = 2.9 Hz, 1H, H-7); ^{19}F NMR (376 MHz, DMSO-d_6/C_6F_6) δ 77.2 (s, CF_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 18.3, 58.0, 98.6 (q, ^2J = 35.0 Hz, C-11a), 119.1, 119.2, 119.6, 121.0, 121.5 (q, ^1J = 294.4 Hz, CF_3), 122.5, 132.2, 133.1, 134.7, 143.1, 143.3, 143.5, 145.5, 158.8, 175.9. Anal. Calcd for $C_{18}H_{11}F_3N_2O_6$: C, 52.95; H, 2.72; N, 6.86. Found: C, 52.74; H, 2.87; N, 6.89.

*4.3. Compounds **9a–d***

*4.3.1. 4-Hydroxy-3-methyl-6-oxo-11a-(trifluoromethyl)-11a,13-dihydro-6H-1-benzopyrano[3′,2′:6,7]oxepino[3,4-c]pyridin-2-ium chloride (**9a**)*

IR (KBr) 3480, 2592, 2358, 1683, 1610, 1538, 1464 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.71 (s, 3H, Me), 5.14 (d, J = 13.8 Hz, 1H, C-13′), 5.26 (d, J = 13.8 Hz, 1H, C-13″), 7.22–7.28 (m, 1H, H-8, H-10), 7.78 (ddd, J = 8.3, 7.3, 1.6 Hz, 1H, H-9), 7.96 (dd, J = 7.8, 1.7 Hz, 1H, H-7), 8.41 (s, 1H, H-1), 8.45 (s, 1H, H-5); ^{19}F NMR (376 MHz, DMSO-d_6/C_6F_6) δ 82.2 (s, CF_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 16.5 (Me), 63.6 (C-13), 102.1 (q, C-11a, ^2J = 31.7 Hz), 117.6 (C-10), 119.0 (C-6a), 121.7 (q, CF_3, ^1J = 291.7 Hz), 123.6 (C-8), 127.2 (C-7), 130.4 (C-1), 131.6 (C-13a), 133.2 (C-5a), 135.2 (C-4a), 136.8 (C-5), 137.8 (C-9), 146.1 (C-3), 153.7 (C-4), 157.4 (C-10a), 179.9 (C-6); ^{15}N NMR (50.7 MHz, DMSO-d_6/NH_3) δ 234.5. Anal. Calcd for $C_{18}H_{13}ClF_3NO_4{\cdot}1.5H_2O$: C, 50.66; H, 3.78; N, 3.28. Found: C, 50.45; H, 3.80; N, 3.19.

*4.3.2. 4-Hydroxy-3,8-dimethyl-6-oxo-11a-(trifluoromethyl)-11a,13-dihydro-6H-1-benzopyrano[3′,2′:6,7]oxepino[3,4-c]pyridin-2-ium chloride (**9b**)*

IR (KBr) 3338, 2580, 2392, 1680, 1641, 1616, 1532, 1488 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.34 (s, 3H, Me-8), 2.59 (s, 3H, Me-3), 5.00 (d, J = 13.5 Hz, 1H, C-13′), 5.12 (d, J = 13.5 Hz, 1H, C-13″), 7.18 (d, J = 8.4 Hz, 1H, H-10), 7.57 (dd, J = 8.4, 1.5 Hz, 1H, H-9), 7.72 (d, J = 1.5 Hz, 1H, H-7), 8.26 (s, 1H, H-1), 8.46 (s, 1H, H-5); ^{19}F NMR (376 MHz, DMSO-d_6/C_6F_6) δ 82.3 (s, CF_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 16.5 (Me), 19.9 (Me), 63.5 (C-13), 102.0 (q, C-11a, ^2J = 32.0 Hz), 117.4, 118.7, 121.6 (q, CF_3, ^1J = 291.3 Hz), 126.6, 130.5, 131.5, 132.9, 133.3, 135.0, 136.6, 138.6, 146.0, 153.5, 155.5, 179.9 (C-6). Anal. Calcd for $C_{19}H_{15}ClF_3NO_4{\cdot}1.5H_2O$: C, 51.77; H, 4.12; N, 3.18. Found: C, 51.80; H, 4.03; N, 2.99.

*4.3.3. 8-Chloro-4-hydroxy-3-methyl-6-oxo-11a-(trifluoromethyl)-11a,13-dihydro-6H-1-benzopyrano[3′,2′:6,7]oxepino[3,4-c]pyridin-2-ium chloride (**9c**)*

IR (KBr) 3332, 2597, 1685, 1645, 1622, 1608, 1538, 1472 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.63 (s, 3H, Me), 5.10 (d, J = 13.7 Hz,

1H, C-13′), 5.18 (d, J = 13.7 Hz, 1H, C-13″), 7.38 (d, J = 8.8 Hz, 1H, H-10), 7.81 (dd, J = 8.8, 2.7 Hz, 1H, H-9), 7.90 (d, J = 2.7 Hz, 1H, H-7), 8.33 (s, 1H, H-1), 8.47 (s, 1H, H-5); ^{19}F NMR (376 MHz, DMSO-d_6/C_6F_6) δ 82.2 (s, CF_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 17.8 (Me), 64.0 (C-13), 102.3 (q, C-11a, ^2J = 32.0 Hz), 119.9, 120.2, 121.6 (q, CF_3, ^1J = 291.2 Hz), 125.9, 127.5, 128.7, 132.9, 133.7, 137.0, 138.5, 143.5, 147.4, 152.9, 156.0, 179.1 (C-6). Anal. Calcd for $C_{18}H_{12}Cl_2F_3NO_4{\cdot}2.5H_2O$: C, 45.11; H, 3.58; N, 2.92. Found: C, 44.87; H, 3.61; N, 2.77.

4.3.4. 4-Hydroxy-3-methyl-8-nitro-6-oxo-11a-(trifluoromethyl)-11a,13-dihydro-6H-1-benzopyrano[3′,2′:6,7]oxepino[3,4-c]pyridin-2-ium chloride (**9d**)

IR (KBr) 3321, 2576, 1689, 1643, 1615, 1588, 1536, 1474 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.68 (s, 3H, Me), 5.22 (d, J = 13.7 Hz, 1H, C-13′), 5.28 (d, J = 13.7 Hz, 1H, C-13″), 7.59 (d, J = 9.1 Hz, 1H, H-10), 8.42 (s, 1H, H-1), 8.52 (s, 1H, H-5), 8.57 (dd, J = 9.1, 2.8 Hz, 1H, H-9), 8.66 (d, J = 2.8 Hz, 1H, H-7); ^{19}F NMR (376 MHz, DMSO-d_6/C_6F_6) δ 82.0 (s, CF_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 16.4 (Me), 63.9 (C-13), 102.8 (q, C-11a, ^2J = 32.5 Hz), 119.0, 119.5, 121.4 (q, CF_3, ^1J = 291.0 Hz), 122.8, 130.1, 131.0, 131.4, 131.9, 135.0, 138.3, 143.0, 146.4, 154.1, 161.1, 178.7 (C-6). Anal. Calcd for $C_{18}H_{12}ClF_3N_2O_6{\cdot}3.5H_2O$: C, 42.57; H, 3.77; N, 5.52. Found: C, 42.72; H, 3.64; N, 5.38.

4.4. Compounds **10** and **11**

4.4.1. 11a-(Difluoromethyl)-4-hydroxy-3-methyl-8-nitro-11a,13-dihydro-6H-1-benzopyrano[3′,2′:6,7]oxepino[3,4-c]pyridin-6-one (**10**)

Yield 0.51 g (65%), mp > 300 °C (decomp.). IR (KBr) 1691, 1648, 1620, 1591, 1558, 1528, 1471, 1441, 1343 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.64 (s, 3H, Me), 5.07 (d, J = 13.8 Hz, 1H, C-13′), 5.16 (d, J = 13.8 Hz, 1H, C-13″), 6.31 (t, $^2J_{H,F}$ = 53.8 Hz, 1H, CHF_2), 7.50 (d, J = 9.1 Hz, 1H, H-10), 8.34 (s, 1H, H-1), 8.46 (s, 1H, H-5), 8.52 (dd, J = 9.1, 2.8 Hz, 1H, H-9), 8.62 (s, J = 2.8 Hz, 1H, H-7); ^{19}F NMR (376 MHz, DMSO-d_6/C_6F_6) δ 32.0 (dd, 1F, CH*F*F, $^1J_{F,H}$ = 283.5 Hz, $^2J_{F,H}$ = 53.8 Hz), 34.4 (dd, 1F, CHF*F*, $^1J_{F,H}$ = 283.5 Hz, $^2J_{F,H}$ = 53.8 Hz). Anal. Calcd for $C_{18}H_{12}F_2N_2O_6$: C, 55.39; H, 3.10; N, 7.18. Found: C, 55.10; H, 2.97; N, 7.34.

4.4.2. 6-(Hydroxymethyl)-2,2,9-trimethyl-10a-(trifluoromethyl)-2,3-dihydro-4H,10aH-pyrano[3′,2′:5,6]pyrano[2,3-c]pyridin-4-one (**11**)

Yield 0.57 g (83%), mp 104–105 °C (colorless powder). IR (KBr) 3236, 1704, 1627, 1554, 1402; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 3H, Me), 1.54 (s, 3H, Me), 1.96 (br s, 1H, OH), 2.56 (s, 3H, Me-9), 2.59 (d, J = 17.8 Hz, 1H, C*H*H), 2.78 (d, J = 17.6 Hz, 1H, CH*H*), 4.79 (d, J = 12.5 Hz, 1H, C*H*HOH), 4.85 (d, J = 12.5 Hz, 1H, CH*H*OH), 8.05 (s, 1H, H-5), 8.19 (s, 1H, H-7); ^{19}F NMR (376 MHz, $CDCl_3$/C_6F_6) δ 74.6 (s, CF_3). Anal. Calcd for $C_{16}H_{16}F_3NO_4$: C, 55.98; H, 4.70; N 4.08. Found: C, 55.68; H, 4.43; N, 3.88.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2012.06.001.

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