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7-Polyfluoroalkylnorkhellins: synthesis and reactions with alkyl mercaptoacetates

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Abstract—New R^F-containing benzofuran derivatives of 2-oxa-7-thiabicyclo[3.2.1]octane and dihydrothienopsoralens were synthesized from 7-polyfluoroalkylnorkhellins and alkyl mercaptoacetates.

1. Introduction

Modification of natural compounds by the replacement of an alkyl group with a polyhaloalkyl group is of considerable interest because electron-acceptor R^F- and CCl_3 groups affect the electron-density distribution in the molecule and hence the reactivity towards nucleophilic agents. Previously,[1] similar studies were performed in the series of retinoids, steroids, purines and pyrimidines. However, there are no data concerning the target-oriented synthesis of halogenated analogues of natural 2-alkylchromones, except for the synthesis of 7-chloromethyl- and 7-iodomethylnorvisnagin,[2,3] 2- and 3-fluorokhellin[4] and 7-iodomethylnorkhellin.[5]

The natural furochromone khellin (4,9-dimethoxy-7-methyl-5*H*-furo[3,2-*g*]chromen-5-one), obtained from the fruits and seeds of *Ammi visnaga* L. possesses a high antiatherosclerotic and lipid-altering activity[6] and is the active constituent of many modern medicines.[7] In view of the unique biological properties displayed by khellin on the one hand and by many fluorinated heterocyclic compounds[8] on the other hand, we have described recently[9] the synthesis of 7-trifluoro- and trichloromethylnorkhellins, which are highly reactive building blocks for the preparation of new khellin derivatives with a potential biological activity. The present work is devoted to the synthesis of 7-polyfluoroalkylnorkhellins and the study of the interaction of these compounds with alkyl mercaptoacetates (preliminary communication[10]).

2. Results and discussion

Condensation of khellinone **1** with R^FCO_2Et in the presence of LiH in boiling THF proceeded at the acetyl group of **1** and afforded benzofuran derivatives **2a–f**, which are a cyclic hemiketal form **A** of the corresponding β-diketones in DMSO-d_6. In a solution in $CDCl_3$ compound **2a** also exists as a cyclic form **A**. In contrast to **2a**, the ^{1}H NMR spectra of compounds **2d–f** in a $CDCl_3$ solution exhibited three sets of signals; one of them corresponds to furochromanone form **A** (50–78%), and the other, to ketoenol **B** (14–47%) and diketo **C** (3–8%) forms (Scheme 1). Previously,[11] 7-hydroxydihydrokhellin, a non-fluorinated analogue of compound **2a**, was synthesised by the treatment of khellinone **1** with *t*-butyl lithioacetate in toluene at 100°C.

The boiling of furochromanones **2a–f** in acetic acid with a catalytic amount of HCl afforded 7-polyfluoroalkylnorkhellins **3a–f** in high yields (73–88%). The presence of the electron-withdrawing R^F group in furochromones **3a–f** enhances the electrophilic character of the C(7) atom of the pyrone cycle, from the attack of which, as a rule, the interaction of chromones with nucleophilic agents begins.[12,13] Due to this fact, compounds **3** are promising substrates for synthesis of new khellin derivatives containing the polyfluoroalkyl group along with the natural fragment and exhibiting, owing to this, potential biological activity.

Next we examined reactions of the 7-polyfluoroalkylnorkhellins **3a–f** with an excess of alkyl mercaptoacetates. It is known[14] that the reaction of 3,3-dialkyl-6-trifluoromethyl-2,3-dihydro-4-pyrones with alkyl mercaptoacetates in the presence of Et_3N involves both electrophilic centers of dihydropyrones and occurs without ring cleavage to give derivatives of 2-oxa-7-thiabicyclo[3.2.1]octane **4**. At the same time, the interaction of 2-trifluoromethylchromones with a three-fold excess of ethyl mercaptoacetate is a redox

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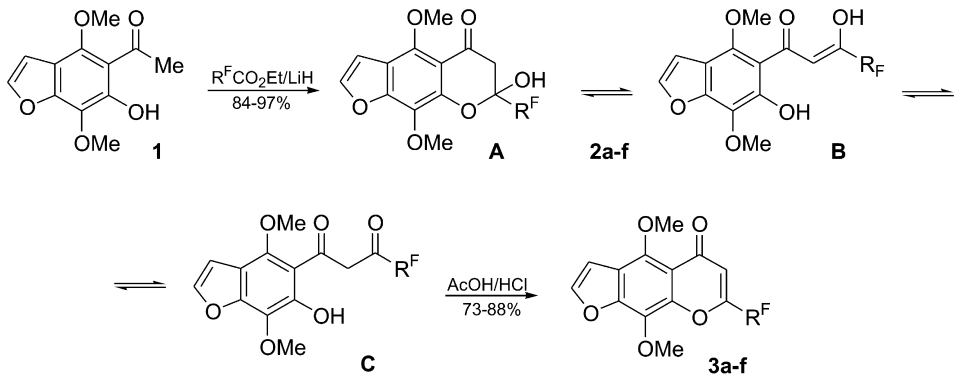
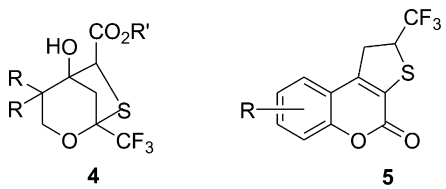


R^F = CF_3 (**a**), CF_2H (**b**), $(CF_2)_2H$ (**c**), C_2F_5 (**d**), C_3F_7 (**e**), C_4F_9 (**f**)

Scheme 1.



Scheme 2.

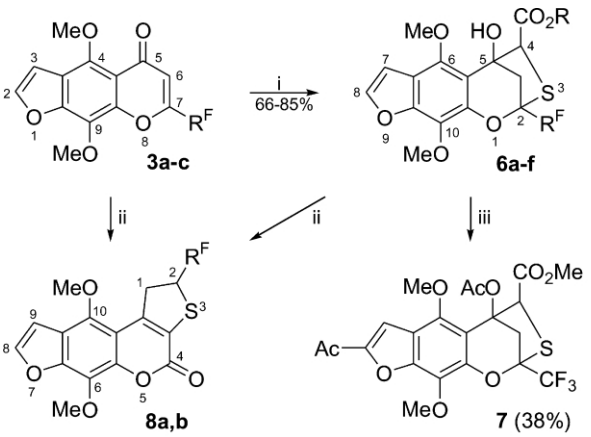
process that affords dihydrothienocoumarins **5** and diethyl 3,4-dithiadipate in a high yield[15] (Scheme 2).

Taking into account the results of previous work,[14,15] we could expect that 7-polyfluoroalkylnorkhellins **3a**–**f**, being chromones, would react with alkyl mercaptoacetates to form the dihydrothienocoumarin system **5**. However, we found that, despite the structural similarity with chromones, they behave in this reaction as dihydropyrones.[14] Indeed, treatment of **3a**–**f** with alkyl mercaptoacetates in the presence of Et_3N for 2 days at room temperature yielded products **6a**–**f** in 66–85% yields which were characterized on the basis of IR, ^1H NMR and microanalysis (Scheme 3). This is a rare case of a meta-bridging reaction in the heterocyclic series. It should be noted that khellin, 7-perfluorobutyl- and 7-trichloromethylnorkhellins do not react with alkyl mercaptoacetates under these conditions and we failed to isolate the individual reaction products from 7-perfluoroethyl- and 7-perfluoropropylnorkhellins. Acetylation of **6d** with Ac_2O in the presence of a catalytic amount of concentrated H_2SO_4 proceeds at room temperature for 1 min to give diacetyl derivative **7**.

The IR spectra of compounds **6a**–**f** showed strong bands in the regions 3420–3500 and 1730–1750 cm^{-1} due to the OH group and the ester carbonyl, respectively. A characteristic feature of the ^1H NMR spectra of **6a**–**f** is the appearance of two AX doublets (J_{AX}=11.6–12.1 Hz) at δ 2.45–2.56 and 3.33–3.50 ppm for the CH_2 group and two singlets at δ 4.25–4.31 and 5.85–5.92 ppm for CH and OH protons, respectively. According to the ^1H NMR data, which exhibit only one set of signals, the reaction is highly stereoselective and results in the formation of only one diastereomer with $2R^*,4S^*,5S^*$ configuration. Further information about the structure of compounds **6** was obtained by X-ray diffraction study of crystals **6c**, the results of which are discussed below.

We then investigated the possibility of the preparation of dihydrothienopsoralens **8** from furochromones **3** and benzofuran derivatives of 2-oxa-7-thiabicyclo[3.2.1]octane **6**. When fluorokhellins **3a**–**c** were heated in a sealed ampoule at 140–150°C for 1.5 h with an excess of $HSCH_2CO_2Et$ in the presence of Et_3N, we succeeded in obtaining dihydrothienopsoralens **8a**,**b** in moderate yields; fluorokhellin **3c** does not react under these conditions. A similar heterocyclic system with an aryl group instead of the polyfluoroalkyl substituent has recently[16] been synthesized from the corresponding *o*-hydroxychalcones and ethyl mercaptoacetate. According to the ^1H NMR spectrum of **8b**, this product contained an admixture of thienopsoralen **9**, 2-difluoromethyl-6,10-dimethoxy-4*H*-furo[3,2-*g*]thieno-[2,3-*c*]chromen-4-one (11%) (see Section 3).

Treatment of compound **6a** with ethyl mercaptoacetate under similar conditions gave dihydrothienopsoralen **8a** in 64% yield (in the absence of Et_3N, this reaction does not proceed), which indicates the intermediacy of compounds **6** in the transformation of khellins **3** into psoralens **8**. A similar reaction with compound **6b** gave corresponding



3a, 8a R^F= CF_3; **3b, 8b** R^F= CF_2H; **3c** R^F= $(CF_2)_2H$;
6a R^F= CF_3, R = Et; **6b** R^F= CF_2H, R = Et; **6c** R^F= $(CF_2)_2H$, R = Et;
6d R^F= CF_3, R = Me; **6e** R^F= CF_2H, R = Me; **6f** R^F= $(CF_2)_2H$, R = Me

Scheme 3. *Reactions and conditions*: (i) $HSCH_2CO_2R$, Et_3N, −20°C, 2 days; (ii) $HSCH_2CO_2R$, Et_3N, 140–150°C, 1.5 h; (iii) Ac_2O, −20°C, 1 min.

psoralen **8b** only in 14% yield and no trace of psoralen was isolated from the reaction of **6c** with ethyl mercaptoacetate.

2.1. X-Ray diffraction study of compound 6c

The benzofuran fragment of the molecule **6c** together with the non-hydrogen atoms directly bound to it is flattened (the mean deviation from the root-mean square plane is 0.019(2) Å). The six-membered cycle C(5),C(6),C(8),C(9), O(2),C(10) exists in the 'twist' conformation with deviations of the C(9) and C(8) atoms from the mean square planer of other atoms of −0.262(3) and +0.626(3) Å, respectively. The five-membered cycle C(6),C(7),S(1),C(9),C(8) also has the 'twist' conformation with the C(6) and C(8) atoms deviated by −0.292(3) and +0.515(3) Å (Fig. 1).

The bond lengths and bond angles in molecule **6c** are close to standard.[17] The difference in the C–S bond lengths (S(1)–C(7) 1.815(2) Å and S(1)–C(9) 1.838(2) Å), which are referred to the same S–C_{sp3} type, is observed. The weakening of the S(1)–C(9) bond can most likely be related to the different compositions of the C_{sp3} node: C(6)HC(15) and C(8)C(18)O(2) for C(7) and C(9), respectively. The main distinction is the presence of the O(2) oxygen atom at the C(9) atom, while the C(7) has no similar acceptors of electronic density. It is of interest that a similar tendency is characteristics of another compound containing the nitrogen analogue (the oxygen atom is replaced by the nitrogen atom) of the central fragment considered.[18] In it the S(1)–C(9) 1.867 Å distance (in designations for **6c**) is somewhat longer, than S(1)–C(7) 1.835 Å, which also could be explained by the presence of the nitrogen atom at the C(9) atom.

The other worth mentioning structural specific features of molecule **6c** are the relative configuration of the asymmetrical C(6) and C(7) centers and the orientation of the carboxyl fragment about the C(7)–C(15) bond. The crystal of compound **6c** contains only enantiomers with the close to *cis*-arrangement of the C(6)–O(5) and C(7)–C(15) bonds. The O(5)–C(6)–C(7)–C(15) torsion angle is close to 34.0(2)°. This conformation could additionally be stabilized by the formation of the O(5)–H···O(6) IMHB. However, this does not occur, and the angle between the O(5)–C(6)–C(7) and O(6)–C(15)–O(7) planes is 88.8(2)°. In our opinion, the most probable reason for such an arrangement is inevitable steric hindrances for packing of molecules with the bulky ethoxycarbonyl substituent. In this case, the plane of this substituent is almost coplanar to the plane of the benzofuran fragment (the angle between the planes is ~20°), which flattens the molecule as a whole and simplifies packing. Nevertheless, in crystal the H(5) hydrogen atom of the hydroxyl group is involved in the formation of the O(5)–H(5)···O(4) IMHB with the parameters H···O 1.97(3), O···O 2.665(2), O–H 0.82(3) Å, angle O–H···O 142(3)°.

Finally, we would like to attract attention to some deviation of the C(19)–F(3) bond length (1.319(3) Å) from a standard value of 1.349 Å.[17] In our case, this can be related to the formation of the intermolecular F···F contact 2.573(3) Å. No other intermolecular contacts were found in structure **6c**. The geometrical packing of **6c** can be described as that consisting of bulky layers parallel to the crystallographic plane (011).

Thus, as expected,[9] the replacement of the methyl group in khellin by the polyfluoroalkyl group substantially increases the reactivity of the pyrone ring of the khellin system toward nucleophiles and makes it possible to design from its new fluoro-containing heterocycles, which may be of interest as analogues of biologically active compounds.

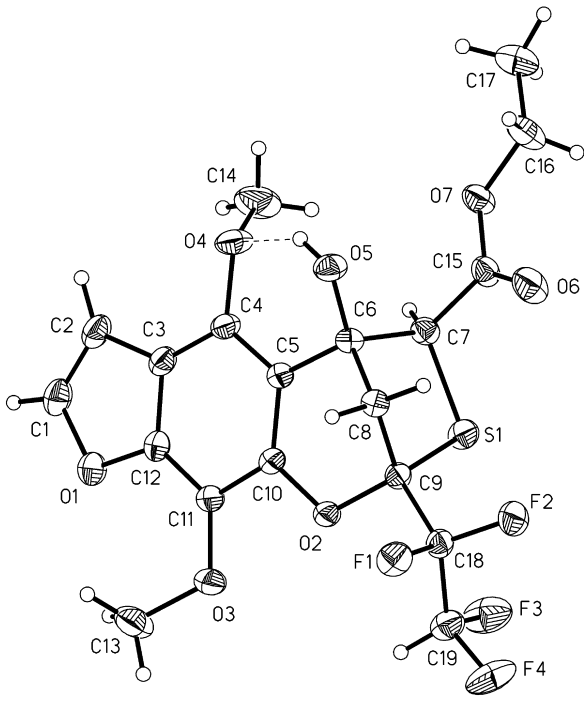


Figure 1. Molecular structure of **6c**.

3. Experimental

3.1. General

^{1}H NMR spectra were recorded on a Bruker WM-250 and Bruker DRX-400 spectrometers operating at 250.13 and 400.13 MHz in $CDCl_3$ or DMSO-d_6 solutions with TMS as the internal standard. IR spectra were measured on an IKS-29 instrument as suspensions in vaseline oil. Elementary analyses were performed at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. Melting points are uncorrected. The starting furochromanones **2a–f** (a yellow powders) were prepared by condensation of the appropriate R^FCO_2Et with khellinone according to described procedure for 2-hydroxy-2-trifluoromethylchromanones.[19]

3.2. Crystallographic data for 6c ($C_{19}H_{18}F_4O_7S$)

The depositlion number CCDC 201071. The crystal system is triclinic at 295 K: a=9.183(2) Å, b=10.431(2) Å, c=11.633(3) Å, α=66.77(2)°, β=74.56(2)°, γ=80.99(2)°, V=985.3(4) Å^3, d_{calc}=1.572 g/cm^{-3}, μ=0.243 mm^{-1}, space group P-1, Z=2. The intensities of 5782 independent reflections (R_{int}=0.03) were measured on a Siemens

P3/PC diffractometer, λ (Mo Kα)=0.71073 Å, graphite monochromator, $\theta/2\theta$-scanning technique, $2\theta_{max}$=60°. The intensities of all measured reflections were corrected for the Lorentz and polarisation factors;[20] absorption was obtained by the use of the standard Ψ-scanning procedure (maximum and minimum transmission coefficients 0.977 and 0.940). The structure was solved by the direct method using the SHELXTL PLUS 5.0 program package.[21] Non-hydrogen atoms were refined by the full-matrix least-squares procedure on F^2 in an anisotropic approximation. The positions of hydrogen atoms were found by a difference Fourier synthesis and refined isotropically. The final discrepancy factors were as follows: R_1=0.0526 (based on F for 4171 reflections with $I>2\sigma(I)$), wR_2=0.1404 (calculated based on F^2 for all 57880 reflections, used at the final stage of the refinement); the total number of the parameters in the refinement was 352, GOOF=1.034.

3.2.1. 7-Hydroxy-4,9-dimethoxy-7-(trifluoromethyl)-6,7-dihydro-5*H*-furo[3,2-*g*]chromen-5-one (2a). Yield 94%, mp 181–182°C (toluene); (Found: 50.54; H, 3.38. $C_{14}H_{11}F_3O_6$ requires C, 50.61; H, 3.34%); ν_{max} 3355 (OH), 3160 (=CH), 1660 (C=O), 1605, 1560 (arom.) cm^{-1}; δ_H (400 MHz, $CDCl_3$) **A** (100%) 3.00 (1H, d, J_{AB}=16.4 Hz, C*H*H), 3.14 (1H, d, J_{AB}=16.4 Hz, CH*H*), 4.03 (3H, s, MeO), 4.05 (3H, s, MeO), 5.03 (1H, s, OH), 6.88 (1H, d, J=2.3 Hz, H^3), 7.50 (1H, d, J=2.3 Hz, H^2); δ_H (250 MHz, DMSO-d_6) **A** (100%) 2.77 (1H, d, J_{AX}=16.0 Hz, C*H*H), 3.30 (1H, br d, J_{AX}=16.0 Hz, CH*H*), 3.94 (3H, s, MeO), 3.98 (3H, s, MeO), 7.20 (1H, d, J=2.3 Hz, H^3), 7.97 (1H, d, J=2.3 Hz, H^2), 8.72 (1H, d, $^4J_{H,OH}$=1.6 Hz, OH).

3.2.2. 7-(Difluoromethyl)-7-hydroxy-4,9-dimethoxy-6,7-dihydro-5*H*-furo[3,2-*g*]chromen-5-one (2b). Yield 97%, mp 202–203°C (toluene–BuOH); (Found: C, 53.50; H, 3.68. $C_{14}H_{12}F_2O_6$ requires C, 53.51; H, 3.85%); ν_{max} 3380 (OH), 3155 (=CH), 1660, (C=O), 1595, 1555 (arom.) cm^{-1}; δ_H (250 MHz, DMSO-d_6) **A** (100%) 2.62 (1H, d, J_{AX}=15.9 Hz, C*H*H), 3.16 (1H, dd, J_{AX}=15.9 Hz, $^4J_{H,OH}$=1.6 Hz, CH*H*), 3.93 (3H, s, MeO), 3.96 (3H, s, MeO), 6.16 (1H, t, $^2J_{H,F}$=54.5 Hz, CHF_2), 7.17 (1H, d, J=2.2 Hz, H^3), 7.95 (1H, d, J=2.2 Hz, H^2), 7.98 (1H, d, $^4J_{H,OH}$=1.6 Hz, OH).

3.2.3. 7-Hydroxy-4,9-dimethoxy-7-(1,1,2,2-tetrafluoroethyl)-6,7-dihydro-5*H*-furo[3,2-*g*]chromen-5-one (2c). Yield 91%, mp 182–183°C (toluene); (Found: C, 49.45; H, 3.28. $C_{15}H_{12}F_4O_6$ requires C, 49.46; H, 3.32%); ν_{max} 3220 (OH), 3160 (=CH), 1655, (C=O), 1605, 1555 (arom.) cm^{-1}; δ_H (250 MHz, DMSO-d_6) **A** (100%) 2.76 (1H, d, J_{AX}=16.2 Hz, C*H*H), 3.27 (1H, d, J_{AX}=16.2 Hz, CH*H*), 3.92 (3H, s, MeO), 3.98 (3H, s, MeO), 6.71 (1H, tdd, $^2J_{H,F}$=51.6 Hz, $^3J_{H,F}$=7.1, 5.8 Hz, CHF_2CF_2), 7.20 (1H, d, J=2.3 Hz, H^3), 7.97 (1H, d, J=2.3 Hz, H^2), 8.60 (1H, s, OH).

3.2.4. 7-Hydroxy-4,9-dimethoxy-7-(perfluoroethyl)-6,7-dihydro-5*H*-furo[3,2-*g*]chromen-5-one (2d). Yield 84%, mp 166–167°C (toluene); (Found: C, 47.18; H, 2.98. $C_{15}H_{11}F_5O_6$ requires C, 47.13; H, 2.90%); ν_{max} 3250 (OH), 1655 (C=O), 1605 (arom.) cm^{-1}; δ_H (400 MHz, $CDCl_3$) **A** (66%) 3.02 (1H, d, J_{AB}=16.3 Hz, C*H*H), 3.20 (1H, dd, J_{AB}=16.3 Hz, $^4J_{H,OH}$=2.0 Hz, CH*H*), 4.02 (3H, s, MeO), 4.07 (3H, s, MeO), 4.12 (1H, br s, OH), 6.94 (1H, d, J=2.3 Hz, H^3), 7.54 (1H, d, J=2.3 Hz, H^2); **B** (30%) 4.07 (3H, s, MeO), 4.08 (3H, s, MeO), 6.88 (1H, d, J=2.3 Hz, H^3), 7.21 (1H, s, =CH), 7.53 (1H, d, J=2.3 Hz, H^2), 11.60 (1H, s, OH phenolic), 14.23 (1H, br s, OH enolic); **C** (4%) 4.04 (3H, s, MeO), 4.14 (3H, s, MeO), 4.41 (2H, s, CH_2), 6.90 (1H, d, J=2.3 Hz, H^3), 7.52 (1H, d, J=2.3 Hz, H^2), 12.52 (1H, s, OH); δ_H (400 MHz, DMSO-d_6) **A** (100%) 2.81 (1H, d, J_{AX}=16.1 Hz, C*H*H), 3.39 (1H, d, J_{AX}=16.1 Hz, CH*H*), 3.90 (3H, s, MeO), 4.00 (3H, s, MeO), 7.24 (1H, d, J=2.3 Hz, H^3), 8.01 (1H, d, J=2.3 Hz, H^2), 8.94 (1H, s, OH).

3.2.5. 7-Hydroxy-4,9-dimethoxy-7-(perfluoropropyl)-6,7-dihydro-5*H*-furo[3,2-*g*]chromen-5-one (2e). Yield 87%, mp 157–158°C (toluene); (Found: C, 44.41; H, 2.68. $C_{16}H_{11}F_7O_6$ requires C, 44.46; H, 2.57%); ν_{max} 3260 (OH), 1660 (C=O), 1610 (arom.) cm^{-1}; δ_H (400 MHz, $CDCl_3$) **A** (78%) 3.03 (1H, d, J_{AB}=16.2 Hz, C*H*H), 3.21 (1H, d, J_{AB}=16.2 Hz, CH*H*), 4.02 (3H, s, MeO), 4.07 (3H, s, MeO), 4.20 (1H, br s, OH), 6.94 (1H, d, J=2.3 Hz, H^3), 7.54 (1H, d, J=2.3 Hz, H^2); **B** (14%) 4.07 (6H, s, 2MeO), 6.88 (1H, d, J=2.4 Hz, H^3), 7.19 (1H, s, =CH), 7.53 (1H, d, J=2.4 Hz, H^2), 11.57 (1H, s, OH phenolic); **C** (8%) 4.04 (3H, s, MeO), 4.14 (3H, s, MeO), 4.41 (2H, s, CH_2), 6.90 (1H, d, J=2.4 Hz, H^3), 7.52 (1H, d, J=2.4 Hz, H^2), 12.52 (1H, s, OH).

3.2.6. 7-Hydroxy-4,9-dimethoxy-7-(perfluorobutyl)-6,7-dihydro-5*H*-furo[3,2-*g*]chromen-5-one (2f). Yield 88%, mp 151–152°C (toluene); (Found: C, 42.45; H, 2.36. $C_{17}H_{11}F_9O_6$ requires C, 42.34; H, 2.30%); ν_{max} 3250 (OH), 3170 (=CH), 1660 (C=O), 1610, 1560 (arom.) cm^{-1}; δ_H (250 MHz, $CDCl_3$) **A** (50%) 3.05 (1H, d, J_{AB}=16.3 Hz, C*H*H), 3.23 (1H, d, J_{AB}=16.3 Hz, CH*H*), 4.00 (3H, s, MeO), 4.07 (3H, s, MeO), 5.38 (1H, s, OH), 6.88 (1H, d, J=2.3 Hz, H^3), 7.52 (1H, d, J=2.3 Hz, H^2); **B** (47%): 4.00 (3H, s, MeO), 4.07 (3H, s, MeO), 6.84 (1H, d, J=2.3 Hz, H^3), 7.20 (1H, s, =CH), 7.47 (1H, d, J=2.3 Hz, H^2), 11.59 (1H, s, OH phenolic), 14.28 (1H, br s, OH enolic); **C** (3%) 4.04 (3H, s, MeO), 4.15 (3H, s, MeO), 4.42 (2H, s, CH_2), 6.90 (1H, d, J=2.3 Hz, H^3), 7.52 (1H, d, J=2.3 Hz, H^2), 12.53 (1H, s, OH); δ_H (400 MHz, DMSO-d_6) **A** (100%) 2.83 (1H, d, J_{AX}=16.0 Hz, C*H*H), 3.40 (1H, d, J_{AX}=16.0 Hz, CH*H*), 3.89 (3H, s, MeO), 4.00 (3H, s, MeO), 7.24 (1H, d, J=2.3 Hz, H^3), 8.01 (1H, d, J=2.3 Hz, H^2), 8.97 (1H, s, OH).

3.3. General procedure for preparation of furochromones 3a–f

A mixture of furochromanone **2** (4.1 mmol), AcOH (3 mL), and concentrated HCl (3 drops) was boiled for 5 min. Then the reaction mixture was cooled and diluted with 5 mL of ethanol and the crystalline material was isolated by filtration, washed with cold ethanol, and dried to give the compounds **3** as a yellow crystals.

3.3.1. 4,9-Dimethoxy-7-(trifluoromethyl)-5*H*-furo[3,2-*g*]-chromen-5-one (3a). Yield 81%, mp 166–167°C; (Found: C, 53.60; H, 2.81. $C_{14}H_9F_3O_5$ requires C, 53.52; H, 2.89%); ν_{max} 3165, 3140 (=CH), 1670 (C=O), 1650 (C=C), 1615, 1550 (arom.) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 4.07 (3H, s,

MeO), 4.21 (3H, s, MeO), 6.60 (1H, s, =CH), 7.05 (1H, d, J=2.3 Hz, H^3), 7.68 (1H, d, J=2.3 Hz, H^2).

3.3.2. 7-(Difluoromethyl)-4,9-dimethoxy-5*H*-furo[3,2-*g*]-chromen-5-one (3b). Yield 85%, mp 156–157°C; (Found: C, 56.84; H, 3.40. $C_{14}H_{10}F_2O_5$ requires C, 56.77; H, 3.40%); ν_{max} 3150 (=CH), 1670 (C=O), 1650 (C=C), 1615 (arom.) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 4.07 (3H, s, MeO), 4.20 (3H, s, MeO), 6.48 (1H, s, =CH), 6.48 (1H, t, $^2J_{H,F}$=53.8 Hz, CHF_2), 7.04 (1H, d, J=2.3 Hz, H^3), 7.66 (1H, d, J=2.3 Hz, H^2).

3.3.3. 4,9-Dimethoxy-7-(1,1,2,2-tetrafluoroethyl)-5*H*-furo[3,2-*g*]chromen-5-one (3c). Yield 88%, mp 153–154°C; (Found: C, 51.95; H, 2.92. $C_{15}H_{10}F_4O_5$ requires C, 52.04; H, 2.91%); ν_{max} 3135, 3090 (=CH), 1670 (C=O), 1645 (C=C), 1620, 1595, 1555 (arom.) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 4.08 (3H, s, MeO), 4.18 (3H, s, MeO), 6.18 (1H, tt, $^2J_{H,F}$=53.0 Hz, $^3J_{H,F}$=3.8 Hz, CHF_2CF_2), 6.61 (1H, s, =CH), 7.04 (1H, d, J=2.3 Hz, H^3), 7.67 (1H, d, J=2.3 Hz, H^2).

3.3.4. 4,9-Dimethoxy-7-(perfluoroethyl)-5*H*-furo[3,2-*g*]-chromen-5-one (3d). Yield 87%, mp 145–146°C; (Found: C, 49.50; H, 2.49. $C_{15}H_9F_5O_5$ requires C, 49.47; H, 2.49%); ν_{max} 3110 (=CH), 1670 (C=O), 1650 (C=C), 1620, 1545 (arom.) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.09 (3H, s, MeO), 4.17 (3H, s, MeO), 6.65 (1H, s, =CH), 7.05 (1H, d, J=2.3 Hz, H^3), 7.68 (1H, d, J=2.3 Hz, H^2).

3.3.5. 4,9-Dimethoxy-7-(perfluoropropyl)-5*H*-furo[3,2-*g*]-chromen-5-one (3e). Yield 73%, mp 140–141°C; (Found: C, 46.37; H, 2.11. $C_{16}H_9F_7O_5$ requires C, 46.39; H, 2.19%); ν_{max} 3150 (=CH), 1670 (C=O), 1655 (C=C), 1615, 1600, 1550 (arom.) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.10 (3H, s, MeO), 4.17 (3H, s, MeO), 6.64 (1H, s, =CH), 7.06 (1H, d, J=2.3 Hz, H^3), 7.69 (1H, d, J=2.3 Hz, H^2).

3.3.6. 4,9-Dimethoxy-7-(perfluorobutyl)-5*H*-furo[3,2-*g*]-chromen-5-one (3f). Yield 87%, mp 146–148°C; (Found: C, 43.99; H, 2.02. $C_{17}H_9F_9O_5$ requires C, 43.98; H, 1.95%); ν_{max} 3150 (=CH), 1670 (C=O), 1660 (C=C), 1620, 1610, 1560 (arom.) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 4.10 (3H, s, MeO), 4.17 (3H, s, MeO), 6.65 (1H, s, =CH), 7.06 (1H, d, J=2.3 Hz, H^3), 7.69 (1H, d, J=2.3 Hz, H^2).

3.4. General procedure for preparation of 6a–f

A mixture of 7-polyfluoroalkylnorkhellin **3** (3.2 mmol), alkyl mercaptoacetate (17.0 mmol) and Et_3N (1 mL) was stirred for 2 days at room temperature. Then the reaction mixture was diluted with 10 mL of 70% ethanol and the crystalline material was isolated by filtration and washed with ethanol to give the compounds **6**. After recrystallisation from ethanol, the melting point did not change.

3.4.1. Ethyl 5-hydroxy-6,10-dimethoxy-2-(trifluoromethyl)-4,5-dihydro-2,5-methanofuro[3,2-*h*][1,3]benzoxathiepine-4-carboxylate (6a). Yield 72%, colourless crystals, mp 148–149°C; (Found: C, 49.80; H, 3.75. $C_{18}H_{17}F_3O_7S$ requires C, 49.77; H, 3.94%); ν_{max} 3480 (OH), 3170, 3140 (=CH), 1740 (C=O), 1630, 1610, 1540 (arom.) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.35 (3H, t, J=7.1 Hz, *Me*CH_2), 2.52 (1H, d, J_{AX}=11.7 Hz, C*H*H), 3.50 (1H, d, J_{AX}=11.7 Hz, CH*H*), 4.01 (3H, s, MeO), 4.23 (3H, s, MeO), 4.28 (2H, q, J=7.1 Hz, CH_2Me), 4.29 (1H, s, CH), 5.91 (1H, s, OH), 6.87 (1H, d, J=2.3 Hz, H^7), 7.56 (1H, d, J=2.3 Hz, H^8).

3.4.2. Ethyl 2-(difluoromethyl)-5-hydroxy-6,10-dimethoxy-4,5-dihydro-2,5-methanofuro[3,2-*h*][1,3]benzoxathiepine-4-carboxylate (6b). Yield 85%, colourless crystals, mp 162–163°C; (Found: C, 52.02; H, 4.42. $C_{18}H_{18}F_2O_7S$ requires C, 51.92; H, 4.36%); ν_{max} 3480 (OH), 3170 (=CH), 1745 (C=O), 1630, 1610, 1550 (arom.) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, t, J=7.1 Hz, *Me*CH_2), 2.45 (1H, d, J_{AX}=11.8 Hz, C*H*H), 3.34 (1H, d, J_{AX}=11.8 Hz, CH*H*), 4.02 (3H, s, MeO), 4.22 (3H, s, MeO), 4.27 (1H, s, CH), 4.28 (2H, q, J=7.1 Hz, CH_2Me), 5.89 (1H, s, OH), 6.18 (1H, t, $^2J_{H,F}$=54.7 Hz, CHF_2), 6.86 (1H, d, J=2.3 Hz, H^7), 7.55 (1H, d, J=2.3 Hz, H^8).

3.4.3. Ethyl 5-hydroxy-6,10-dimethoxy-2-(1,1,2,2-tetrafluoroethyl)-4,5-dihydro-2,5-methanofuro[3,2-*h*][1,3]-benzoxathiepine-4-carboxylate (6c). Yield 74%, a light yellow crystals, mp 112–113°C; (Found: C, 49.13; H, 3.78. $C_{19}H_{18}F_4O_7S$ requires C, 48.93; H, 3.89%); ν_{max} 3470 (OH), 3170, 3140 (=CH), 1740 (C=O), 1625, 1610, 1545 (arom.) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, t, J=7.1 Hz, *Me*CH_2), 2.55 (1H, d, J_{AX}=11.6 Hz, C*H*H), 3.47 (1H, d, J_{AX}=11.6 Hz, CH*H*), 3.98 (3H, s, MeO), 4.22 (3H, s, MeO), 4.25 (1H, s, CH), 4.29 (2H, q, J=7.1 Hz, CH_2Me), 5.85 (1H, s, OH), 6.32 (1H, tdd, $^2J_{H,F}$=52.8 Hz, $^3J_{H,F}$=7.1, 4.2 Hz, CHF_2CF_2), 6.87 (1H, d, J=2.3 Hz, H^7), 7.56 (1H, d, J=2.3 Hz, H^8).

3.4.4. Methyl 5-hydroxy-6,10-dimethoxy-2-(trifluoromethyl)-4,5-dihydro-2,5-methanofuro[3,2-*h*][1,3]benzoxathiepine-4-carboxylate (6d). Yield 76%, colourless crystals, mp 182–183°C; (Found: C, 48.52; H, 3.71. $C_{17}H_{15}F_3O_7S$ requires C, 48.57; H, 3.60%); ν_{max} 3500 (OH), 3180, 3140 (=CH), 1750 (C=O), 1620, 1545 (arom.) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 2.52 (1H, d, J_{AX}=11.6 Hz, C*H*H), 3.49 (1H, d, J_{AX}=11.6 Hz, CH*H*), 3.83 (3H, s, CO_2Me), 4.00 (3H, s, MeO), 4.23 (3H, s, MeO), 4.31 (1H, s, CH), 5.90 (1H, s, OH), 6.87 (1H, d, J=2.4 Hz, H^7), 7.55 (1H, d, J=2.4 Hz, H^8).

3.4.5. Methyl 2-(difluoromethyl)-5-hydroxy-6,10-dimethoxy-4,5-dihydro-2,5-methanofuro[3,2-*h*][1,3]benzoxathiepine-4-carboxylate (6e). Yield 83%, colourless crystals, mp 173–174°C; (Found: C, 50.73; H, 4.28. $C_{17}H_{16}F_2O_7S$ requires C, 50.75; H, 4.01%); ν_{max} 3420 (OH), 1730 (C=O), 1630, 1545 (arom.) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.46 (1H, d, J_{AX}=11.9 Hz, C*H*H), 3.33 (1H, d, J_{AX}=11.9 Hz, CH*H*), 3.82 (3H, s, CO_2Me), 4.02 (3H, s, MeO), 4.23 (3H, s, MeO), 4.29 (1H, d, $^4J_{H,OH}$= 1.8 Hz, CH), 5.92 (1H, s, OH), 6.20 (1H, t, $^2J_{H,F}$=54.7 Hz, CHF_2), 6.87 (1H, d, J=2.3 Hz, H^7), 7.55 (1H, d, J=2.3 Hz, H^8).

3.4.6. Methyl 5-hydroxy-6,10-dimethoxy-2-(1,1,2,2-tetrafluoroethyl)-4,5-dihydro-2,5-metanofuro[3,2-*h*][1,3]benzoxathiepine-4-carboxylate (6f). Yield 66%, a light yellow crystals, mp 135–136°C; (Found: C, 47.78; H, 3.58. $C_{18}H_{16}F_4O_7S$ requires C, 47.79; H, 3.57%); ν_{max} 3490

(OH), 3170, 3150 (=CH), 1735 (C=O), 1625, 1545 (arom.) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.56 (1H, dd, J_{AX}= 12.1 Hz, $J_{H,OH}$=1.6 Hz, C*H*H), 3.47 (1H, d, J_{XA}=12.1 Hz, CH*H*), 3.83 (3H, s, CO_2Me), 3.98 (3H, s, MeO), 4.23 (3H, s, MeO), 4.27 (1H, s, CH), 5.88 (1H, s, OH), 6.33 (1H, tdd, $^2J_{H,F}$=52.8 Hz, $^3J_{H,F}$=7.2, 4.2 Hz, CHF_2CF_2), 6.88 (1H, d, J=2.3 Hz, H^7), 7.56 (1H, d, J=2.3 Hz, H^8).

3.4.7. Methyl 5-acetoxy-8-acetyl-6,10-dimethoxy-2-(trifluoromethyl)-4,5-dihydro-2,5-methanofuro[3,2-*h*][1,3]-benzoxathiepine-4-carboxylate (7). A mixture of the compound **6d** (200 mg, 0.48 mmol), Ac_2O (2 mL) and 1 drop of conc. H_2SO_4 was stirred for 1 min at room temperature and then was diluted with water (50 mL). The solid product obtained on standing was collected by filtration, washed with water, dried and crystallised from ethanol to give the title compound **7**, (90 mg, 38%) as colourless crystals, mp 201–202°C; (Found: C, 49.95; H, 3.60. $C_{21}H_{19}F_3O_9S$ requires C, 50.00; H, 3.80%); ν_{max} 3100 (=CH), 1750, 1685 (C=O), 1625 (arom.) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.10 (3H, s, OCOMe), 2.60 (3H, s, COMe), 3.42 (1H, d, J=11.7 Hz, C*H*H), 3.44 (1H, d, J=11.7 Hz, CH*H*), 3.83 (3H, s, CO_2Me), 4.03 (3H, s, MeO), 4.13 (3H, s, MeO), 4.48 (1H, s, CH), 7.60 (1H, s, =CH).

3.4.8. 6,10-Dimethoxy-2-(trifluoromethyl)-1,2-dihydro-4*H*-furo[3,2-*g*]thieno[2,3-*c*]chromen-4-one (8a). A mixture of trifluorokhellin **3a** (0.25 g, 0.8 mmol) and ethyl mercaptoacetate (0.5 g, 4.2 mmol) in the presence of Et_3N (5 drops) was heated in a sealed tube at 140–150°C for 1.5 h. After cooling, the reaction mixture was diluted with 5 mL of 70% ethanol and the crystalline material was isolated by filtration and washed with aqueous ethanol to give the title compound **8a** (0.10 g, 34%) as a yellow crystals, mp 187–188°C; (Found: C, 51.63; H, 2.89. $C_{16}H_{11}F_3O_5S$ requires C, 51.62; H, 2.98%); ν_{max} 1720 (C=O), 1610, 1580, 1550 (arom.) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.00 (1H, dd, ^2J=19.3 Hz, ^3J=10.8 Hz, C*H*H), 4.14 (1H, dd, ^2J=19.3 Hz, ^3J=10.8 Hz, CH*H*), 4.13 (3H, s, MeO), 4.16 (3H, s, MeO), 4.31–4.41 (1H, m, CH), 6.98 (1H, d, J=2.3 Hz, H^3), 7.64 (1H, d, J=2.3 Hz, H^2). Compound **8a** was also obtained in 64% yield from reaction of **6a** with ethyl mercaptoacetate under similar conditions. In the absence of Et_3N the reaction does not occur and the initial **6a** was isolated.

3.4.9. 2-(Difluoromethyl)-6,10-dimethoxy-1,2-dihydro-4*H*-furo[3,2-*g*]thieno[2,3-*c*]chromen-4-one (8b). The title compound was prepared from difluorokhellin **3b** analogously to **8a**. Yield 33%, mp 183–184°C; (Found: C, 52.60; H, 3.27. $C_{16}H_{12}F_2O_5S{\cdot}0.5H_2O$ requires C, 52.89; H, 3.61%); ν_{max} 1720 (C=O), 1605, 1580, 1550w (arom.) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.86 (1H, dd, ^2J= 19.1 Hz, ^3J=10.2 Hz, C*H*H), 4.06 (1H, dd, ^2J=19.1 Hz, ^3J=3.8 Hz, CH*H*), 4.08–4.18 (1H, m, CH), 4.12 (3H, s, MeO), 4.16 (3H, s, MeO), 5.84 (1H, ddd, $^2J_{H,F}$=56.7, 55.9 Hz, $^3J_{H,H}$=5.0 Hz, CHF_2), 6.97 (1H, d, J=2.3 Hz, H^3), 7.63 (1H, d, J=2.3 Hz, H^2). Product **8b** contained 11% an impurity of 2-(difluoromethyl)-6,10-dimethoxy-4*H*-furo-[3,2-*g*]thieno[2,3-*c*]chromen-4-one **9**, which was not isolated in a pure state, δ_H 4.21 (3H, s, MeO), 4.22 (3H, s, MeO), 7.00 (1H, td, $^2J_{H,F}$=55.7 Hz, $^4J_{H,H}$=0.6 Hz, CHF_2), 7.05 (1H, d, J=2.3 Hz, H^3), 7.67 (1H, d, J=2.3 Hz, H^2), 8.29 (1H, td, $^4J_{H,F}$=1.7 Hz, $^4J_{H,H}$=0.6 Hz, =CH). Compound **8b** was also obtained in 14% yield from reaction of **6b** with ethyl mercaptoacetate.

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