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4-Chloro-3-(trifluoroacetyl)- and 4-chloro-3-(methoxalyl)coumarins as novel and efficient building blocks for the regioselective synthesis of 3,4-fused coumarins

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ABSTRACT

4-Chloro-3-(trifluoroacetyl)- and 4-chloro-3-(methoxalyl)coumarins react with electron-rich amino-heterocycles, dimethyl 1,3-acetonedicarboxylate, hydrazines, alkyl thioglycolates, and methyl sarcosinate to give a variety of 3,4-heteroannulated coumarins. The starting materials were prepared by the reaction of 4-hydroxycoumarin with trifluoroacetic anhydride and methyl 2-chloro-2-oxoacetate in the presence of trimethylsilylchloride. An NMR study and X-ray crystallographic analysis are reported.

1. Introduction

Coumarins (2*H*-1-benzopyran-2-ones, 2*H*-chromen-2-ones) are very attractive targets for combinatorial library synthesis due to their wide range of valuable biological activities. Many natural and synthetic coumarins have occupied an important place in drug research, as a one of the so-called privileged drug scaffold.[1] The therapeutic potential of these compounds is immense. Coumarins have been reported to exhibit antibacterial and antifungal activity and to act as diuretics and analgesics.[2] There have also been reports that structures containing the coumarin ring reduce tissue swelling due to various kinds of trauma or disease, display hypolipidaemic, vasorelaxant, antiplatelet aggregation, antioxidant, antiinflammatory, and immunosuppressive activities.[1] Coumarins also exhibit a variety of anticancer activities, displaying antimutagenic, and antitumor properties.[3] In addition, this scaffold is present in promising drug candidates as nonpeptidic HIV protease inhibitors,[4] topoisomerase II,[5] and tyrosine kinase[6] inhibitors. On the other hand, they have also found application as photosensitizers, fluorescent, and laser dyes,[7] and represent useful synthetic building blocks in organic and medicinal chemistry.[8]

The biological and industrial importance of coumarins has led to a considerable amount of synthetic work in the field of coumarins with 3,4-carbocyclic- and 3,4-heterocyclic fused ring systems.[9] For these purposes the structure most commonly used is 4-chloro-3-formylcoumarin (**1a**).[10,11] Being essentially *gem*-activated alkene with a good leaving group (chlorine atom), this compound exhibits a variety of properties and can react with substituted anilines,[12] aryl isocyanides,[13] arylhydrazines,[10,14] amidines,[15] hydroxylamine,[14] benzylamines,[16] sodium azide,[17] ethyl cyanoacetate,[18] ethyl 3-aminocrotonate,[19] 1,3-bis(trimethylsilyloxy)-1,3-butadienes,[20] Wittig phosphoranes,[21] and ethyl glycinates.[22] Having electron-withdrawing formyl group at the 3-position, **1a** undergo conjugated addition–elimination reactions with dinucleophiles at the 4-position of the coumarin system, followed by intramolecular cyclization via electrophilic formyl function to coumarins 3,4-fused to pyrazoles, isoxazoles, pyrimidines, pyrroles, pyridines, quinolines and other heterocycles (formal [3+2] and [3+3] cycloadditions). At the same time, very scarce information is available

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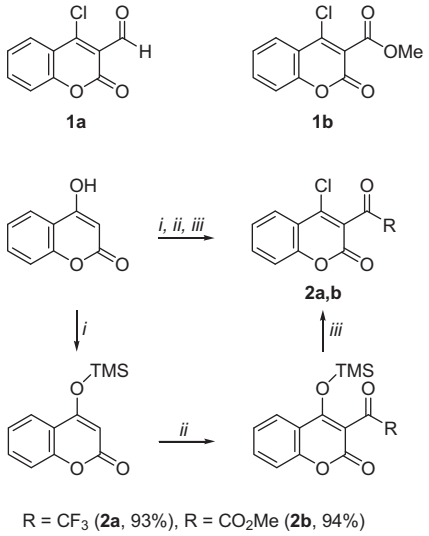
about the reactivity of 4-chloro-3-(methoxycarbonyl)coumarin (**1b**) (Scheme 1). Only two papers describing its reactions with sodium azide[23] and *S*-methylisothiourea[24] are present in the literature. It should be noted that all these reactions proceed via nucleophilic 1,4- or 1,2-addition to give coumarin derivatives without opening of the coumarin ring.



Scheme 1. One-pot three step synthesis of 4-chloro-3-(trifluoroacetyl)- and 4-chloro-3-(methoxalyl)coumarins (**2a**,**b**). Reagents and conditions: (i) 1,4-dioxane, Py (2.1 equiv), 30 min, TMSCl (1.2 equiv), 60 min, rt; (ii) TFAA or $ClCOCO_2Me$ (1.3 equiv), 2 h, 80–90 °C; (iii) $POCl_3$ (1.0 equiv), 60 °C, 2 h.

We envisaged that introduction of such powerful electron-withdrawing groups as trifluoroacetyl and methoxalyl into the 3-position of 4-chlorocoumarin would increase its reactivity toward nucleophilic reagents and open up a broad synthetic scope of this important oxygen-containing heterocyclic system. So far, 4-chloro-3-(trifluoroacetyl)coumarin (**2a**) and 4-chloro-3-(methoxalyl) coumarin (**2b**) have not received much attention despite their potential interest as building blocks in organic synthesis for the construction of 3,4-fused coumarins (Scheme 1). To the best of our knowledge, there has been only our preliminary communication on the synthesis of **2a** and its reaction with aromatic amines.[25] On the other hand, 3-substituted chromones (3-formyl-,[26] 3-trifluoroacetyl-,[27] 3-dichloroacetyl-,[28] 3-methoxalyl-,[29] 3-cyano-,[30] and 3-nitrochromones[31]) are widely used as valuable synthetic intermediates in the preparation of pharmacologically relevant products and new heterocyclic systems.

Based on the retrosynthetic analysis and on our previous work related to the development of new cyclocondensation reactions of electron-rich aminoheterocycles and other dinucleophilic reagents,[27–31] we envisaged that compounds **2a**,**b** are suitable substrates for the synthesis of 3,4-heteroannulated coumarins. We are reporting now on the formation of this type of heterocycles from coumarins **2a**,**b** as 1,3-dielectrophiles and various 1,3-dinucleophiles (heterocyclic amines, morpholine-4-carboxamidine, dimethyl 1,3-acetonedicarboxylate) and 1,2-dinucleophiles (hydrazines, alkyl thioglycolates, methyl sarcosinate).

2. Results and discussion

In the initial study we have developed the synthesis of the hitherto unknown 4-chloro-3-(trifluoroacetyl)- and 4-chloro-3-(methoxalyl) coumarins (**2a**,**b**) starting from commercially available 4-hydroxycoumarin by a one-pot procedure depicted in Scheme 1. The synthetic route consists of three steps: firstly, 4-hydroxycoumarin was silylated by TMSCl in dioxane using dry pyridine as HCl acceptor; secondly, acylation by trifluoroacetic anhydride or methyl 2-chloro-2-oxoacetate delivers in situ the corresponding acetylated intermediates, which were treated with $POCl_3$ to form **2a**,**b** in excellent yield. This reaction sequence is a straightforward and convenient route to 4-chloro-3-(trifluoroacetyl)- and 4-chloro-3-(methoxalyl) coumarins (**2a**,**b**), which makes these previously unknown compounds suitable for further investigations and has advantages with regard to ease of operation and the ready availability of starting materials. Although the method represents a three-step process, it is experimentally simple and may be of value in CF_3-containing building blocks chemistry.

4-Chloro-3-(trifluoroacetyl)coumarin (**2a**) is, as previously described for 3-(trifluoroacetyl)coumarins,[32] sensitive to moisture. Therefore, all reactions and storage was performed under dry inert atmosphere. Compounds **2a**,**b** are stable in dry and inert solvents under inert atmosphere at least for 48 h. This gave us a chance to use NMR spectroscopy to confirm their structure and purity.[25]

Continuing our research program dedicated to the design and synthesis of novel fused pyridines and in view of the unique biological properties displayed by many coumarin derivatives[1] we have started our investigation in this area by the study of the reactions of **2a**,**b** with electron-rich aminoheterocycles **3**–**7** (Fig. 1) in order to obtain the corresponding 5*H*-chromeno[3,4-*c*]pyridin-5-one ring system. The latter represents an important synthetic target due to its interesting biological properties.[9,19,33]

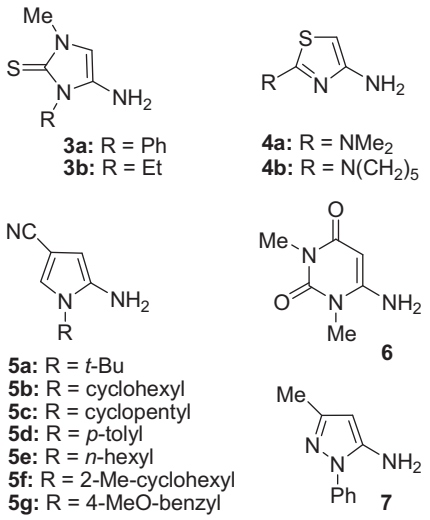
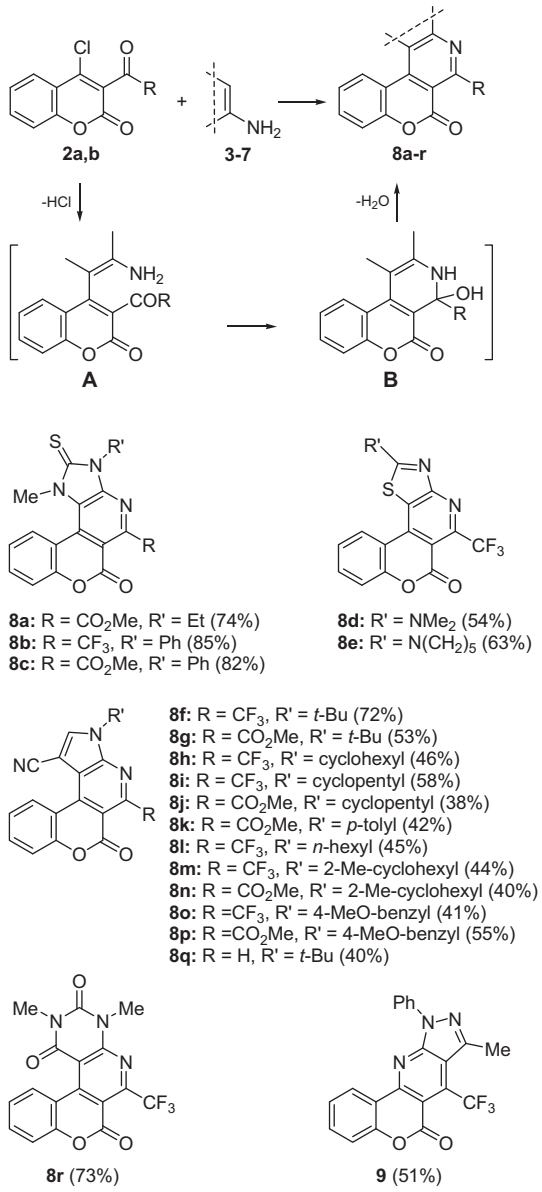


Fig. 1. Electron-rich heterocyclic amines **3**–**7** used for the synthesis of 3,4-heteroannulated coumarins.

After some optimization, it was found that treatment of coumarins **2** with amines **3**–**6** (1.1 equiv) in dry DFM at 100–120 °C for 2–12 h in the presence of TMSCl as a water scavenger resulted in the formation of heteroannulated chromeno[3,4-*c*]pyridin-5-ones **8a**–**r** with an excellent regioselectivity and in good yields (54–85%). In most cases, the reaction was complete after 6–8 h and the products could be isolated by simple filtration of the precipitate formed or by column chromatography over silica gel. The progress of the reaction was monitored by TLC, and the results are summarized in Scheme 2. Note that coumarin **2a** is more reactive than **2b**, which failed to react with **4a**,**b** and **6**. It is important that a wide range of 2-aminopyrroles **5a**–**g** can effectively participate in the reaction with **2a**,**b**, providing a variety of chromeno[4,3-*d*]pyrrolo[2,3-*b*]pyridines **8f**–**p** in moderate to good yield (38–72%). The analogous reaction of 4-chloro-3-formylcoumarin (**1a**) with **5a** gave compound **8q** in 40% yield. The regiochemistry of **8b**, **8f**, and

8g was unambiguously confirmed by X-ray single crystal analyses (Figs. 3–5). This result clearly shows that the present methodology could be applicable to various types of heterocyclic amines, providing a rapid route to the synthesis of a wide range of the heteroannulated pyridines fused to 3,4-position of the coumarin, including CF_3-containing derivatives.



Scheme 2.

Analyzing the crystal structures of compounds **8b**, **8f**, and **8g**, which at first glance should be planar, it was found that in the case of CF_3-substituted pyridines **8b** and **8f** the heterocyclic core is twisted. The chiefly points of distortion in both structures are α-pyrone rings; the corresponding dihedral angles for **8f** are C(7) C(6)–C(14)O(1) of 4.1(2)°, C(6)C(5)–C(16)C(15) of 12.4(2)°, and C(14)C(6)–C(7)C(13) of 13.1(2)°. Distortion of the planar geometry was also observed for **8b**, the molecular conformation of which is more twisted, dihedral angle C(13)C(12)–C(17)C(O2) is 10.8(2)°, C(12)C(11)–C(15)C(16) is 17.8(1)°, and C(17)C(12)–C(13)C(14) is 16.4(1)°. In contrary, in the case of **8g**, the core of heterocyclic framework is planar, the carbonyl group is out of the plane of the heterocycle, dihedral angle N(1)C(5)–C(13)O(1) was detected to be

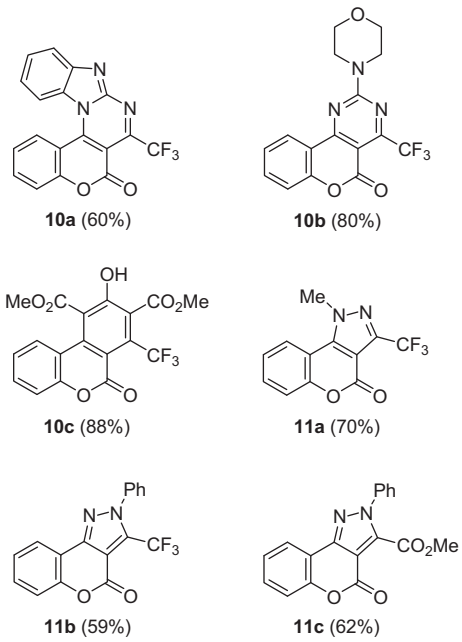


Fig. 2. Structures of the products obtained.

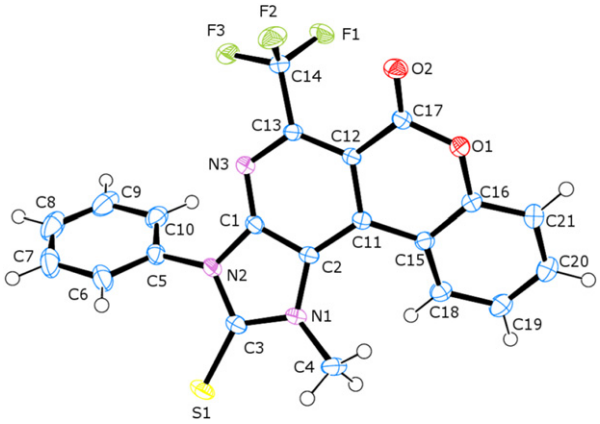


Fig. 3. Molecular structure of compound **8b**.

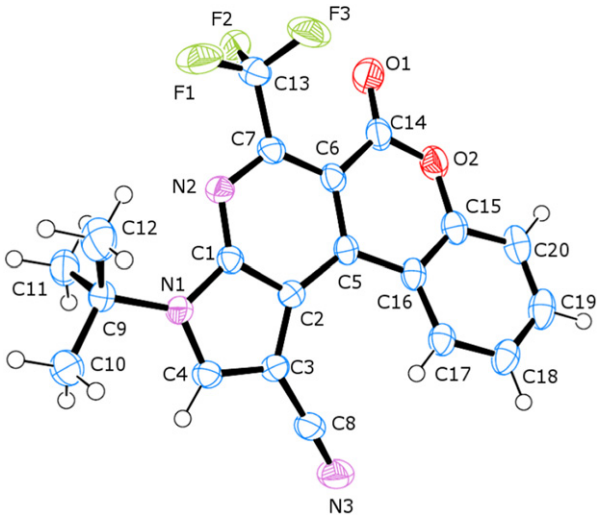


Fig. 4. Molecular structure of compound **8f**.

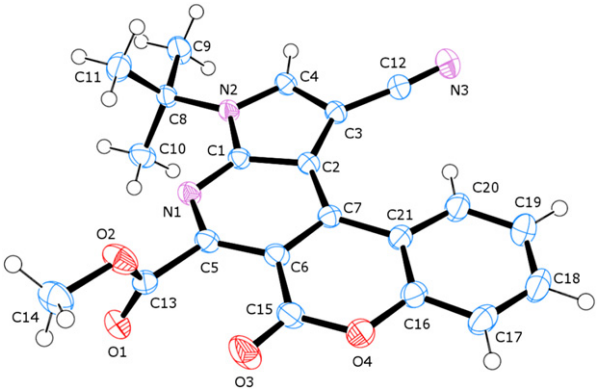


Fig. 5. Molecular structure of compound **8g**.

77.1(2)°. The logical explanation of this fact can be given by taking into account the van der Waals radii of the CF_3 group, which by the overlapping with carbonyl group in its vicinity triggers visible distortion of core geometry.

Because of the ambident character of heterocyclic amine, a nucleophilic attack of nitrogen or carbon on coumarin **2** would lead to different products. The first step of the reaction leading to **8** apparently involves an attack of the internal enamine β-carbon (in general, this atom is more nucleophilic than the primary amino group) at C-4 of **2** with concomitant elimination of HCl (intermediate **A**). Subsequent intramolecular attack of the amino group at the carbonyl group via intermediate **B** leads to the fused coumarin derivatives **8**. At the same time, for the initial attack of the 4-position by the amino group the reaction through the elimination–ring-closure sequence would result in isomeric γ-CF_3–pyridines. This direction was observed only in the case of 5-amino-3-methyl-1-phenylpyrazole (**7**), which reacts with coumarin **2a** as an aromatic amine[25] to give under the same conditions compound **9** with a completely different regiochemistry pattern (yield 51%, Scheme 2). The exact structure of **9** was established by ^1H, ^{13}C, and ^{19}F NMR spectra, in which we have observed the appearance of a quartet of methyl protons at 2.75 ppm ($^6J_{H,F}$=3.7 Hz), quartet of methyl carbon at 16.9 ppm ($^5J_{C,F}$=6.8 Hz), and quartet of the CF_3 group at −55.0 ppm ($^6J_{F,H}$=3.7 Hz). This can be regarded as a prove for structure **9**, where the methyl and trifluoromethyl groups are situated near each other.

Thus, the most important step determining the structure of a product is the addition to the first center of dinucleophile. From this point of view, it clearly appears that the less aromatic aminoheterocycles **3**–**6** have a proclivity to the formation of fused α-CF_3–pyridines **8**, while in aminopyrazole **7** and arylamines[25] the high degree of aromatization of the ring would be responsible for their observed different reactivity. The reaction of heterocyclic amines with coumarins **2** makes the latter compounds very useful for a combinatorial approach to the synthesis of novel heteroannulated pyridines with potential biological activity. However, it is necessary to mentioned that not all electron-rich aminoheterocycles reacted with **2** with the formation of the corresponding pyridines; in the cases of ethyl 5-aminothiophene-2-carboxylate, ethyl 5-aminofuran-2-carboxylate, and 5-aminouracil the reactions failed or leaded to the mixture of inseparable regioisomers.

It was also found that the condensation of coumarin **2a** with 1,3-*N*,*N*-dinucleophiles, such as 2-aminobenzimidazole and morpholine-4-carboxamidine, under the same reaction conditions affords target products **10a** and **10b** in high yields. Previously, non-fluorinated analogue of chromenopyrimidobenzimidazolone **10a** was obtained by the reaction of 2-aminobenzimidazole with **1a** in the presence of triethylamine and its structure was confirmed by X-ray diffraction analysis.[15] Molecules of this type consist of five planar ring fragments, however their molecular conformation apparently cannot be planar due to repulsion of the hydrogen atoms at C-1 and C-13. Hence, these molecules have a helical conformation and are chiral even though there are no asymmetric atoms, possessing so-called helical chirality.

The reaction of coumarin **2a** with dimethyl 1,3-acetonedicarboxylate in dioxane in the presence of triethylamine gave the expected benzo[*c*]coumarin **10c** in 88% yield, whereas the similar reaction of **2b** afforded a complex mixture of many unidentified products as well as low quantities of the corresponding triester, which was not isolated in a pure form (Fig. 2). The formation of compounds **10a**–**c** can proceed via both the 1,4- and 1,2-addition of the nitrogen or carbon atom of a 1,3-dinucleophile with subsequent ring closure, however we prefer the first mechanism since only 4-anilino-3-(trifluoroacetyl)coumarins are formed in high yields in the reaction of **2a** with aromatic amines.[25]

Further experiments were conducted to expand the utility of the reaction and substrate scope with a series of 1,2-dinucleophiles, such as hydrazines, alkyl thioglycolates, and methyl sarcosinate. We found that coumarin **2a**, when treated with methylhydrazine in refluxing toluene, underwent transformation into 1-methyl-3-(trifluoromethyl)chromeno[4,3-*c*]pyrazol-4(1*H*)-one **11a** (70% yield). This reaction exhibits high regioselectivity and pyrazole **11a** was isolated as the single product, the structures of which were independently confirmed by X-ray crystal structure analysis (Fig. 6). The formation of this pyrazole may be rationalized by initial 1,4-addition of the more nucleophilic secondary nitrogen atom of methylhydrazine on the C-4 atom of **2a** with concomitant elimination of HCl followed by the intramolecular attack at the CF_3CO group by the primary amino group. Attempts to use coumarin **2b** in the reaction with methylhydrazine failed to produce the desired product, affording a complex mixture of unidentified compounds.

It is of interest that coumarins **2a**,**b** react in different manner with phenylhydrazine to provide a completely different regiochemistry. Treatment of **2a**,**b** with phenylhydrazine in refluxing toluene produced 2-phenylchromeno[4,3-*c*]pyrazol-4-ones **11b**,**c** in 59–62% yields (Fig. 2). The choice between 2-phenyl- and 1-phenylchromeno[4,3-*c*]pyrazoles was made in favor of the former on the basis of spectroscopic data. It is known that a carbon adjacent to a substituted nitrogen (pyrrole-like) resonates upfield of the signal of that same carbon in the other isomer (pyridine-like) in isomeric pyrazoles.[34] The ^{13}C NMR spectra of **11a** and **11b** clearly demonstrated their structures by comparison of the C-3 signals (for **11a** 137.7 ppm, q, $^2J_{C,F}$=38.1 Hz; for **11b** 132.4 ppm, q, $^2J_{C,F}$=41.0 Hz). Moreover, a similar increase in $^2J_{C,F}$ values has been noted earlier for *N*-substituted 3-CF_3- and 5-CF_3–pyrazoles. On the whole, the

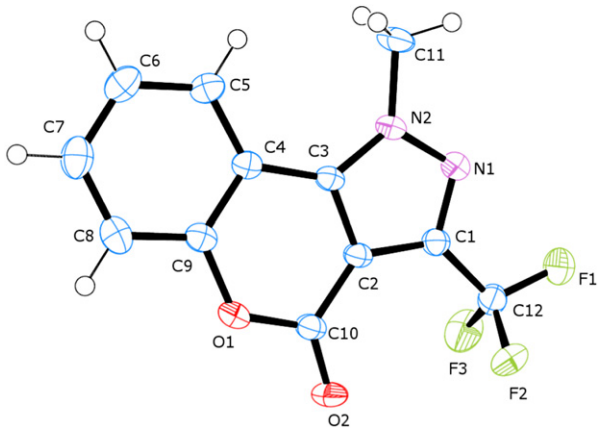
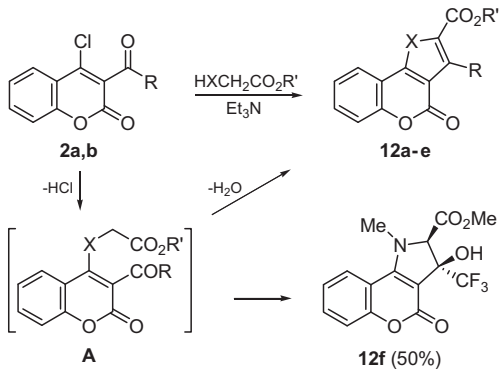


Fig. 6. Molecular structure of compound **11a**.

constant $^2J_{C,F}$ for *N*-substituted 3-CF_3–pyrazoles ranges from 36 to 40 Hz, while that for 5-CF_3–pyrazoles is known to vary from 38 to 43 Hz.[35] Additional support for the assignments was provided by the ^{1}H NMR spectra of **11a**–**c** on the basis of the H-9 signals, which were observed at 8.23, 8.09, and 8.13 ppm, respectively. Because of unfavorable steric interactions with the *peri*-H atom in the 1-phenylchromeno[4,3-*c*]pyrazoles, the phenyl substituent should predominantly be located in the non-planar position toward the coumarin ring and exerts a shielding effect on the H-9 proton. As a result, this proton should appear in a stronger field (in the series of 1-phenylchromeno[4,3-*c*]pyrazol-4-ones it is observed at 6.9–7.5 ppm).[34] Interestingly, although the chemistry of the tricyclic chromeno[4,3-*c*]pyrazol-4-one system has been well documented,[9,10,14,34,36] we have found that compounds **11a**–**c** are hitherto unreported.

Next, taking into account the above results and that the thiophene and pyrrole rings are important structural fragments of many natural and biologically active substances,[37] it was of interest to evaluate the behavior of coumarins **2a**,**b** in their reactions with alkyl thioglycolates and methyl sarcosinate. In this context, two papers are of interest when 4-hydroxycoumarin and 4-chloro-3-formylcoumarin (**1a**) are reacted with these 1,2-dinucleophiles to obtain the corresponding 3,4-fused coumarins.[11,22] We anticipated that alkyl thioglycolates and methyl sarcosinate might undergo a similar [3+2] cycloaddition with **2a**,**b** to give 3,4-heteroannulated coumarins **12**. In fact, it was found that treatment of **2a**,**b** with alkyl thioglycolates or methyl sarcosinate (1.1–2.0 equiv) in dichloromethane or DMF in the presence of triethylamine at room temperature for several hours resulted in the formation of the previously unknown coumarin derivatives **12a**–**e** in variable yields (24–83%).

In all cases, conjugated addition–elimination at the 4-position takes place (intermediate **A**, Scheme 3) with subsequent annulation of the thiophene or pyrrole core. The formation of the other regioisomer is not observed in these examples. The structure of the product **12a** was confirmed by X-ray crystal structure analysis (Fig. 7). In the case of **2a** and methyl sarcosinate, compound **12f** was obtained as the only isolated product in 50% yield. In contrast to the formation of chromeno[4,3-*b*]pyrrole **12e**, no elimination of the hydroxyl group and aromatization occurs; many attempts to dehydrate this product failed (AcOH/reflux, *p*-TSA/EtOH, DMF/TMSC). The X-ray crystal structure of **12f** unambiguously confirmed that the CO_2Me and CF_3 groups are situated trans to each other (Fig. 8).



12a: X = S, R = CF_3, R' = Me (83%)
12b: X = S, R = CO_2Me, R' = Me (58%)
12c: X = S, R = CF_3, R' = CH_2CH(Et)Bu (47%)
12d: X = S, R = CO_2Me, R' = CH_2CH(Et)Bu (54%)
12e: X = N, R = CO_2Me, R' = Me (24%)

Scheme 3.

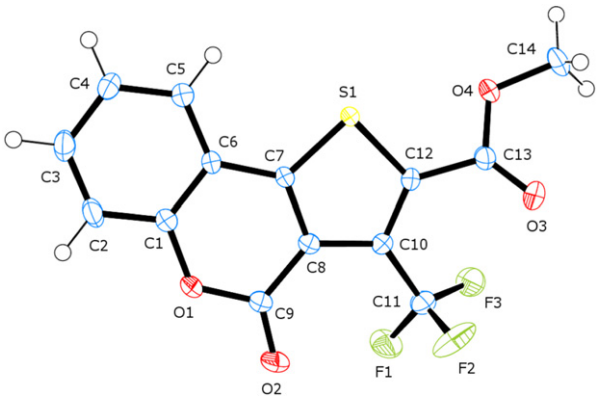


Fig. 7. Molecular structure of compound **12a**.

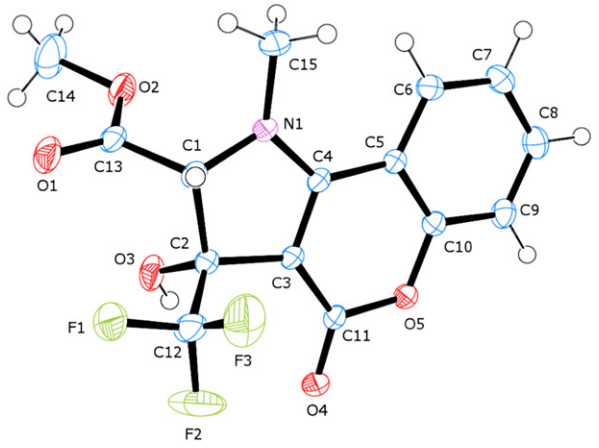


Fig. 8. Molecular structure of compound **12f**.

3. Conclusion

In conclusion, we have developed a simple and convenient method for the synthesis of 3,4-heteroannulated coumarins by formal [3+3] and [3+2] cyclocondensations of 4-chloro-3-substituted coumarins with electron-rich aminoheterocycles, hydrazines, alkyl thioglycolates, and methyl sarcosinate. The products constitute an important structural subunit of a variety of biologically active compounds, which are not readily available by other methods. The biological evaluation of the synthesized compounds is currently studied in our laboratories.

4. Experimental

4.1. General

NMR spectra were recorded on a Brucker AV 300 instruments. IR spectra were recorded on a Perkin–Elmer FT IR 1600 spectrometer (ATR). Mass spectra were obtained on a Hewlett–Packard HPGC/MS 5890/5972 instrument (EI, 70 eV) by GC inlet or on an MX-1321 instrument (EI, 70 eV) by direct inlet. Column chromatography was performed on silica gel (63–200 mesh, Merck), silica gel Merck 60 F_{254} plates were used for TLC. All solvents were purified and dried by standard methods. The starting 4-chloro-4-(trifluoroacetyl)coumarin (**2a**) was prepared according to described procedure.[25]

*4.1.1. Procedure for the synthesis of 4-chloro-4-(methoxalyl)coumarin (**2b**).* Synthesis was conducted in a pressure tube. To the suspension of 4-hydroxycoumarin (2.5 g, 15.4 mmol) in dry 1,4-

dioxane (20 mL) was added dry pyridine (2.56 g, 32.4 mmol). After a brief stirring, when the mixture became completely homogeneous, was added trimethylsilylchloride (2.01 g, 18.5 mmol). The reaction mixture was stirred for 1 h at room temperature. Then was added methyl oxalyl chloride (2.44 g, 20.0 mmol) and the mixture was stirred for another 2 h at 80–90 °C. To the cooled reaction mass was added 2.36 g (15.4 mmol) of phosphorus oxychloride and the mixture was stirred for 2 h at 60 °C. Then the reaction mass was diluted with ice water and extracted with chloroform (50 mL), the chloroform layer was separated, and the water phase was extracted two times with chloroform (50 mL). The combined extract was dried under sodium sulfate, chloroform was removed and the residue was dried in a high vacuum on a boiling water bath. Yield 3.83 g (94%), white solid, mp 110–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 3H), 7.37–7.46 (m, 2H), 7.69–7.74 (m, 1H), 8.01 (dd, 1H, J=8.0, 1.4 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 53.5, 117.2, 117.7, 121.4, 125.6, 127.0, 135.2, 151.3, 152.7, 157.5, 161.1, 181.5; MS (GC, 70 eV) m/z (%) 266 ([M]$^+$, 100); HRMS (EI): calcd for $C_{12}H_7ClO_5$ [M]$^+$ 266.01250, found 266.01255; IR (ATR, cm^{-1}) $\tilde{\nu}$ 1761 (m), 1712 (s), 1604 (m), 1544 (m), 1496 (w), 1451 (m), 1355 (w), 1314 (m), 1294 (m), 1261 (m), 1205 (m), 1087 (m), 1036 (m), 1003 (m), 960 (m), 881 (w), 856 (m), 759 (s), 732 (s), 662 (m), 584 (m).

4.2. General procedure for the synthesis of compounds 8–10

Coumarin **2a** or **2b** (2 mmol) and the corresponding aminoheterocycle (2.2 mmol) were placed in a pressure tube under the flow of dry argon and dissolved in dry DMF (10 mL) containing 1 mL of TMSCl. The mixture was heated at 100–120 °C during 2–12 h (controlled by TLC). Then this solution was evaporated under reduced pressure, treated with water, filtered, and dried on the air and recrystallized from an appropriate solvent, or was subjected to a column chromatography over silica gel.

*4.2.1. Methyl 3-ethyl-1-methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydrochromeno[4,3-d]imidazo[4,5-b]pyridine-5-carboxylate (**8a**).* Yield 74%, red solid, mp >375 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (t, 3H, J=7.0 Hz), 3.93 (s, 3H), 4.05 (s, 3H), 4.53 (q, 2H, J=7.0 Hz), 7.38–7.45 (m, 2H), 7.59–7.65 (m, 1H), 7.85 (dd, 1H, J=8.0, 1.2 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 12.8, 38.5, 39.6, 53.4, 109.7, 114.2, 118.2, 121.4, 124.4, 125.6, 128.3, 132.7, 148.5, 149.8, 152.0, 158.6, 166.8, 175.6; MS (GC, 70 eV) m/z (%) 369 ([M]$^+$, 100), 340 (30); HRMS (ESI): calcd for $C_{18}H_{15}N_3O_4S$ [M+H]$^+$ 370.08560, found 370.08576; IR (ATR, cm^{-1}) $\tilde{\nu}$ 2925 (w), 1726 (s), 1643 (w), 1608 (w), 1586 (w), 1480 (m), 1455 (m), 1426 (m), 1392 (s), 1284 (m), 1218 (s), 1145 (m), 1088 (m), 1047 (m), 1027 (m), 992 (s), 950 (m), 868 (m), 812 (m), 754 (s), 692 (s).

*4.2.2. 1-Methyl-3-phenyl-2-thioxo-5-(trifluoromethyl)-2,3-dihydrochromeno[4,3-d]imidazo[4,5-b]pyridin-6(1H)-one (**8b**).* Yield 85%, yellow solid, mp >375 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (s, 3H), 7.42–7.60 (m, 6H), 7.65–7.69 (m, 2H), 7.81–7.84 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 38.3, 111.9, 114.0, 116.9, 121.2 (q, $^1J_{C,F}$=274.0 Hz), 123.8, 124.6, 127.5, 128.2, 128.4, 129.2, 129.4, 132.9, 133.9, 141.6 (q, $^2J_{C,F}$=35.5 Hz), 147.4, 151.1, 155.9, 176.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −60.3 (CF_3); MS (GC, 70 eV) m/z (%) 427 ([M]$^+$, 92), 426 (100), 406 (23), 204 (15); HRMS (EI): calcd for $C_{21}H_{12}F_3N_3O_2S$ [M]$^+$ 427.05186, found 427.05165; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3038 (w), 1744 (m), 1592 (w), 1503 (w), 1475 (m), 1432 (m), 1374 (w), 1322 (m), 1305 (m), 1268 (w), 1246 (m), 1146 (s), 1075 (m), 1036 (m), 996 (m), 895 (w), 860 (m), 804 (w), 768 (s), 747 (s), 725 (s), 679 (s), 613 (m), 578 (s).

*4.2.3. Methyl 1-methyl-6-oxo-3-phenyl-2-thioxo-1,2,3,6-tetrahydrochromeno[4,3-d]imidazo[4,5-b]pyridine-5-carboxylate (**8c**).* Yield 82%, yellow solid, mp >375 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.84, 3.92 (both s, 3H), 7.53–7.58 (m, 5H), 7.58–7.67 (m, 2H), 7.71–7.76 (m, 2H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 38.5, 52.9, 109.6, 114.1, 117.4, 122.2, 124.7, 125.8, 128.6, 129.4, 129.5, 132.8, 134.1, 148.3, 149.0, 151.3, 158.4, 166.1, 175.9, 179.4; MS (GC, 70 eV) m/z (%) 417 ([M]$^+$, 2), 317 (29), 260 (39), 43 (100); HRMS (ESI): calcd for $C_{22}H_{15}N_3O_4S$ [M+H]$^+$ 418.0856, found 418.0857; IR (ATR, cm^{-1}) $\tilde{\nu}$ 2952 (w), 1739 (s), 1592 (m), 1495 (w), 1468 (w), 1428 (m), 1366 (m), 1334 (m), 1301 (s), 1267 (m), 1217 (s), 1173 (m), 1146 (m), 1075 (m), 1040 (m), 1019 (s), 953 (m), 865 (w), 794 (m), 758 (s), 745 (s), 707 (s), 647 (m).

*4.2.4. 2-(Dimethylamino)-5-(trifluoromethyl)-6H-chromeno[4,3-d][1,3]thiazolo[4,5-b]pyridin-6-one (**8d**).* Yield 54%, light brown solid, mp 251–252 °C; ^{1}H NMR (300 MHz, 80 °C, DMSO-d_6) δ 3.38 (s, 6H), 7.51 (d, 1H, J=8.4 Hz), 7.57 (t, 1H, J=7.2 Hz), 7.77 (t, 1H, J=8.0 Hz), 8.22 (d, 1H, J=8.0 Hz); ^{19}F NMR (282 MHz, DMSO-d_6) δ −62.8 (CF_3); MS (GC, 70 eV) m/z (%) 365 ([M]$^+$, 100), 350 (24), 336 (71), 330 (44), 316 (34); HRMS (ESI): calcd for $C_{16}H_{10}F_3N_3O_2S$ [M+H]$^+$ 366.05186, found 366.05212; IR (ATR, cm^{-1}) $\tilde{\nu}$ 2953 (w), 1742 (s), 1611 (m), 1586 (m), 1543 (m), 1510 (m), 1458 (w), 1433 (m), 1411 (m), 1392 (s), 1357 (m), 1309 (m), 1274 (m), 1211 (m), 1197 (m), 1178 (s), 1145 (s), 1066 (s), 985 (s), 910 (s), 855 (m), 840 (w), 802 (m), 756 (s), 733 (s), 700 (m), 676 (m), 657 (m).

*4.2.5. 2-(1-Piperidinyl)-5-(trifluoromethyl)-6H-chromeno[4,3-d][1,3]thiazolo[4,5-b]pyridin-6-one (**8e**).* Yield 63%, brown solid, mp 244–245 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79 (br s, 6H), 3.84 (br s, 4H), 7.34–7.42 (m, 2H), 7.57–7.63 (m, 1H), 8.00 (dd, 1H, J=8.0, 0.8 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.0, 25.5, 50.1, 107.9, 115.3, 117.9, 120.2, 121.2 (q, $^1J_{C,F}$=274.2 Hz), 124.6, 125.8, 132.8, 138.9 (q, $^2J_{C,F}$=35.4 Hz), 152.6, 155.9, 158.7, 166.7, 171.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.3 (CF_3); MS (GC, 70 eV) m/z (%) 405 ([M]$^+$, 100), 376 (54), 349 (29), 249 (15); HRMS (ESI): calcd for $C_{19}H_{14}F_3N_3O_2S$ [M+H]$^+$ 406.08316, found 406.08282; IR (ATR, cm^{-1}) $\tilde{\nu}$ 2933 (w), 2867 (w), 1742 (s), 1601 (w), 1584 (m), 1543 (m), 1506 (m), 1453 (w), 1422 (s), 1393 (m), 1358 (m), 1333 (m), 1307 (m), 1262 (m), 1198 (s), 1174 (s), 1145 (s), 1168 (s), 1008 (m), 983 (s), 907 (w), 884 (m), 852 (m), 803 (m), 756 (s), 732 (s), 701 (m), 671 (m), 657 (m).

*4.2.6. 3-(tert-Butyl)-6-oxo-5-(trifluoromethyl)-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-1-carbonitrile (**8f**).* Yield 72%, white solid isolated by preparative chromatography (heptane/AcOEt 2:1), mp 267–269 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (s, 9H), 7.43–7.56 (m, 2H), 7.65–7.72 (m, 1H), 8.32 (s, 1H), 8.70 (dd, 1H, J=8.1, 1.2 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 29.2, 60.7, 86.1, 110.6, 114.6, 115.8, 116.0, 117.3, 121.3 (q, $^1J_{C,F}$=275.1 Hz), 124.4, 129.2, 133.4, 139.5, 140.7, 143.4 (q, $^2J_{C,F}$=36.6 Hz), 146.5, 152.0, 156.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −54.6 (CF_3); MS (EI, 70 eV) m/z (%) 385 ([M]$^+$, 17), 330 (19), 329 (100), 309 (23); HRMS (ESI): calcd for $C_{20}H_{14}F_3N_3O_2$ [M+H]$^+$ 386.11109, found 386.11134; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3472 (w), 2981 (w), 2215 (m), 1747 (m), 1545 (m), 1362 (m), 1147 (s), 1008 (s), 757 (m), 747 (s).

*4.2.7. Methyl 3-(tert-butyl)-1-cyano-6-oxo-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-5-carboxylate (**8g**).* Yield 53%, white solid isolated by preparative chromatography (heptane/AcOEt 2:1), mp 245–247 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.81 (s, 9H), 4.01 (s, 3H), 7.36 (dd, 1H, J=8.1, 1.6 Hz), 7.40–7.46 (m, 1H), 7.54–7.61 (m, 1H), 8.18 (s, 1H), 8.79 (dd, 1H, J=8.1, 1.7 Hz); ^{13}C NMR (63 MHz $CDCl_3$) δ 29.2, 53.4, 60.5, 85.6, 109.2, 113.3, 116.2, 116.7, 117.7, 124.6, 129.1, 133.1, 138.6, 138.9, 148.4, 149.3, 152.1, 159.2, 167.2; MS (EI, 70 eV) m/z (%) 375 ([M]$^+$, 27), 319 (50), 288 (46), 287 (100), 259 (25); HRMS (ESI): calcd for $C_{21}H_{17}N_3O_4$ [M+H]$^+$ 376.12918, found 376.12883; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3438 (w), 2210 (m), 1728 (s), 1544 (s), 1159 (s), 1058 (s), 748 (m), 734 (s).

*4.2.8. 3-Cyclohexyl-6-oxo-5-(trifluoromethyl)-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-1-carbonitrile (**8h**).* Yield 46%, white

solid isolated by preparative chromatography (heptane/AcOEt 2:1), mp 288–290 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.33–2.17 (m, 10H), 4.79–5.26 (m, 1H), 7.34–7.61 (m, 2H), 7.61–7.80 (m, 1H), 8.60 (dd, 1H, J=8.1, 1.6 Hz), 9.28 (s, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −53.7 (CF_3); MS (EI, 70 eV) m/z (%) 411 ([M]$^+$, 39), 330 (24), 329 (100); HRMS (ESI): calcd for $C_{22}H_{16}F_3N_3O_2$ [M+H]$^+$ 412.12674, found 412.12743; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3124 (w), 2228 (m), 1736 (s), 1586 (s), 1180 (s), 1145 (s), 754 (m), 730 (s).

*4.2.9. 3-Cyclopentyl-6-oxo-5-(trifluoromethyl)-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-1-carbonitrile (**8i**).* Yield 58%, white solid isolated by preparative chromatography (heptane/AcOEt 2:1), mp 256–258 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.63–1.82 (m, 2H), 1.84–2.10 (m, 4H), 2.18–2.37 (m, 2H), 5.23–5.41 (m, 1H), 7.41–7.60 (m, 2H), 7.68–7.82 (m, 1H), 8.59 (dd, 1H, J=8.1, 1.1 Hz), 9.24 (s, 1H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 23.6, 32.2, 57.1, 85.8, 110.6, 113.5, 115.6, 116.1, 116.9, 119.2, 121.4 (q, CF_3, $^1J_{C,F}$=275.0 Hz), 124.0, 128.0, 129.0, 129.1, 133.5, 139.9, 142.6 (q, $^2J_{C,F}$=36.5 Hz), 145.8, 151.5, 156.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −52.2 (CF_3); MS (EI, 70 eV) m/z (%) 397 ([M]$^+$, 25), 329 (100), 309 (42); HRMS (EI): calcd for $C_{21}H_{14}N_3F_3O_2$ [M]$^+$ 397.10326, found 397.10325; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3142 (w), 2217 (m), 1746 (s), 1552 (s), 1453 (m), 1359 (m), 1154 (s), 757 (s), 609 (m).

*4.2.10. Methyl 1-cyano-3-cyclopentyl-6-oxo-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-5-carboxylate (**8j**).* Yield 38%, white solid isolated by preparative chromatography (heptane/AcOEt 2:1), mp 225–227 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77–1.95 (m, 6H), 2.23–2.40 (m, 2H), 4.02 (s, 3H), 5.34–5.48 (m, 1H), 7.30–7.51 (m, 2H), 7.55–7.64 (m, 1H), 8.12 (s, 1H), 8.87 (dd, 1H, J=8.1, 1.0 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.0, 33.1, 53.4, 56.9, 87.0, 109.8, 112.1, 116.3, 116.7, 117.8, 124.7, 129.2, 133.2, 138.0, 139.1, 148.2, 150.6, 152.3, 159.2, 167.3; HRMS (ESI): calcd for $C_{22}H_{17}N_3O_4$ [M+H]$^+$ 388.12918, found 388.12886; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3114 (w), 2218 (w), 1729 (s), 1549 (s), 1398 (m), 1216 (s), 763 (s).

*4.2.11. Methyl 1-cyano-3-(4-methylphenyl)-6-oxo-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-5-carboxylate (**8k**).* Yield 42%, yellow solid isolated by preparative chromatography (heptane/AcOEt 2:1), mp 245 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3H), 4.04 (s, 3H), 7.37–7.59 (m, 6H), 7.66–7.75 (m, 1H), 8.34 (s, 1H), 8.96 (dd, 1H, J=8.1, 1.1 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.2, 53.3, 88.1, 110.2, 112.3, 116.1, 117.8, 124.4, 124.7, 125.0, 129.2, 130.3, 133.0, 133.4, 139.3, 139.4, 140.5, 148.0, 151.4, 152.3, 158.9, 166.9; MS (EI, 70 eV) m/z (%) 409 ([M]$^+$, 100), 378 (44), 350 (59), 349 (30), 322 (18); HRMS (EI): calcd for $C_{24}H_{15}N_3O_4$ [M]$^+$ 409.10571, found 409.10597; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3136 (w), 2215 (m), 1727 (s), 1544 (s), 1415 (m), 1225 (s), 756 (m), 660 (s).

*4.2.12. 3-Hexyl-6-oxo-5-(trifluoromethyl)-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-1-carbonitrile (**8l**).* Yield 45%, white solid isolated by preparative chromatography (heptane/AcOEt 2:1), mp 177 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (t, 3H, J=6.3 Hz), 1.24–1.37 (m, 6H), 1.90–1.99 (m, 2H), 4.45–4.54 (m, 2H), 7.37–7.56 (m, 2H), 7.62–7.72 (m, 1H), 8.51 (d, 1H, J=8.1 Hz), 9.15 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 13.8, 21.9, 25.5, 28.8, 30.6, 45.3, 84.7, 109.8, 114.6, 115.5, 116.3, 118.1, 122.8 (q, CF_3, $^1J_{C,F}$=275.0 Hz), 124.4, 124.7, 128.9, 132.6, 146.4 (q, $^2J_{C,F}$=36.5 Hz), 147.9, 149.8, 151.4, 156.9; ^{19}F NMR (282 MHz, DMSO-d_6) δ −53.7 (CF_3); MS (EI, 70 eV) m/z (%) 413 ([M]$^+$, 100), 384 (22), 329 (83); HRMS (EI): calcd for $C_{22}H_{18}F_3N_3O_2$ [M]$^+$ 413.13456, found 413.13447; IR (ATR, cm^{-1}) $\tilde{\nu}$ 2229 (m), 1727 (s), 1589 (s), 1389 (m), 1365 (m), 1145 (s), 755 (s).

*4.2.13. 3-(2-Methylcyclohexyl)-6-oxo-5-(trifluoromethyl)-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-1-carbonitrile (**8m**).* Yield 44%, white solid isolated by preparative chromatography (heptane/AcOEt 2:1), mp 259–261 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.64 (d, 3H, J=6.0 Hz), 1.34–1.63 (m, 3H), 1.77–2.05 (m, 6H), 4.59–4.88 (m, 1H), 7.43–7.55 (m, 2H), 7.66–7.78 (m, 1H), 8.65 (dd, 1H, J=8.0, 1.0 Hz), 9.30 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 12.0, 18.6, 25.1, 25.3, 32.2, 33.9, 57.7, 85.4, 110.2, 114.8, 116.2, 116.4, 118.3, 122.8 (q, $^1J_{C,F}$=275.0 Hz), 124.7, 124.8, 124.9, 132.7, 144.7 (q, $^2J_{C,F}$=35.1 Hz), 148.1, 150.1, 151.5, 157.0; ^{19}F NMR (282 MHz, DMSO-d_6) −53.6 (CF_3); MS (EI, 70 eV) m/z (%) 425 ([M]$^+$, 33), 330 (72), 329 (100); HRMS (EI): calcd for $C_{23}H_{18}F_3N_3O_2$ [M]$^+$ 425.13456, found 425.13425; IR (ATR, cm^{-1}) $\tilde{\nu}$ 2228 (m), 1746 (s), 1586 (s), 1397 (m), 1367 (m), 1161 (s), 754 (s).

*4.2.14. Methyl 1-cyano-3-(2-methylcyclohexyl)-6-oxo-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-5-carboxylate (**8n**).* Yield 40%, white solid isolated by preparative chromatography (heptane/AcOEt 2:1), mp 230–232 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.63 (d, 3H, J=6.0 Hz), 1.30–1.60 (m, 3H), 1.67–2.18 (m, 6H), 4.05 (s, 3H), 4.68 (br s, 1H), 7.41–7.56 (m, 2H), 7.61–7.71 (m, 1H), 8.62 (d, 1H, J=7 Hz), 9.08 (s, 1H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 12.0, 18.5, 25.1, 25.3, 30.8, 32.3, 33.9, 52.5, 83.7, 108.1, 113.4, 115.8, 116.9, 118.7, 124.2, 124.4, 124.9, 132.4, 136.2, 147.4, 149.1, 151.6, 159.2, 164.9; HRMS (EI): calcd for $C_{24}H_{21}N_3O_4$ (M$^+$) 415.15326, found 415.15328; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3093 (w), 2930 (w), 2221 (m), 1739 (s), 1582 (m), 1398 (m), 1210 (s), 1053 (s), 754 (s).

*4.2.15. 3-(4-Methoxybenzyl)-6-oxo-5-(trifluoromethyl)-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-1-carbonitrile (**8o**).* Yield 41%, white solid isolated by preparative chromatography (heptane/AcOEt 2:1), mp 264–266 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.74 (s, 3H), 5.70 (s, 2H), 6.93–7.00 (m, 2H), 7.45–7.59 (m, 4H), 7.67–7.85 (m, 1H), 8.63–8.71 (m, 1H), 9.28 (s, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −53.7 (CF_3); MS (EI, 70 eV) m/z (%) 449 ([M]$^+$, 25), 122 (16), 121 (100), 63 (18), 44 (11); HRMS (ESI): calcd for $C_{24}H_{14}F_3N_3O_3$ [M]$^+$ 449.09818, found 449.09833; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3461 (w), 2220 (m), 1736 (s), 1513 (s), 1145 (s), 1008 (s), 762 (m), 757 (s).

*4.2.16. Methyl 1-cyano-3-(4-methoxybenzyl)-6-oxo-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-5-carboxylate (**8p**).* Yield 55%, white solid isolated by preparative chromatography (heptane/AcOEt 2:1), mp 227–229 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.72, 4.10 (both s, 3H), 5.50 (s, 2H), 6.79–6.84 (m, 2H), 7.18–7.29 (m, 4H), 7.43–7.51 (m, 1H), 7.78 (s, 1H), 8.55 (dd, 1H, J=8.1, 1.7 Hz); ^{13}C NMR (63 MHz, DMSO-d_6) δ 48.3, 52.5, 55.0, 83.5, 108.1, 113.2, 114.1, 115.8, 116.8, 118.6, 124.2, 124.9, 127.9, 129.4, 129.7, 132.3, 136.2, 142.6, 147.5, 148.5, 151.5, 159.1, 164.8; HRMS (EI): calcd for $C_{25}H_{17}N_3O_5$ [M]$^+$ 439.11627, found 439.11640; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3131 (w), 2217 (m), 1730 (s), 1514 (s), 1224 (s), 1168 (s), 753 (s).

*4.2.17. 3-(tert-Butyl)-6-oxo-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-1-carbonitrile (**8q**).* Yield 40%, yellow solid isolated by preparative chromatography (heptane/AcOEt 2:1), mp 252–254 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.86 (s, 9H), 7.41–7.56 (m, 2H), 7.65–7.80 (m, 1H), 8.76 (dd, 1H, J=8.1, 1.1 Hz), 8.93 (s, 1H), 9.18 (s, 1H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 28.6, 59.9, 83.6, 111.6, 112.1, 116.4, 117.6, 124.1, 128.5, 132.0, 132.8, 136.2, 140.9, 145.8, 149.6, 151.9, 159.9; HRMS (EI): calcd for $C_{19}H_{15}N_3O_2$ [M]$^+$ 317.11588, found 317.11601; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3132 (w), 2216 (w), 1726 (s), 1592 (m), 1364 (m), 1181 (s), 1081 (m), 758 (s), 745 (s).

*4.2.18. 2,4-Dimethyl-6-(trifluoromethyl)-1H-chromeno[4′,3′:4,5]pyrido[2,3-d]pyrimidine-1,3,7(2H,4H)-trione (**8r**).* Yield 73%, white solid, mp >250 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.37, 3.66 (both s, 3H), 7.27–7.33 (m, 1H), 7.43 (dd, 1H, J=8.4, 1.1 Hz), 7.67–7.73 (m, 1H), 8.15 (dd, 1H, J=8.4, 1.4 Hz); ^{19}F NMR (282 MHz, DMSO-d_6) δ −64.3 (CF_3); MS (GC, 70 eV) m/z (%) 377 ([M]$^+$, 100); HRMS (ESI): calcd for

$C_{17}H_{10}F_3N_3O_4$ $[M+H]^+$ 378.06962, found 378.06916; IR (ATR, cm^{-1}) $\tilde{\nu}$ 1757 (m), 1715 (s), 1660 (s), 1589 (m), 1552 (s), 1461 (s), 1366 (m), 1289 (w), 1231 (s), 1214 (s), 1193 (s), 1155 (s), 1134 (m), 1081 (m), 1011 (s), 970 (w), 935 (m), 823 (w), 775 (s), 733 (s), 684 (s).

*4.2.19. 8-Methyl-10-phenyl-7-(trifluoromethyl)chromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(10H)-one (**9**).* Yield 51%, yellow solid, mp 219 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 2.75 (q, 3H, $^6J_{H,F}$=3.7 Hz), 7.30–7.41 (m, 3H), 7.53–7.62 (m, 3H), 8.22–8.26 (m, 2H), 8.51 (dd, 1H, J=7.9, 1.5 Hz); ^{13}C NMR (300 MHz, DMSO-d_6) δ 16.9 (q, $^5J_{C,F}$=6.8 Hz), 109.6, 114.8, 116.8, 118.4, 121.5, 121.9 (q, $^1J_{C,F}$=276.6 Hz), 124.8, 125.6, 126.9, 129.2, 133.2, 136.6 (q, $^2J_{C,F}$=36.6 Hz), 138.1, 144.0, 151.8, 152.0, 152.5, 157.4; ^{19}F NMR (282 MHz, DMSO-d_6) δ −55.0 (q, $^6J_{F,H}$=3.7 Hz, CF_3); MS (GC, 70 eV) m/z (%) 395 ($[M]^+$, 100); HRMS (ESI): calcd for $C_{21}H_{12}F_3N_3O_2$ $[M+H]^+$ 396.09544, found 396.09499; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3072 (w), 1738 (s), 1593 (w), 1568 (s), 1498 (m), 1466 (m), 1420 (m), 1390 (w), 1364 (m), 1275 (w), 1242 (m), 1213 (s), 1175 (s), 1136 (s), 1075 (m), 991 (w), 886 (m), 835 (w), 797 (w), 768 (s), 752 (s), 686 (m), 656 (m).

*4.2.20. 7-(Trifluoromethyl)-6H-chromeno[3′,4′:5,6]pyrimido[1,2-a]benzimidazol-6-one (**10a**).* Yield 60%, brown solid, mp 275–276 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 7.51–7.59 (m, 2H), 7.68–7.76 (m, 2H), 7.96 (t, 1H, J=7.2 Hz), 8.08 (d, 1H, J=8.2 Hz), 8.16 (d, 1H, J=8.5 Hz), 8.53 (d, 1H, J=7.5 Hz); ^{13}C NMR (63 MHz, DMSO-d_6) δ 101.6, 116.4, 117.6, 118.3, 120.2 (q, $^1J_{C,F}$=278.1 Hz), 120.9, 123.0, 123.9, 125.6, 127.9, 128.6, 132.9, 136.5, 145.8, 148.5 (q, $^2J_{C,F}$=38.0 Hz), 151.4, 152.9, 155.0; ^{19}F NMR (282 MHz, DMSO-d_6) δ −65.1 (CF_3); MS (GC, 70 eV) m/z (%) 355 ($[M]^+$, 100), 326 (10); HRMS (EI): calcd for $C_{18}H_8F_3N_3O_2$ $[M^+]$ 355.05630, found 355.06687; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3077 (w), 1745 (s), 1675 (w), 1604 (m), 1590 (m), 1562 (w), 1497 (m), 1479 (m), 1453 (m), 1374 (m), 1313 (m), 1266 (w), 1253 (m), 1229 (w), 1183 (s), 1145 (s), 1087 (m), 1044 (m), 1027 (m), 1010 (m), 958 (m), 920 (m), 885 (w), 842 (w), 794 (w), 754 (s), 746 (s), 663 (w), 622 (w).

*4.2.21. 2-Morpholino-4-(trifluoromethyl)-5H-chromeno[4,3-d]pyrimidin-5-one (**10b**).* Yield 80%, yellow solid, mp >375 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 3.04 (br s, 8H, CH_2), 7.45–7.71 (m, 2H), 8.22–8.50 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ −65.0 (CF_3); MS (GC, 70 eV) m/z (%) 351 ($[M]^+$, 100); HRMS (EI): calcd for $C_{16}H_{12}F_3N_3O_3$ $[M]^+$ 351.0825, found 351.0826; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3072 (w), 1737 (s), 1593 (w), 1568 (m), 1497 (m), 1466 (m), 1419 (m), 1390 (w), 1365 (m), 1341 (w), 1275 (w), 1241 (s), 1212 (s), 1175 (s), 1136 (s), 1074 (m), 1021 (m), 886 (m), 835 (w), 797 (s), 768 (s), 751 (s), 730 (m), 686 (s), 656 (s).

*4.2.22. Dimethyl 9-hydroxy-6-oxo-7-(trifluoromethyl)-6H-benzo[c]chromene-8,10-dicarboxylate (**10c**).* To a dry 1,4-dioxane solution (10 mL) of 4-chloro-3-(trifluoroacetyl)coumarin **2a** (0.25 g, 0.9 mmol) were added dimethyl 1,3-acetonedicarboxylate (0.174 g, 1 mmol) and triethylamine (0.136 g, 1.35 mmol) and the reaction mixture was refluxed for 3 h. After the reaction was completed (TLC control), the solvent was removed and the residue was washed with water to remove the salts. Then the crude product was purified by column chromatography (silica gel, ethyl acetate, R_f=0.51 ethyl acetate/MeOH=20:1) to give **10c**. Yield 88% (0.312 g), white solid, mp 198–199 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 3.84, 3.93 (both s, 3H), 7.35–7.43 (m, 2H), 7.59–7.64 (m, 2H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 52.9, 53.1, 115.5, 117.3, 121.6, 122.6 (q, $^1J_{C,F}$=274.2 Hz), 124.5, 124.9, 129.4 (q, $^2J_{C,F}$=34.0 Hz), 131.9, 135.6, 150.7, 155.9, 159.9, 160.1, 165.4, 167.4, 175.5; ^{19}F NMR (282 MHz, DMSO-d_6) δ −54.3 (CF_3); MS (GC, 70 eV) m/z (%) 396 ($[M]^+$, 10), 321 (100); HRMS (ESI): calcd for $C_{18}H_{11}F_3O_7$ $[M+H]^+$ 397.0513, found 397.0514; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3340 (m), 1740 (w), 1719 (m), 1577 (w), 1561 (w), 1497 (w), 1454 (w), 1421 (w), 1358 (w), 1317 (w), 1243 (m), 1205 (m), 1161 (m), 1146 (m), 1124 (m), 972 (m), 893 (w), 850 (m), 810 (m), 755 (s), 702 (s), 643 (s).

4.3. General procedures for the synthesis of compounds 11

To a toluene solution of coumarin **2a** or **2b** (1 mmol) was slowly added the corresponding hydrazine (2.2 mmol) and the reaction mixture was reflux for 3–4 h. After the reaction was finished (TLC control), the solvent was removed, the residue was treated with water and finally dried in vacuum. The purification was performed by column chromatography (silica gel).

*4.3.1. 1-Methyl-3-(trifluoromethyl)chromeno[4,3-c]pyrazol-4(1H)-one (**11a**).* Yield 70%, yellow solid, mp 231–232 °C; ^1H NMR (250 MHz, DMSO-d_6) δ 4.39 (s, 3H), 7.44–7.53 (m, 2H), 7.65–7.72 (m, 1H), 8.23 (d, 1H, J=8.0 Hz); ^{13}C NMR (63 MHz, DMSO-d_6) δ 40.9, 104.4, 110.8, 117.6, 120.1 (q, $^1J_{C,F}$=269.0 Hz), 123.8, 124.9, 132.1, 137.7 (q, $^2J_{C,F}$=38.1 Hz), 142.9, 152.3, 154.1; ^{19}F NMR (282 MHz, DMSO-d_6) δ −56.0 (CF_3); MS (GC, 70 eV) m/z (%) 268 ($[M]^+$, 100); HRMS (ESI): calcd for $C_{12}H_7F_3N_2O_2$ $[M+H]^+$ 269.0532, found 269.0533; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3108 (s), 1740 (m), 1614 (m), 1556 (w), 1511 (w), 1442 (w), 1327 (m), 1291 (m), 1237 (w), 1181 (s), 1132 (s), 1040 (m), 1019 (s), 982 (s), 891 (s), 759 (s), 729 (s), 705 (m), 663 (m).

*4.3.2. 2-Phenyl-3-(trifluoromethyl)chromeno[4,3-c]pyrazol-4(2H)-one (**11b**).* Yield 59%, pink solid, mp 166–167 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 7.44 (dt, 1H, J=7.3, 1.0 Hz), 7.52 (dd, 1H, J=8.3, 0.8 Hz), 7.62–7.71 (m, 6H), 8.09 (dd, 1H, J=7.8, 1.5 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 107.5, 113.0, 117.2, 118.4 (q, $^1J_{C,F}$=268.0 Hz), 122.5, 125.1, 126.3, 129.4, 130.8, 131.6, 132.4 (q, $^2J_{C,F}$=41.0 Hz), 138.4, 148.5, 152.3, 154.3; ^{19}F NMR (282 MHz, DMSO-d_6) δ −54.9 (CF_3); MS (GC, 70 eV) m/z (%) 330 ($[M]^+$, 100), 309 (11), 77 (18); HRMS (ESI): calcd for $C_{17}H_9F_3N_2O_2$ $[M+H]^+$ 331.0689, found 331.0692; IR (ATR, cm^{-1}) $\tilde{\nu}$ 1754 (s), 1619 (w), 1592 (w), 1592 (w), 1567 (w), 1520 (w), 1497 (w), 1448 (w), 1393 (w), 1328 (m), 1220 (m), 1191 (s), 1158 (m), 1125 (s), 1082 (m), 1033 (m), 999 (s), 982 (m), 898 (s), 769 (m), 754 (s), 687 (s), 661 (m).

*4.3.3. Methyl 4-oxo-2-phenyl-2,4-dihydrochromeno[4,3-c]pyrazole-3-carboxylate (**11c**).* Yield 62%, pink solid, mp 255–256 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 3H), 7.32 (dt, 1H, J=7.8, 1.1 Hz), 7.39 (dd, 1H, J=8.3, 0.9 Hz), 7.47–7.57 (m, 6H), 8.13 (dd, 1H, J=7.8, 1.5 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 53.6, 108.2, 113.9, 117.5, 122.9, 124.6, 124.7, 129.4, 129.8, 131.0, 135.7, 138.9, 149.0, 153.0, 156.0, 159.4; MS (GC, 70 eV) m/z (%) 320 ($[M]^+$, 100), 289 (21), 261 (11), 143 (11), 77 (28); HRMS (ESI): calcd for $C_{18}H_{12}N_2O_4$ $[M+H]^+$ 321.08698, found 321.08716; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3062 (s), 1755 (w), 1721 (s), 1620 (m), 1593 (m), 1557 (m), 1515 (w), 1496 (m), 1447 (m), 1427 (m), 1393 (m), 1325 (m), 1275 (m), 1235 (s), 1163 (m), 1041 (s), 1015 (s), 983 (m), 945 (m), 912 (w), 897 (m), 830 (m), 786 (m), 758 (s), 743 (s), 732 (m), 701 (m), 688 (s).

4.4. General procedures for the synthesis of compounds 12

The coumarin derivative (1.0 mmol) was dissolved in 3 mL of dry dichloromethane, then 1.1–2.0 equiv of the corresponding alkyl thioglycolate or methyl sarcosinate in a small amount of dichloromethane and 4–5 equiv of NEt_3 were added dropwise at 0 °C. After removal of the ice bath the solution was stirred at ~20 °C for several hours (3–16 h). Subsequently water was added and the mixture was extracted with dichloromethane or ethyl acetate. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by washing with acetone or by column chromatography to give the desired products as white solids.

*4.4.1. Methyl 4-oxo-3-(trifluoromethyl)-4H-thieno[3,2-c]chromene-2-carboxylate (**12a**).* Yield 83% (196 mg), mp 222–223 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.95 (s, 3H), 7.44 (m, 1H), 7.53 (dd, 1H, J=8.2, 0.8 Hz), 7.70 (m, 1H), 8.05 (dd, 1H, J=7.7, 1.5 Hz); ^{13}C NMR (63 MHz, DMSO-d_6) δ 54.3, 115.0, 117.1, 120.4 (q, $^1J_{C,F}$=272.7 Hz), 121.4 (q, $^3J_{C,F}$=1.4 Hz), 124.5, 125.4, 128.1 (q, $^2J_{C,F}$=37.7 Hz), 135.7 (q, $^3J_{C,F}$=3.7 Hz), 133.0, 151.2, 151.3, 153.6, 160.4; ^{19}F NMR (282 MHz, DMSO-d_6) δ −55.7 (CF_3); MS (EI, 70 eV) m/z (%) 328 ([M]$^+$, 100), 297 (99), 225 (13), 213 (15), 169 (9), 144 (10); HRMS (EI): calcd for $C_{14}H_7O_4F_3S$ [M]$^+$ 328.00117, found 328.00074; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3446 (w), 3026 (w), 2953 (w), 2846 (w), 1738 (s), 1610 (m), 1586 (m), 1536 (m), 1503 (m), 1482 (m), 1438 (m), 1402 (m), 1369 (w), 1317 (m), 1281 (m), 1261 (m), 1250 (m), 1229 (s), 1170 (s), 1133 (s), 1078 (m), 1030 (m). Anal. Calcd for $C_{14}H_7F_3O_4S$ (328.26): C, 51.22; H, 2.15. Found: C, 51.00; H, 2.33.

*4.4.2. Dimethyl 4-oxo-4H-thieno[3,2-c]chromene-2,3-dicarboxylate (**12b**).* Yield 58% (139 mg), mp 229–231 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.89, 3.91 (both s, 3H), 7.43 (dt, 1H, J=7.6, 0.9 Hz), 7.52 (dd, 1H, J=8.5, 0.8 Hz), 7.68 (m, 1H), 8.04 (dd, 1H, J=7.8, 1.4 Hz); ^{13}C NMR (63 MHz, DMSO-d_6) δ 53.4, 53.7, 115.7, 117.6, 122.6, 125.0, 125.6, 129.4, 133.1, 138.3, 151.6, 152.0, 155.1, 160.1, 163.5; MS (EI, 70 eV) m/z (%) 318 ([M]$^+$, 83), 287 (100), 259 (6), 229 (8), 202 (14), 144 (9); HRMS (ESI-TOF/MS): calcd for $C_{15}H_{10}O_6S$ [M+H]$^+$ 319.0271, found 319.0272; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3020 (w), 2961 (w), 1747 (m), 1735 (m), 1709 (s), 1606 (m), 1583 (m), 1537 (m), 1494 (m), 1481 (m), 1440 (m), 1425 (m), 1403 (m), 1332 (w), 1293 (s), 1275 (m), 1238 (s), 1218 (s), 1187 (m), 1161 (m), 1139 (s), 1118 (m), 1082 (m), 1059 (m), 1037 (m), 1007 (s). Anal. Calcd for $C_{15}H_{10}O_6S$ (318.30): C, 56.60; H, 3.17. Found: C, 56.49; H, 3.38.

*4.4.3. 2-Ethylhexyl 4-oxo-3-(trifluoromethyl)-4H-thieno[3,2-c]chromene-2-carboxylate (**12c**).* 4-Chloro-3-(trifluoroacetyl)coumarin **2a** (200 mg, 0.72 mmol) and 2-ethylhexylthioglycolate (0.2 mL, 0.95 mmol) were dissolved in 6 mL of dry DMF and cooled to 0 °C. Then NEt_3 (0.44 mL, 3.17 mmol) was added dropwise. After stirring at 20 °C for 16 h, TMSCl (0.46 mL, 3.60 mmol) was added. The mixture was stirred at 100 °C for 6 h and then poured onto ice water. The resulting precipitate was washed with water and purified by column chromatography (heptane/EtOAc=30:1→15:1) to give **12c** as a white solid. Yield 47% (145 mg), mp 104–105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.8–1.0 (m, 6H), 1.50–1.2 (m, 8H), 1.71 (sept, 1H, J=5.8 Hz), 4.30 (d, 2H, J=5.7 Hz), 7.34 (t, 1H, J=7.6 Hz), 7.41 (d, 1H, J=8.3 Hz), 7.70 (d, 1H, J=7.7 Hz), 7.57 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.9, 14.0, 22.9, 23.7, 28.8, 30.2, 38.7, 69.7, 115.1, 117.5, 120.1 (q, $^1J_{C,F}$=273.1 Hz), 121.9 (q, $^3J_{C,F}$=1.1 Hz), 123.4, 125.0, 130.1 (q, $^2J_{C,F}$=38.7 Hz), 132.5, 136.1 (q, $^3J_{C,F}$=3.3 Hz), 150.8, 151.6, 153.6, 160.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −56.7 (CF_3); MS (EI, 70 eV) m/z (%) 426 ([M]$^+$, 11), 316 (8), 315 (30), 314 (100), 297 (31), 70 (13); HRMS (EI): calcd for $C_{21}H_{21}F_3O_4S$ [M]$^+$ 426.11072, found 426.11019; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3121 (w), 3058 (w), 3028 (w), 2961 (m), 2931 (m), 2874 (m), 1811 (w), 1756 (s), 1693 (s), 1609 (m), 1590 (m), 1532 (w), 1501 (m), 1483 (m), 1468 (m), 1434 (m), 1393 (m), 1289 (s), 1277 (s), 1232 (s), 1175 (s), 1139 (s), 1095 (m), 1034 (m). Anal. Calcd for $C_{21}H_{21}F_3O_4S$ (426.45): C, 59.15; H, 4.96. Found: C, 59.28; H, 4.92.

*4.4.4. 2-(2-Ethylhexyl) 3-methyl 4-oxo-4H-thieno[3,2-c]chromene-2,3-dicarboxylate (**12d**).* Yield 54% (168 mg), mp 113–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3H, J=6.8 Hz), 0.94 (t, 3H, J=7.4 Hz), 1.5–1.2 (m, 8H), 1.69 (sept, 1H, J=6.0 Hz), 4.04 (s, 3H), 4.26 (m, 2H), 7.34 (dt, 1H, J=7.6, 1.0 Hz), 7.42 (dd, 1H, J=8.6, 1.0 Hz), 7.57 (m, 1H), 7.73 (dd, 1H, J=7.8, 1.5 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 10.9, 14.0, 22.9, 23.6, 28.8, 30.2, 38.7, 53.4, 68.9, 115.8, 117.8, 123.1, 123.8, 125.1, 130.6, 132.3, 138.3, 151.6, 151.8, 155.1, 160.1, 163.9; MS (EI, 70 eV) m/z (%) 416 ([M]$^+$, 18), 304 (100), 287 (30), 273 (71), 229 (55), 202 (38); HRMS (ESI-TOF/MS): calcd for $C_{22}H_{24}O_6S$ [M+Na]$^+$ 439.1186, found 439.1187; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3459 (w), 3391 (w), 3118 (w), 3033 (w), 2949 (m), 2926 (m), 2871 (m), 2860 (m), 1737 (s), 1699 (s), 1608 (m), 1585 (m), 1542 (m), 1502 (m), 1484 (m), 1464 (m), 1456 (m), 1441 (m), 1402 (m), 1392 (m), 1331 (m), 1293 (s), 1275 (m), 1238 (s), 1219 (s), 1190 (m), 1163 (m), 1139 (s), 1119 (m), 1080 (m), 1036 (m), 1013 (m). Anal. Calcd for $C_{22}H_{24}O_6S$ (416.49): C, 63.44; H, 5.81. Found: C, 63.47; H, 6.04.

*4.4.5. Dimethyl 1-methyl-4-oxo-1,4-dihydrochromeno[4,3-b]pyrrole-2,3-dicarboxylate (**12e**).* 4-Chloro-3-(methoxalyl)coumarine **2b** (250 mg, 0.94 mmol) and methyl sarcosinate hydrochloride (136 mg, 1.03 mmol) were dissolved in 5 mL of dry DMF and cooled to 0 °C. Then NEt_3 (0.63 mL, 4.69 mmol) was added dropwise. The reaction mixture was stirred for 5 h at 20 °C and subsequently poured onto water. The resulting precipitate was washed with acetone to give **6e** as a white solid. Yield 24% (70 mg), mp 245–247 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.85, 3.86 (both s, 3H), 4.36 (s, 3H), 7.46 (m, 1H), 7.54 (dd, 1H, ^3J=8.2 Hz, ^4J=1.1 Hz), 7.64 (m, 1H), 8.32 (dd, 1H, ^3J=8.2 Hz, ^4J=1.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.0, 52.7, 52.8, 106.2, 113.2, 118.0, 122.1, 123.8, 124.8, 125.1, 130.8, 137.4, 152.4, 156.1, 159.8, 164.3; HRMS (ESI-TOF/MS): calcd for $C_{16}H_{13}NO_6$ [M+Na]$^+$ 338.06351, found 338.06332; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3436 (w), 3077 (w), 3051 (w), 3009 (w), 2955 (w), 2845 (w), 1741 (s), 1727 (s), 1715 (s), 1651 (w), 1633 (w), 1610 (w), 1583 (w), 1554 (w), 1511 (m), 1457 (m), 1429 (m), 1403 (w), 1379 (m), 1311 (w), 1293 (m), 1253 (m), 1227 (s), 1211 (s), 1197 (s), 1170 (m), 1144 (s), 1119 (m), 1105 (s), 1063 (m), 1050 (s), 1011 (s). Anal. Calcd for $C_{16}H_{13}NO_6$ (315.28): C, 60.95; H, 4.16; N, 4.44. Found: C, 61.06; H, 4.41; N, 4.33.

*4.4.6. Methyl 3-hydroxy-1-methyl-4-oxo-3-(trifluoromethyl)-1,2,3,4-tetrahydrochromeno[4,3-b]pyrrole-2-carboxylate (**12f**).* Yield 50% (156 mg), mp 198–200 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.42, 3.74 (both s, 3H), 4.92 (s, 1H), 7.19 (s, 1H), 7.33–7.40 (m, 1H), 7.42 (dd, 1H, J=8.3, 0.9 Hz), 7.69–7.76 (m, 1H), 8.24 (dd, 1H, J=8.3, 1.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.4, 52.6, 74.5, 79.6 (q, $^2J_{C,F}$=32.3 Hz), 92.8, 111.8, 117.7, 124.0, 124.8 (q, $^1J_{C,F}$=285.7 Hz), 125.6, 133.9, 155.8, 156.3, 158.7, 166.3; ^{19}F NMR (282 MHz, DMSO-d_6) δ −77.8 (CF_3); MS (EI, 70 eV) m/z (%) 343 ([M]$^+$, 14), 274 (100), 267 (33), 266 (22), 215 (62), 214 (22), 207 (26); HRMS (ESI): calcd for $C_{15}H_{12}F_3NO_5$ [M+H]$^+$ 344.0740, found 344.0733; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3169 (w), 3098 (w), 3002 (w), 2951 (w), 2909 (w), 2849 (w), 1743 (s), 1682 (s), 1612 (m), 1592 (m), 1532 (s), 1477 (w), 1454 (w), 1438 (w), 1417 (w), 1383 (m), 1326 (m), 1299 (m), 1280 (s), 1259 (m), 1245 (s), 1220 (s), 1197 (s), 1177 (m), 1149 (s), 1134 (s), 1121 (s), 1076 (w), 1052 (s), 1023 (m). Anal. Calcd for $C_{15}H_{12}F_3NO_5$ (343.25): C, 52.49; H, 3.52; N, 4.08. Found: C, 52.35; H, 3.64; N, 3.81.

4.5. X-ray crystallographic data

X-ray crystallographic data (excluding structure factors) for the structures **8b**, **8f**, **8g**, **11a**, **12a**, and **12f**, reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 834695–834700, can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk, or via www.ccdc.cam.ac.uk/data_request/cif.

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