Tetrahedron 67 (2011) 4179–4184

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Efficient three-component synthesis of tetrahydrothieno[3,2-*f*]quinolines

Wim Van Snick, Anastasia Parchina, Wim Dehaen *

Department of Chemistry, K.U.Leuven, Celestijnenlaan 200F, 3001 Leuven, Belgium

ARTICLE INFO

Article history:
Received 8 March 2011
Received in revised form 8 April 2011
Accepted 15 April 2011
Available online 21 April 2011

ABSTRACT

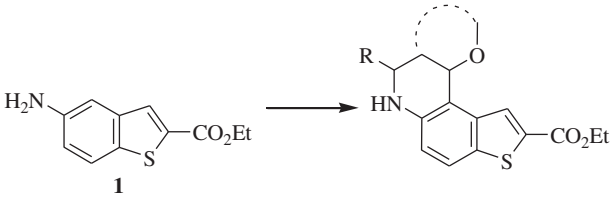
An efficient one-pot method for the synthesis of tetrahydrothieno[3,2-*f*]quinolines is described, using the imino Diels–Alder reaction between ethyl-5-aminobenzothiophene-2-carboxylate, aromatic aldehydes and cyclic enol ethers. Furthermore, hydroxyalkyl-substituted tetrahydrothieno[3,2-*f*]quinolines were synthesized in good yields, by performing the same imino Diels–Alder reaction in absence of aldehydes. The intramolecular aza-Diels–Alder reaction of 5-aminobenzothiophene with *o*-(allyloxy)benzaldehyde was also performed resulting in the fully oxidized thienoquinoline derivative.

1. Introduction

A limited number of methods exists for the synthesis of tetrahydrothieno[3,2-*f*]quinolines. The thermally induced cyclization reaction of thienyl-substituted dienamines is one of the most applicable methods found in literature.[1] However, the use of high temperatures (up to 200 °C) in this procedure is an important drawback and limits the number of possible substituents. The tetrahydroquinoline moiety is a widely used scaffold in the synthesis of pharmaceutically relevant compounds,[2] showing a wide range of biological activities, such as antitumoral,[3] antioxidant,[4] antimalarial,[5] antagonist activity on the FSH receptor[6] and NMDA antagonist activities.[7] A variety of approaches have been developed for the synthesis of this tetrahydroquinoline skeleton.[2] The [4+2] cycloaddition between *N*-arylimines and electron-rich alkenes is probably the most powerful synthetic tool for the construction of *N*-containing heterocyclic compounds, such as tetrahydroquinolines. This imino Diels–Alder reaction (or Povarov reaction)[8,9] has been reported to be catalyzed by various Lewis acid catalysts, such as $BiCl_3$, $BF_3{\cdot}Et_2O$, $InCl_3$, TFA and *p*-TsOH.[10–19] Fluorinated alcohols were also reported to promote this imino Diels–Alder reaction.[20] Moreover, this imino Diels–Alder method allows the generation of tetrahydroquinoline derivatives with several degrees of structural diversity.

Our point of interest goes to the synthesis of 4,5-annulated benzothiophenes with *N*-containing heterocycles, thus providing easy strategies towards the synthesis of (new) benzothiophene fused structures. Therefore, we use the 5-aminobenzothiophene scaffold as a starting material. In our preceding work we described the synthesis of this compound, being ethyl-5-aminobenzothiophene-2-carboxylate (**1**).[21] This compound was conveniently prepared by the condensation of 2-chloro-4-nitrobenzaldehyde with ethyl-2-mercaptoacetate, followed by reduction of the nitro group.

In this manuscript, we wish to report the synthesis of tetracyclic tetrahydrothieno[3,2-*f*]quinolines in moderate to high yields via the three-component imino Diels–Alder reaction of 5-aminobenzothiophene **1**, aromatic aldehyde and cyclic enol ethers (Scheme 1). In addition, we also performed this imino Diels–Alder reaction in the absence of aldehyde. This resulted in the formation of alkoxy-substituted tetrahydrothienoquinolines (R=alkoxy). We also wish to report the cyclocondensation of the benzothiophene scaffold **1** with 2-(allyloxy)benzaldehyde, resulting in the fully unsaturated thienoquinoline derivative.



Scheme 1. Synthesis of tetrahydrothieno[3,2-*f*]quinolines.

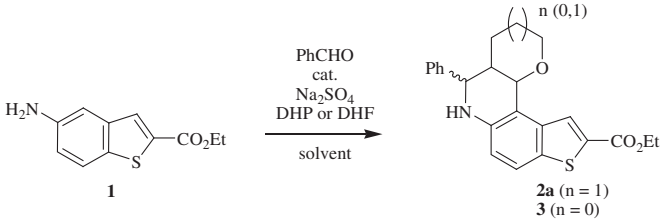
2. Results and discussion

The imino Diels–Alder reaction performed herein is a LUMO$_{diene}$-controlled Diels–Alder reaction between an electron-deficient 2-azadiene (formed in situ from **1** with an aromatic aldehyde) and electron-rich dienophiles, such as cyclic enol ethers.[10,11] This aza-Diels–Alder reaction was first optimized using benzaldehyde and 3,4-dihydro-2*H*-pyran (DHP). So, different catalysts and solvents (acetonitrile and CH_2Cl_2) were used, as is depicted in Table 1, entries

* Corresponding author. Fax: +32 (16) 327990; e-mail address: wim.dehaen@chem.kuleuven.be (W. Dehaen).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.04.053

Table 1
Varying reaction conditions for reaction of **1** with benzaldehyde and dihydropyran or dihydrofuran



1

2a (n = 1)
3 (n = 0)

Entry	Catalyst[a]	Dienophile	Solvent	Temperature	Time (h)	**2a**/**3**, yield[b] (%)	trans/cis[c]
1	$BiCl_3$	DHP	CH_3CN	60 °C	1	**2a**, 90	65/35
2	$BiCl_3$	DHP	CH_2Cl_2	Reflux	3.5	**2a**, 71	60/40
3	$BF_3{\cdot}OEt_2$	DHP	CH_3CN	25 °C	1.5	**2a**, 72	55/45
4	$BF_3{\cdot}OEt_2$	DHP	CH_2Cl_2	Reflux	5	**2a**, 40	70/30
5	$AlCl_3$	DHP	CH_3CN	60 °C	2	**2a**, 43	94/6
6	*p*-TsOH	DHP	CH_3CN	60 °C	2	**2a**, 58	70/30
7	TFA	DHP	CH_3CN	25 °C	2	**2a**, 54	60/40
8	$BiCl_3$	DHF	CH_3CN	25 °C	0.5	**3**, 84	60/40
9	$BiCl_3$	DHF	CH_2Cl_2	25 °C	1.5	**3**, 54	60/40
10	$BF_3{\cdot}OEt_2$	DHF	CH_3CN	25 °C	25 min	**3**, 69	52/48
11	$BF_3{\cdot}OEt_2$	DHF	CH_2Cl_2	Reflux	1	**3**, 73	50/50

[a] Catalyst (10 mol %) is used.
[b] Yields refer to isolated products.
[c] Product ratio is based on ^{1}H NMR analysis.

1–7. Thereafter we performed the same imino Diels–Alder reaction of 5-aminobenzothiophene **1** with benzaldehyde in the presence of 2,3-dihydrofuran (DHF), using either $BiCl_3$ or $BF_3{\cdot}Et_2O$ in acetonitrile or CH_2Cl_2 (Table 1, entries 8–11). This resulted for both enol ethers (DHP and DHF) in the same optimized reaction condition, being $BiCl_3$ in acetonitrile with yields of 90% and 84% (for **2a** and **3**, respectively). It is worth noting that reactions with the more strained DHF run faster and at lower temperatures than those with DHP.

Generally, the aza-Diels–Alder reaction using asymmetrical anilines can result in mixtures of tetrahydroquinoline isomers, because of the possible reaction at both *ortho*-positions.[22] In this paper, we want to point out that 5-aminobenzothiophene **1** solely reacts in the 4-position, resulting in the formation of angular thienoquinoline, as only product (Scheme 1 and Table 1). So, no linear products, as result of reaction at the *ortho*-position 6, were observed.

This aza-Diels–Alder reaction always results in the formation of two pairs of diastereomers (wavy bond in Table 1), in which the phenyl-substituent is situated cis or trans towards protons H_{4a}, H_{11c} or the pyran ring (Fig. 1). Herein, both protons always take a cis configuration, since the enol ether approaches the azadiene *endo* or *exo*. Moreover, the presence of small coupling constants for protons H_{4a} and H_{11c} (1.8–2.8 Hz) proves this cis ring junction between the pyran and the quinoline rings. The relative ratio between both isomers was derived from ^{1}H NMR spectral data, and assigned by comparison of literature NMR data.[10,12,14] The stereochemistry was determined on the basis of the coupling constants between protons

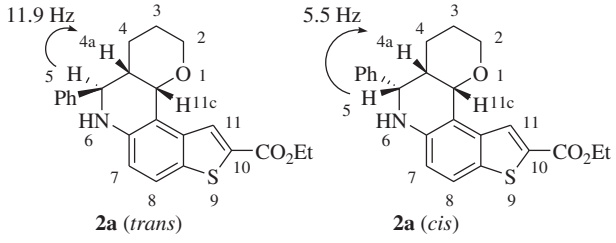


Fig. 1. Coupling constants between H-4a and H-5.

H_{4a} and H_5, as shown in Fig. 1. The structures of **2a**, both cis and trans, were also confirmed by COSY, HMQC, HMBC and NOE experiments.

The large coupling constant (11.9 Hz) in the trans isomer indicates that H_{4a} and H_5 are in a trans configuration, and thus having the phenyl group cis towards both protons H_{4a} and H_{11c}, and trans towards the pyran ring. The cis isomer shows a coupling constant of 5.5 Hz, which depicts the cis configuration between both protons H_{4a} and H_5. In this case, the phenyl group is in a cis configuration with the pyran ring.

Next, we explored this imino Diels–Alder reaction of **1** and DHP with different aromatic aldehydes using the optimized reaction condition ($BiCl_3$ in acetonitrile). The results of these reactions are listed in Table 2. From these results we can conclude that reactions with electron-poor aldehydes run faster and mostly at lower temperatures and they result in higher yields. Electron-withdrawing substituents in *ortho* or *para*-position lower the LUMO of the 2-azadiene. This lowers the energy gap between $HOMO_{dienophile}$ and $LUMO_{azadiene}$ and makes it easier to reach the transition state.[10] The reaction with indole-3-carboxaldehyde did not result in any product. We want to point out that the use of aldehydes with electron-withdrawing substituents leads to almost equal ratios of both isomers (cis/trans). Conversely, aldehydes with electron-donating substituents give rise to more of the trans isomer (**2h**,**i**, Table 2). There is no specific explanation for this difference in ratios.

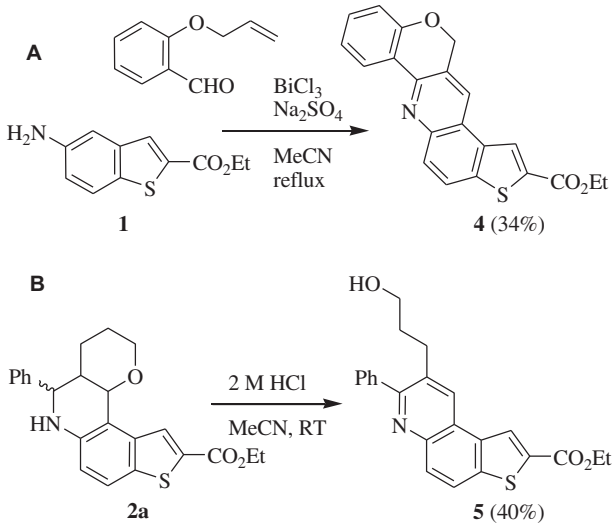
Table 2
Results of $BiCl_3$-catalyzed imino Diels–Alder reaction of **1** with DHP using different aldehydes

	Substituent-CHO	Temp (°C)	Time (h)	Yield[a] (%)	trans/cis[b]
2b	4-Nitrophenyl	25	1	57	51/49
2c	4-(Trifluoromethyl)phenyl	25	1	70	52/48
2d	2-Chlorophenyl	25	1.5	80	59/41
2e	4-Fluorophenyl	60	1	70	65/35
2f	4-Cyanophenyl	60	0.3	77	63/37
2g	2-Furanyl	25	0.5	59	60/40
2h	4-Methoxyphenyl	60	3	51	91/9
2i	4-Acetamidophenyl	60	2	66	86/14
2j	3-Indolyl	60	48	—	—

[a] Yields refer to isolated products.
[b] Product ratio is based on ^{1}H NMR analysis.

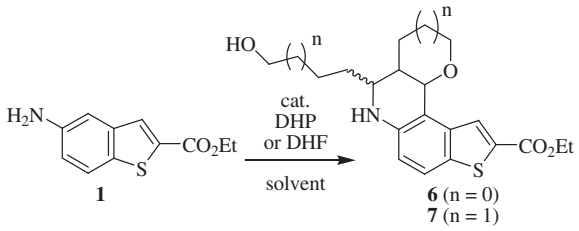
In addition, we performed the imino Diels–Alder reaction of **1** with 2-(allyloxy)benzaldehyde (Scheme 2A).[9,23,24] In analogy to the previous results, one should expect to observe the formation of the tetrahydrothienoquinoline. Nevertheless, we obtained the fully aromatized thienoquinoline derivative **4**. The side product, formed in this reaction, was the reduced form of the imine-intermediate. So, it seems likely that the imine behaves as an oxidant of the final product. The highest possible yield for **4** is the one we observed (34%), because twice the amount of imine is needed in this oxidation side-reaction. The formation of chromenoquinolines through Diels–Alder cycloaddition has also been reported in literature.[23,24] We tried to block this side-reaction by the addition of DMSO or DDQ as oxidizing agents, but this was to no avail. We briefly studied the possibility to convert the synthesized tetrahydrothienoquinoline into the fully aromatic thienoquinoline (Scheme 2B). Using acidic conditions (2 M HCl in acetonitrile),[19,25] **2a** was air-oxidized into **5** with a non-optimized yield of 40%.

As a last part, we performed the imino Diels–Alder procedure without the addition of aldehyde.[15–18,26,27] So, the alkoxy-substituted tetrahydrothienoquinolines **6** and **7** were prepared as shown in Table 3. The use of 2 equiv of enol ether, DHP or DHF, and molecular iodine as catalyst resulted in good yields. In these reactions, both cis and trans configurations were formed, with the trans isomer in excess (about 80%).



Scheme 2. (A) Intramolecular aza-Diels–Alder reaction; (B) aromatization of tetrahydrothienoquinoline.

Table 3
Imino Diels–Alder reaction of **1** with cyclic enol ether



Catalyst[a]	Dienophile[b]	Solvent	Time (h)	**6**, **7**, Yield[c] (%)	trans/cis[d]
$BiCl_3$	DHF	CH_3CN	3	**6**, 65	74/26
I_2	DHF	CH_3CN	2	**6**, 71	81/19
I_2	DHF	CH_2Cl_2	0.5	**6**, 76	86/14
I_2[e]	DHP	CH_3CN	3	**7**, 71	82/18

[a] Catalyst (10 mol %) used.
[b] Dienophile (2.2 equiv) was used.
[c] Yields refer to isolated products.
[d] Product ratio is based on ^1H NMR analysis of crude mixture.
[e] I_2 (20 mol %) used.

The relative ratio between both isomers was derived from ^1H NMR spectral data, and assigned by comparison with literature NMR data.[15,16,26,27] In compound **6**, the small coupling constant (5.6–8.0 Hz) for proton H_{10c} shows that the furan and quinoline rings are cis fused, as both protons H_{3a} and H_{10c} have a cis configuration. However, a coupling constant for protons H_4 and H_{3a} could not be derived from the ^1H NMR spectrum, making it difficult to determine the configuration of the isomers. In accordance with literature data,[15,16,26,27] we thus appointed the cis and trans configurations by comparison of the coupling constants for proton H_{10c} in both isomers. The trans isomer of compound **6** has a coupling constant J_{H10c}=5.6 Hz (4.83 ppm), while the corresponding cis isomer of **6** has a coupling constant J_{H10c}=8.0 Hz (5.47 ppm). In addition, compound **7** shows the same analogy with literature, having a coupling constant J_{H11c}=5.5 Hz (5.35 ppm) for the cis isomer and J_{H11c}=2.3 Hz (4.76 ppm) for the trans isomer.

In conclusion, we have reported an efficient procedure for the synthesis of tetrahydrothieno[3,2-*f*]quinolines, using the imino Diels–Alder approach. Different catalysts and solvents were examined and the best results were obtained with $BiCl_3$ in acetonitrile. Both isomers (cis/trans) were assigned by analysis of ^1H NMR spectra. Tetrahydrothienoquinolines were obtained in moderate to good yields with electron-withdrawing and electron-donating aromatic aldehydes. Aromatic thienoquinolines were obtained by oxidation of the tetrahydroquinoline in acidic medium, and via the intramolecular aza-Diels–Alder reaction with allyloxybenzaldehyde. Performing the imino Diels–Alder reaction using electron-rich olefins, without the addition of aldehyde, results in the formation of alkoxy-substituted tetrahydrothienoquinolines.

3. Experimental section

3.1. General

Melting points (not corrected) were determined using a Reichert Thermovar apparatus. IR spectra were recorded using a Bruker ALPHA-P spectrometer. ^1H and ^{13}C NMR spectroscopy was performed on commercial instruments (Bruker Avance 300 MHz and Bruker AMX 400 MHz) and chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (TMS) (^1H) or the carbon signal of deuterated solvents (^{13}C). Mass spectra were run using a HP5989A apparatus (CI and EI, 70 eV ionization energy) with Apollo 300 data system, and a Kratos MS50TC instrument for exact mass measurements (performed in the EI mode at a resolution of 10,000). For column chromatography 70–230 mesh silica 60 (E.M. Merck) was used as the stationary phase. Chemicals received from commercial sources were used without further purification. The synthetic procedure for the preparation of ethyl 5-aminobenzo[*b*]thiophene-2-carboxylate (**1**) is described in our previous work.[21]

3.2. Typical procedure for the preparation of pyrano[3,2-*c*]thieno[3,2-*f*]quinolines (2)

The aldehyde (1.10 mmol) was added to a mixture of ethyl 5-aminobenzo[*b*]thiophene-2-carboxylate (**1**) (221 mg; 1.00 mmol), Na_2SO_4 (284 mg; 2.00 mmol) and $BiCl_3$ (31.5 mg; 10 mol %) in CH_3CN (4 mL). After 15 min stirring at room temperature, DHP (120 μL; 1.30 mmol) was added. This mixture was stirred for the appropriate time and at the temperature, as indicated in Tables 1 and 2. After complete conversion, as indicated by TLC, the solvent was removed under reduced pressure, diluted with CH_2Cl_2 and filtered. The organic layer was washed with water and brine and dried over $MgSO_4$. The mixture was filtered, evaporated to dryness, and the residue was purified by column chromatography (silica, eluent: CH_2Cl_2) to afford a mixture of both isomers. For some of the products, the isomers were separated by column chromatography, using a mixture of petroleum ether and ethyl acetate as eluent. In case, the isomers were not separated. The ^1H NMR data of both isomers were assigned by comparison with previously synthesized compounds and based on the relative ratio between both isomers.

*3.2.1. Ethyl 5-phenyl-3,4,4a,5,6,11c-hexahydro-2H-pyrano[3,2-c]thieno[3,2-f]quinoline-10-carboxylate (**2a**).* Both isomers were separated by column chromatography (silica, eluent: petroleum ether/EtOAc (90/10)) to afford pure products.

trans-**2a**. Obtained as a yellow solid; mp 158–161 °C; IR: 3359, 3323, 2922, 1712, 1233 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.41 (t, J=7.0 Hz, 3H, CH_3), 1.64–1.97 (m, 4H, H_3 and H_4), 2.13 (dd, J=11.0, 1.8 Hz, 1H, H_{4a}), 3.84 (dt, J=11.9, 1.8 Hz, 1H, H_2), 4.14 (m, 2H, H_2 and H_6), 4.39 (q, J=7.0 Hz, 2H, CO_2CH_2), 4.76 (d, J=11.9 Hz, 1H, H_5), 4.82 (d, J=2.8 Hz, 1H, H_{11c}), 6.71 (d, J=8.6 Hz, 1H, H_7), 7.33–7.48 (m, 5H, Ph), 7.53 (d, J=8.6 Hz, 1H, H_8), 8.07 (s, 1H, H_{11}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 22.0, 24.1, 38.8, 54.9, 61.5, 69.1, 72.2, 114.6, 117.5, 123.5, 127.8, 128.1, 128.2, 128.9, 132.8, 134.4, 139.7, 141.9, 142.5, 163.3; HRMS (EI): m/z calcd for $C_{23}H_{23}O_3NS$ (M^+): 393.1399; found 393.1385.

cis-**2a**. Obtained as a yellow solid; mp 162–165 °C; IR: 3387, 2932, 2846, 1698, 1235 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.40 (t, J=7.3 Hz, 3H, CH_3), 1.50–1.75 (m, 4H, H_3 and H_4), 2.25 (m, 1H, H_{4a}),

3.15 (dt, J=11.0, 1.8 Hz, 1H, H_2), 3.62 (dd, J=10.0, 1.8 Hz, 2H, H_2), 3.94 (br s, 1H, H_6), 4.37 (q, J=7.1 Hz, 2H, CO_2CH_2), 4.66 (d, J=1.8 Hz, 1H, H_{11c}), 5.62 (d, J=5.5 Hz, 1H, H_5), 6.79 (d, J=8.8 Hz, 1H, H_7), 7.29–7.49 (m, 5H, Ph), 7.56 (d, J=8.6 Hz, 1H, H_8), 8.56 (s, 1H, H_{11}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 18.5, 25.0, 39.1, 59.8, 61.3, 61.5, 73.2, 114.6, 117.6, 122.6, 127.0, 127.8, 128.6, 130.7, 134.2, 134.3, 138.6, 141.0, 143.4, 163.4; HRMS (EI): m/z calcd for $C_{23}H_{23}O_3NS$ (M^+): 393.1399; found 393.1385.

*3.2.2. Ethyl 5-(4-nitrophenyl)-3,4,4a,5,6,11c-hexahydro-2H-pyrano[3,2-c]thieno[3,2-f]quinoline-10-carboxylate (**2b**).* Both isomers were separated by column chromatography (silica, eluent: petroleum ether/EtOAc (80/20)) to afford pure product.

trans-**2b**. Obtained as a yellow solid; mp 224–231 °C; IR: 3367, 2929, 1711, 1232 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (t, J=7.1 Hz, 3H, CH_3), 1.80 (m, 4H, H_3 and H_4), 2.15 (d, J=11.0 Hz, 1H, H_{4a}), 3.86 (t, J=11.0 Hz, 1H, H_2), 4.16 (m, 2H, H_2 and H_6), 4.40 (q, J=7.1 Hz, 2H, CO_2CH_2), 4.84 (d, J=2.8 Hz, 1H, H_{11c}), 4.90 (d, J=11.1 Hz, 1H, H_5), 6.77 (d, J=8.8 Hz, 1H, H_7), 7.57 (d, J=8.6 Hz, 1H, H_8), 7.64 (d, J=8.6 Hz, 2H, Ph), 8.07 (s, 1H, H_{11}), 8.25 (d, J=8.6 Hz, 1H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 22.0, 24.1, 39.1, 54.7, 61.7, 69.1, 71.9, 114.8, 117.5, 123.8, 124.1, 127.6, 129.0, 133.4, 134.8, 139.6, 141.9, 147.9, 149.5, 163.2; HRMS (EI): m/z calcd for $C_{23}H_{22}O_5N_2S$ (M^+): 438.1249; found 438.1254.

cis-**2b**. Obtained as a yellow solid; mp 228–236 °C; IR: 3364, 2922, 1682, 1234 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (t, J=7.1 Hz, 3H, CH_3), 1.50–1.82 (2 m, 4H, H_3 and H_4), 2.30 (m, 1H, H_{4a}), 3.18 (t, J=11.0 Hz, 1H, H_2), 3.64 (m, 1H, H_2), 3.98 (s, 1H, H_6), 4.40 (q, J=7.3 Hz, 2H, CO_2CH_2), 4.79 (d, J=1.8 Hz, 1H, H_{11c}), 5.64 (d, J=5.5 Hz, 1H, H_5), 6.85 (d, J=8.6 Hz, 1H, H_7), 7.61 (d, J=8.6 Hz, 1H, H_8), 7.64 (d, J=8.8 Hz, 2H, Ph), 8.26 (d, J=8.8 Hz, 2H, Ph), 8.56 (s, 1H, H_{11}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 18.7, 24.8, 29.9, 39.0, 59.5, 61.4, 72.9, 114.8, 117.7, 123.0, 123.8, 127.9, 130.5, 134.6, 134.9, 138.6, 142.6, 147.6, 148.7, 163.3; HRMS (EI): m/z calcd for $C_{23}H_{22}O_5N_2S$ (M^+): 438.1249; found 438.1254.

*3.2.3. Ethyl 5-(4-(trifluoromethyl)phenyl)-3,4,4a,5,6,11c-hexahydro-2H-pyrano[3,2-c]thieno[3,2-f]quinoline-10-carboxylate (**2c**).* The isomers were not separated. The ^{1}H NMR data of both isomers were assigned by comparison with previously synthesized compounds and based on the relative ratio between both isomers. Obtained as a yellow solid; mp 155–166 °C; IR: 3358, 3329, 2937, 1715, 1686, 1232 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *trans*-**2c**: δ 1.38 (t, J=7.3 Hz, 3H, CH_3), 1.40–1.90 (m, 4H, H_3 and H_4), 2.15 (d, J=11.0 Hz, 1H, H_{4a}), 3.84 (t, J=11.0 Hz, 1H, H_2), 4.14 (m, 2H, H_2 and H_6), 4.40 (q, J=7.1 Hz, 2H, CO_2CH_2), 4.82 (m, 2H, H_5 and H_{11c}), 6.73 (d, J=8.7 Hz, 1H, H_7), 7.57 (m, 5H, Ph and H_8), 8.06 (s, 1H, H_{11}); *cis*-**2c**: δ 1.38 (t, J=7.3 Hz, 3H, CH_3), 1.40–1.90 (m, 4H, H_3 and H_4), 2.24 (m, 1H, H_{4a}), 3.15 (t, J=11.0 Hz, 1H, H_2), 3.62 (m, 1H, H_2), 3.96 (s, 1H, H_6), 4.40 (q, J=7.3 Hz, 2H, CO_2CH_2), 4.68 (s, 1H, H_{11c}), 5.61 (d, J=5.5 Hz, 1H, H_5), 6.81 (d, J=8.6 Hz, 1H, H_7), 7.57 (m, 5H, Ph and H_8), 8.56 (s, 1H, H_{11}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 18.4, 22.0, 24.0, 24.9, 31.0, 39.0, 54.7, 49.4, 61.3, 61.5, 61.6, 69.1, 72.0, 73.0, 114.6, 117.5, 117.7, 122.8, 123.6, 125.4, 125.5, 125.7, 125.8, 126.0, 127.3, 127.7, 128.5, 130.1, 130.2, 130.6, 130.7, 133.1, 134.3, 134.6, 138.5, 139.6, 142.2, 143.0, 145.2, 146.0, 163.2, 163.4; HRMS (EI): m/z calcd for $C_{24}H_{22}O_3NSF_3$ (M^+): 461.1272; found 461.1257.

*3.2.4. Ethyl 5-(2-chlorophenyl)-3,4,4a,5,6,11c-hexahydro-2H-pyrano[3,2-c]thieno[3,2-f]quinoline-10-carboxylate (**2d**).* The isomers were not separated. The ^{1}H NMR data of both isomers were assigned by comparison with previously synthesized compounds and based on the relative ratio between both isomers. Obtained as a yellow solid; mp 65–76 °C; IR: 3360, 2936, 2854, 1697, 1231 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *trans*-**2d**: δ 1.40 (t, J=7.3 Hz, 3H, CH_3), 1.76–2.04 (m, 4H, H_3 and H_4), 2.23 (m, 1H, H_{4a}), 3.80 (m, 1H, H_2), 4.09 (m, 2H, H_2 and H_6), 4.40 (q, J=7.1 Hz, 2H, CO_2CH_2), 4.84 (d, J=3.0 Hz, 1H, H_{11c}), 5.32 (d, J=10.5 Hz, 1H, H_5), 6.72 (d, J=9.1 Hz, 1H, H_7), 7.21–7.65 (m, 5H, Ph and H_8), 8.09 (s, 1H, H_{11}); *cis*-**2d**: δ 1.40 (t, J=7.3 Hz, 3H, CH_3), 1.76–2.04 (m, 4H, H_3 and H_4), 2.48 (m, 1H, H_{4a}), 3.15 (t, J=11.0 Hz, 1H, H_2), 3.61 (m, 1H, H_2), 3.80 (s, 1H, H_6), 4.40 (q, J=7.3 Hz, 2H, CO_2CH_2), 5.05 (d, J=2.1 Hz, 1H, H_{11c}), 5.65 (d, J=5.6 Hz, 1H, H_5), 6.81 (d, J=8.2 Hz, 1H, H_7), 7.21–7.65 (m, 5H, Ph and H_8), 8.58 (s, 1H, H_{11}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 18.6, 22.6, 24.1, 24.9, 35.0, 56.2, 61.1, 61.4, 61.5, 71.9, 72.7, 114.3, 117.4, 122.5, 123.4, 126.6, 127.3, 127.8, 128.4, 129.0, 129.4, 129.9, 130.6, 132.7, 132.9, 134.0, 134.3, 134.4, 135.1, 137.8, 138.5, 139.5, 142.2, 143.3, 163.2, 163.3, 189.9; HRMS (EI): m/z calcd for $C_{23}H_{22}O_3NSCl$ (M^+): 427.1009; found 427.1011.

*3.2.5. Ethyl 5-(4-fluorophenyl)-3,4,4a,5,6,11c-hexahydro-2H-pyrano[3,2-c]thieno[3,2-f]quinoline-10-carboxylate (**2e**).* Both isomers were separated by column chromatography (silica, eluent: petroleum ether/EtOAc (80/20)) to afford pure products.

trans-**2e**. Obtained as a yellow solid; mp 206–210 °C; IR: 3379, 2924, 2854, 1682, 1255 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, J=7.2 Hz, 3H, CH_3), 1.73 (m, 4H, H_3 and H_4), 2.08 (d, J=11.3 Hz, 1H, H_{4a}), 3.85 (dt, J=11.5 Hz, 2.1 Hz, 1H, H_2), 4.14 (m, 2H, H_2 and H_6), 4.39 (q, J=7.2 Hz, 2H, CO_2CH_2), 4.75 (d, J=11.3 Hz, 1H, H_5), 4.81 (d, J=2.6 Hz, 1H, H_{11c}), 6.72 (d, J=8.2 Hz, 1H, H_7), 7.07 (m, 2H, Ph), 7.40 (m, 2H, Ph), 7.52 (d, J=8.2 Hz, 1H, H_8), 8.05 (s, 1H, H_{11}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 21.8, 23.9, 29.7, 38.8, 54.1, 61.5, 69.0, 72.0, 114.5, 115.5, 115.7, 117.4, 123.5, 127.6, 129.4, 129.5, 132.8, 134.4, 137.4, 137.5, 139.6, 142.3, 160.8, 163.1, 164.1; HRMS (EI): m/z calcd for $C_{23}H_{22}O_3NSF$ (M^+): 411.1304; found 411.1313.

cis-**2e**. Obtained as a yellow solid; mp 183–186 °C; IR: 3339, 2936, 2856, 1697, 1221 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, J=7.2 Hz, 3H, CH_3), 1.62 (m, 4H, H_3 and H_4), 2.21 (m, 1H, H_{4a}), 3.15 (t, J=11.3 Hz, 1H, H_2), 3.61 (d, J=10.5 Hz, 1H, H_2), 3.91 (s, 1H, H_6), 4.39 (q, J=7.2 Hz, 2H, CO_2CH_2), 4.65 (s, 1H, H_{11c}), 5.60 (d, J=5.6 Hz, 1H, H_5), 6.80 (d, J=8.6 Hz, 1H, H_7), 7.07 (m, 2H, Ph), 7.40 (m, 2H, Ph), 7.57 (d, J=8.6 Hz, 1H, H_8), 8.55 (s, 1H, H_{11}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 18.5, 24.9, 39.1, 59.2, 61.3, 61.5, 73.1, 114.6, 115.2, 115.5, 117.7, 122.7, 128.5, 128.6, 130.7, 134.2, 134.4, 136.6, 136.7, 138.6, 143.3, 160.6, 163.4, 163.9; HRMS (EI): m/z calcd for $C_{23}H_{22}O_3NSF$ (M^+): 411.1304; found 411.1313.

*3.2.6. Ethyl 5-(4-cyanophenyl)-3,4,4a,5,6,11c-hexahydro-2H-pyrano[3,2-c]thieno[3,2-f]quinoline-10-carboxylate (**2f**).* The isomers were not separated. The ^{1}H NMR data of both isomers were assigned by comparison with previously synthesized compounds and based on the relative ratio between both isomers. Obtained as a yellow solid; mp 222–240 °C; IR: 3356, 2945, 2860, 2225, 1709, 1235 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *trans*-**2f**: δ 1.41 (t, J=7.3 Hz, 3H, CH_3), 1.73 (m, 4H, H_3 and H_4), 2.10 (d, J=10.7 Hz, 1H, H_{4a}), 3.85 (t, J=10.9 Hz, 1H, H_2), 4.16 (m, 2H, H_2 and H_6), 4.40 (q, J=7.3 Hz, 2H, CO_2CH_2), 4.80 (m, 2H, H_5 and H_{11c}), 6.75 (d, J=8.2 Hz, 1H, H_7), 7.52–7.78 (m, 5H, Ph and H_8), 8.05 (s, 1H, H_{11}); *cis*-**2f**: δ 1.41 (t, J=7.3 Hz, 3H, CH_3), 1.73 (m, 4H, H_3 and H_4), 2.25 (m, 1H, H_{4a}), 3.17 (dt, J=11.3, 1.5 Hz, 1H, H_2), 3.62 (dd, J=11.1, 1.9 Hz, 1H, H_2), 3.98 (s, 1H, H_6), 4.40 (q, J=7.3 Hz, 2H, CO_2CH_2), 4.67 (s, 1H, H_{11c}), 5.59 (d, J=5.5 Hz, 1H, H_5), 6.82 (d, J=8.2 Hz, 1H, H_7), 7.52–7.78 (m, 5H, Ph and H_8), 8.53 (s, 1H, H_{11}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 18.5, 22.0, 24.0, 24.7, 28.8, 38.9, 54.8, 59.5, 61.3, 61.5, 61.6, 69.0, 71.9, 72.9, 111.5, 112.0, 114.6, 114.7, 117.5, 117.7, 118.7, 118.8, 122.8, 123.7, 127.6, 127.8, 128.8, 130.5, 132.3, 132.6, 133.2, 134.4, 134.6, 134.7, 138.5, 139.6, 142.0, 142.7, 146.6, 147.5, 163.1, 163.3; HRMS (EI): m/z calcd for $C_{24}H_{22}O_3N_2S$ (M^+): 418.1351; found 418.1350.

*3.2.7. Ethyl 5-(furan-2-yl)-3,4,4a,5,6,11c-hexahydro-2H-pyrano[3,2-c]thieno[3,2-f]quinoline-10-carboxylate (**2g**).* The isomers were not separated. The ^{1}H NMR data of both isomers were assigned by

comparison with previously synthesized compounds and based on the relative ratio between both isomers. Mp 62–73 °C; IR: 3367, 2936, 2855, 1699, 1231 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *trans*-**2g**: δ 1.39 (t, J=7.3 Hz, 3H, CH_3), 1.52–1.87 (m, 4H, H_3 and H_4), 2.24 (d, J=11.0 Hz, 1H, H_{4a}), 3.78 (t, J=11.0 Hz, 1H, H_2), 4.04–4.17 (m, 2H, H_2 and H_6), 4.39 (q, J=7.3 Hz, 2H, CO_2CH_2), 4.78 (d, J=2.8 Hz, 2H, H_{11c}), 4.83 (d, J=11.1 Hz, 2H, H_5), 6.34 (m, 2H, furan), 6.74 (d, J=9.2 Hz, 1H, H_7), 7.39 (m, 1H, furan), 7.51 (d, J=9.2 Hz, 1H, H_8), 8.03 (s, 1H, H_{11}); *cis*-**2g**: δ 1.39 (t, J=7.3 Hz, 3H, CH_3), 1.52–1.87 (m, 4H, H_3 and H_4), 2.39 (m, 1H, H_{4a}), 3.12 (t, J=10.0 Hz, 1H, H_2), 3.58 (d, J=11.0 Hz, 1H, H_2), 4.05 (br s, 1H, H_6), 4.39 (q, J=7.3 Hz, 2H, CO_2CH_2), 4.56 (d, J=2.1 Hz, 1H, H_{11c}), 5.45 (d, J=5.5 Hz, 1H, H_5), 6.34 (m, 2H, furan), 6.74 (d, J=9.2 Hz, 1H, H_7), 7.39 (m, 1H, furan), 7.51 (d, J=9.2 Hz, 1H, H_8), 8.51 (s, 1H, H_{11}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 18.5, 22.0, 24.0, 24.7, 28.8, 38.9, 54.8, 59.5, 61.3, 61.5, 61.6, 69.0, 71.9, 72.9, 111.5, 112.0, 114.6, 114.7, 117.5, 117.7, 118.7, 118.8, 122.8, 123.7, 127.6, 127.8, 128.8, 130.5, 132.3, 132.6, 133.2, 134.4, 134.6, 134.7, 138.5, 139.6, 142.0, 142.7, 146.6, 147.5, 163.1, 163.3; HRMS (EI): m/z calcd for $C_{21}H_{21}O_4NS$ (M^+): 383.1191; found 383.1168.

*3.2.8. Ethyl 5-(4-methoxyphenyl)-3,4,4a,5,6,11c-hexahydro-2H-pyrano[3,2-c]thieno[3,2-f]quinoline-10-carboxylate (**2h**).* Only 9% of cis isomer was formed, making it difficult to characterize. Obtained as a yellow solid; mp 169–182 °C; IR: 3366, 2950, 2833, 1688, 1233 cm^{-1}; *trans*-**2h**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, J=7.3 Hz, 3H, CH_3), 1.79 (m, 4H, H_3 and H_4), 2.08 (d, J=11.8 Hz, 1H, H_{4a}), 3.82 (m, 4H, OCH_3, H_2), 4.13 (m, 2H, H_2 and H_6), 4.40 (q, J=7.3 Hz, 2H, CO_2CH_2), 4.70 (d, J=11.0 Hz, 1H, H_5), 4.81 (d, J=2.5 Hz, 1H, H_{11c}), 6.69 (d, J=8.6 Hz, 1H, H_7), 6.92 (d, J=8.7 Hz, 2H, Ph), 7.34 (d, J=8.6 Hz, 2H, Ph), 7.51 (d, J=8.7 Hz, 1H, H_8), 8.06 (s, 1H, H_{11}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 22.0, 24.1, 28.8, 54.2, 55.4, 61.5, 69.1, 72.3, 114.2, 114.6, 117.5, 123.5, 127.8, 139.1, 132.7, 133.8, 134.4, 139.7, 142.6, 159.5, 163.2; HRMS (EI): m/z calcd for $C_{24}H_{25}O_4NS$ (M^+): 423.1504; found 423.1487.

*3.2.9. Ethyl 5-(4-acetamidophenyl)-3,4,4a,5,6,11c-hexahydro-2H-pyrano[3,2-c]thieno[3,2-f]quinoline-10-carboxylate (**2i**).* Only a small amount of cis isomer was formed, making it difficult to fully characterize. Obtained as a yellow solid; mp 153–166 °C; IR: 3369, 3250, 2926, 2847, 1712, 1230 cm^{-1}; *trans*-**2i**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.42 (t, J=7.2 Hz, 3H, CH_3), 1.65 (m, 4H, H_3 and H_4), 2.10 (m, 1H, H_{4a}), 2.20 (1, 3H, $COCH_3$), 3.84 (t, J=11.9 Hz, 1H, H_2), 4.13 (m, 2H, H_2 and H_6), 4.39 (q, J=7.3 Hz, 2H, CO_2CH_2), 4.75 (d, J=11.0 Hz, 1H, H_5), 4.82 (d, J=2.6 Hz, 1H, H_{11c}), 6.73 (d, J=8.2 Hz, 1H, H_7), 7.31–7.59 (m, 5H, H_8, Ph), 8.06 (s, 1H, H_{11}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 21.9, 24.0, 24.6, 38.8, 54.3, 61.6, 69.1, 72.2, 114.5, 117.5, 120.3, 123.5, 127.7, 128.5, 132.7, 134.3, 137.6, 137.8, 139.7, 142.5, 163.3, 168.7; HRMS (EI): m/z calcd for $C_{25}H_{26}O_4N_2S$ (M^+): 450.1613; found 450.1604.

3.3. Ethyl 4-phenyl-2,3,3a,4,5,10c-hexahydrofuro[3,2-*c*]thieno[3,2-*f*]quinoline-9-carboxylate (3)

Benzaldehyde (0.11 mL; 1.10 mmol) was added to a mixture of ethyl 5-aminobenzo[*b*]thiophene-2-carboxylate (**1**) (221 mg; 1.00 mmol), Na_2SO_4 (284 mg; 2.00 mmol) and $BiCl_3$ (31.5 mg; 10 mol %) in CH_3CN (4 mL). After 15 min stirring at room temperature, DHF (0.10 mL; 1.30 mmol) was added. This mixture was stirred for 30 min at room temperature. After complete conversion, as indicated by TLC, the solvent was diluted with Et_2O and filtered. The organic layer was extracted with water and brine and dried over $MgSO_4$. The mixture was filtered, evaporated to dryness, and the residue was purified by column chromatography (silica, eluent: CH_2Cl_2) to afford a mixture of both isomers. The isomers were separated by column chromatography using petroleum ether/EtOAc (95/5) as eluent to afford pure products.

trans-**3**. Obtained as a yellow solid; mp 164–170 °C; IR: 3362, 2923, 2852, 1693, 1233 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.41 (t, J=7.0 Hz, 3H, CH_3), 1.76 (m, 1H, H_3), 2.07 (m, 1H, H_3), 2.54 (m, 1H, H_{3a}), 3.83 (d, J=11.1 Hz, 1H, H_4), 3.91 (m, 1H, H_2), 4.07 (m, 1H, H_2), 4.26 (br s, 1H, H_5), 4.39 (q, J=7.0 Hz, 2H, CO_2CH_2), 4.91 (d, J=5.0 Hz, 1H, H_{10c}), 6.80 (d, J=8.6 Hz, 1H, H_6), 7.33–7.48 (m, 5H, Ph), 7.57 (d, J=8.6 Hz, 1H, H_7), 8.21 (s, 1H, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 28.8, 43.3, 58.3, 61.6, 65.6, 74.5, 108.8, 114.5, 117.4, 123.2, 125.3, 128.5, 128.9, 133.4, 134.8, 140.4, 141.4, 143.1, 163.2; HRMS (EI): m/z calcd for $C_{22}H_{21}O_3NS$ (M^+): 379.1242; found 379.1242.

cis-**3**. Obtained as a yellow solid; mp 140–143 °C; IR: 3333, 2922, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.41 (t, J=7.3 Hz, 3H, CH_3), 1.58 (m, 1H, H_3), 2.27 (m, 1H, H_3), 2.91 (m, J=10.6 Hz, 2.5 Hz, 1H, H_{3a}), 3.78 (m, 2H, H_2), 3.92 (s, 1H, H_5), 4.40 (q, J=7.3 Hz, 2H, CO_2CH_2), 4.70 (d, J=2.5 Hz, 1H, H_{10c}), 5.65 (d, J=8.1 Hz, 1H, H_4), 6.79 (d, J=8.8 Hz, 1H, H_6), 7.29–7.54 (m, 5H, Ph), 7.56 (d, J=8.6 Hz, 1H, H_7), 8.26 (s, 1H, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 25.0, 46.4, 58.0, 61.5, 67.3, 74.7, 117.1, 117.7, 122.8, 126.7, 127.9, 128.9, 129.3, 134.3, 134.6, 139.6, 142.0, 142.6, 163.3; HRMS (EI): m/z calcd for $C_{22}H_{21}O_3NS$ (M^+): 379.1242; found 379.1242.

3.4. Ethyl 12*H*-chromeno[4,3-*b*]thieno[3,2-*f*]quinoline-2-carboxylate (4)

2-(Allyloxy)benzaldehyde (178 mg; 1.10 mmol) was added to a solution of ethyl 5-aminobenzo[*b*]thiophene-2-carboxylate (**1**) (221 mg; 1.00 mmol), Na_2SO_4 (284 mg; 2.00 mmol) and $BiCl_3$ (31.5 mg; 10 mol %) in CH_3CN (4 mL). This mixture was refluxed for 48 h. After cooling, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The combined organic layers were washed with brine and dried over $MgSO_4$. The mixture was filtered, evaporated to dryness, and the residue was purified by column chromatography on silica gel using CH_2Cl_2/petroleum ether (50/50) as eluent to afford ethyl 12*H*-chromeno[4,3-*b*]thieno[3,2-*f*]quinoline-2-carboxylate (124 mg, 34%). Mp 170–172 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 1.45 (t, J=7.1 Hz, 3H, CH_3), 4.44 (q, J=7.3 Hz, 2H, CO_2CH_2), 5.42 (s, 1H, CH_2), 7.04 (d, J=8.0 Hz, 1H), 7.17 (t, J=7.6 Hz, 1H), 7.38 (t, J=7.6 Hz, 1H), 8.03 (d, J=9.1 Hz, 1H), 8.11 (d, J=9.0 Hz, 1H), 8.29 (s, 1H), 8.47 (d, J=7.8 Hz, 1H), 8.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 61.9, 68.4, 117.4, 122.7, 123.1, 124.1, 124.2, 125.4, 125.8, 126.7, 127.7, 129.3, 132.0, 134.6, 134.8, 140.8, 147.0, 148.4, 157.2, 162.6; HRMS (EI): m/z calcd for $C_{21}H_{15}O_3NS$ (M^+): 361.0773; found 361.0782.

3.5. Ethyl 8-(3-hydroxypropyl)-7-phenylthieno[3,2-*f*]quinoline-2-carboxylate (5)

2 N HCl (1.5 mL) was added to a solution of ethyl 5-phenyl-3,4,4a,5,6,11c-hexahydro-2*H*-pyrano[3,2-*c*]thieno[3,2-*f*]quinoline-10-carboxylate (**2a**) (197 mg; 0.50 mmol) in CH_3CN (2 mL). This mixture was refluxed for 2.5 h. After cooling, the reaction mixture was neutralized with Na_2CO_3 solution and extracted Et_2O. The organic layer was washed with water and brine and dried over $MgSO_4$. The mixture was filtered, evaporated to dryness, and the residue was purified by column chromatography on silica gel using CH_2Cl_2/EtOAc (90/10) as eluent to afford ethyl 8-(3-hydroxypropyl)-7-phenylthieno[3,2-*f*]quinoline-2-carboxylate (78 mg, 40%). Mp 141–144 °C; IR: 3324, 3341, 2924, 2853, 1699, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (t, J=7.2 Hz, 3H, CH_3), 1.81 (m, 2H, CH_2), 2.95 (t, J=7.5 Hz, 2H, CH_2), 3.54 (m, J=6.2 Hz, 2H, CH_2), 4.45 (q, J=7.1 Hz, 2H, CO_2CH_2), 7.42–7.57 (m, 5H, Ph), 7.98 (d, J=9.0 Hz, 1H), 8.09 (d, J=9.0 Hz, 1H, Ph), 8.50 (s, 1H), 8.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 29.4, 29.8, 33.6, 61.9, 123.7, 124.3, 127.9, 128.4, 128.6, 128.9, 129.1, 131.9, 134.3, 134.4, 134.5, 140.6, 141.1, 145.0, 159.8, 162.7; HRMS (EI): m/z calcd for $C_{23}H_{21}O_3NS$ (M^+): 391.1242; found 391.1245.

3.6. Ethyl 4-(3-hydroxypropyl)-2,3,3a,4,5,10c-hexahydrofuro[3,2-*c*]thieno[3,2-*f*]quinoline-9-carboxylate (6)

DHF (0.17 mL; 2.20 mmol) and I_2 (25.4 mg; 10 mol %) were added to a solution of ethyl 5-aminobenzo[*b*]-thiophene-2-carboxylate (**1**) (221 mg; 1.00 mmol) in CH_2Cl_2 (4.5 mL). This mixture was stirred for 30 min at room temperature. After complete conversion, as indicated by TLC, a saturated solution of $Na_2S_2O_3$ (20 mL) was added, and the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine and dried over $MgSO_4$. The mixture was filtered, evaporated to dryness, and the residue was purified by column chromatography on silica gel using CH_2Cl_2/EtOAc (50/50) as eluent to afford a mixture of both isomers. The cis isomer was obtained as pure product by recrystallization from EtOAc. NMR-values of the trans isomer were determined based on the ratio of both isomers (trans/cis, 86/14). *trans*-**6**. Mp 122–144 °C; IR: 3369, 3280, 2915, 2852, 1695, 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.40 (t, J=7.3 Hz, 3H, CH_3), 1.57–1.94 (m, 6H, CH_2CH_2, H_3), 2.20 (m, 1H, H_{3a}), 2.83 (dt, J=8.2, 2.3 Hz, 1H, H_4), 3.70 (t, J=5.5 Hz, 2H, CH_2OH), 3.84 (m, 2H, H_2, H_5), 3.99 (m, 1H, H_2), 4.39 (q, J=7.3 Hz, 2H, CO_2CH_2), 4.83 (d, J=5.6 Hz, 1H, H_{10c}), 6.79 (d, J=8.8 Hz, 1H, H_6), 7.53 (d, J=8.8 Hz, 1H, H_7), 8.17 (s, 1H, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 28.8, 29.2, 29.8, 41.2, 52.4, 61.5, 62.8, 65.9, 74.2, 117.6, 123.0, 128.7, 133.2, 134.5, 140.2, 142.5, 163.3; MS (CI): m/z=362 (MH^+).

cis-**6**. Mp 169 °C; IR: 3479, 3329, 2931, 1685, 1259 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.40 (t, J=7.3 Hz, 3H, CH_3), 1.69 (m, 5H, CH_2CH_2, H_3), 1.92 (m, 1H, H_3), 2.08 (m, 1H, H_{3a}), 2.74 (m, 1H, H_4), 3.45 (br s, 1H, H_5), 3.74 (t, J=5.5 Hz, 2H, CH_2OH), 3.80 (m, 2H, H_2), 4.40 (q, J=7.3 Hz, 2H, CO_2CH_2), 5.47 (d, J=8.0 Hz, 1H, H_{10c}), 6.71 (d, J=8.6 Hz, 1H, H_6), 7.50 (d, J=8.6 Hz, 1H, H_7), 8.22 (s, 1H, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 24.3, 29.2, 30.8, 43.1, 52.9, 61.5, 62.8, 67.0, 74.5, 117.0, 117.5, 122.6, 129.3, 133.9, 134.4, 139.6, 142.5, 163.3; HRMS (EI): m/z calcd for $C_{19}H_{23}O_4NS$ (M^+): 361.1348; found 361.1358.

3.7. Ethyl 5-(4-hydroxybutyl)-3,4,4a,5,6,11c-hexahydro-2*H*-pyrano[3,2-*c*]thieno[3,2-*f*]quinoline-10-carboxylate (7)

DHP (0.20 mL; 2.20 mmol) and I_2 (50.8 mg; 20 mol %) were added to a solution of ethyl 5-aminobenzo[*b*]-thiophene-2-carboxylate (**1**) (221 mg; 1.00 mmol) in CH_3CN (5 mL). This mixture was stirred for 3 h at room temperature. After complete conversion, as indicated by TLC, a saturated solution of $Na_2S_2O_3$ (20 mL) was added, and the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine and dried over $MgSO_4$. The mixture was filtered, evaporated to dryness, and the residue was purified by column chromatography on silica gel using CH_2Cl_2/EtOAc (50/50) as eluent to afford a mixture of both isomers (trans/cis, 82/18). The isomers were separated by column chromatography, using petroleum ether/EtOAc (90/10) as eluent, to afford pure trans isomer. The cis isomer easily oxidized and was thus not possible to further characterize. *trans*-**7**. Obtained as a yellow solid; mp 53–57 °C; IR: 3369, 2933, 2856, 1697, 1235 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, J=7.3 Hz, 3H, CH_3), 1.40–1.92 (m, 11H), 2.06 (m, 1H), 3.69 (m, 3H, CH_2OH, H_2), 3.84 (dt, J=8.9, 2.3 Hz, 1H, H_2), 4.02 (m, 1H, H_6), 4.40 (q, J=7.3 Hz, 2H, CO_2CH_2), 4.76 (d, J=2.3 Hz, 1H, H_{11c}), 6.72 (d, J=8.6 Hz, 1H, H_7), 7.50 (d, J=8.9 Hz, 1H, H_8), 8.05 (s, 1H, H_{11}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 21.0, 22.2, 24.0, 32.3, 32.9, 36.5, 48.6, 61.5, 62.7, 68.5, 72.3, 114.5, 117.7, 123.3, 127.9, 132.5, 134.2, 139.6, 142.6, 163.3; HRMS (EI): m/z calcd for $C_{21}H_{27}O_4NS$ (M^+): 389.1661; found 389.1661.

Acknowledgements

The authors are grateful to the IWT [Institute for the Promotion of Innovation through Science and Technology in Flanders (IWT-Vlaanderen)] for a doctoral fellowship for W.V.S.

References and notes

1. Reinhard, R.; Glaser, M.; Neumann, R.; Maas, G. *J. Org. Chem.* **1997**, *62*, 7744.
2. Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031.
3. Dorey, G.; Lockhart, B.; Lestage, P.; Casara, P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 935.
4. Wallace, O. B.; Lauwers, K. S.; Dodge, S. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1907.
5. (a) Bendale, P.; Olepu, S.; Suryadevara, P. K.; Bulbule, V. J.; Rivas, K.; Nallan, L.; Smart, B.; Yokoyama, K.; Ankala, S.; Pendyala, P. R.; Floyd, D.; Lombardo, L. J.; Williams, D. K.; Buckner, F. S.; Chakrabarti, D.; Verlinde, C. L. M. J.; Van Voorhis, W. C.; Gelb, M. H. *J. Med. Chem.* **2007**, *50*, 4585; (b) Bulbule, V. J.; Rivas, K.; Verlinde, C. L. M. J.; Van Voorhis, W. C.; Gelb, M. H. *J. Med. Chem.* **2008**, *51*, 384.
6. (a) van Straten, N. C. R.; van Berkel, T. H. J.; Demont, D. R.; Karstens, W.-J. F.; Merkx, R.; oosterom, J.; Schulz, J.; van Someren, R. G.; Timmers, C. M.; van Zandvoort, P. M. *J. Med. Chem.* **2005**, *48*, 1697; (b) Manivannan, E.; Prasanna, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4496.
7. Leeson, P. D.; Carling, R. W.; Moore, K. W.; Mosely, A. M.; Smith, J. D.; Stevenson, G.; Chan, T.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R.; Hoogsteen, K. *J. Med. Chem.* **1992**, *35*, 1954.
8. Povarov, L. S. *Russian Chem. Rev.* **1967**, *36*, 656.
9. Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721.
10. Buonora, P.; Olsen, J.-O.; Oh, T. *Tetrahedron* **2001**, *57*, 6099.
11. Reddy, B. V. S.; Srinivas, R.; Yadav, J. S.; Ramalingam, T. *Synth. Commun.* **2001**, *31*, 1075.
12. Kouznetsov, V. V.; Bohórquez, A. R. R.; Stahenko, E. E. *Tetrahedron Lett.* **2007**, *48*, 8855.
13. Mahesh, M.; Reddy, C. V.; Reddy, K. S.; Raju, P. V. K.; Reddy, V. V. N. *Synth. Commun.* **2004**, *34*, 4089.
14. Srinivasa, A.; Mahadevan, K. M.; Hosamani, K. M.; Hulikal, V. *Monatsh. Chem.* **2008**, *139*, 141.
15. Lin, X.-F.; Cui, S.-L.; Wang, Y.-G. *Tetrahedron Lett.* **2006**, *47*, 4509.
16. Yadav, J. S.; Reddy, B. V. S.; Rao, R. S.; Kumar, S. K.; Kunwar, A. C. *Tetrahedron* **2002**, *58*, 7891.
17. Zhang, J.; Li, C.-J. *J. Org. Chem.* **2002**, *67*, 3969.
18. Chen, L.; Li, C.-J. *Green Chem.* **2003**, *5*, 627.
19. Crousse, B.; Bégué, J.-P.; Bonnet-Delpon, D. *J. Org. Chem.* **2000**, *65*, 5009.
20. (a) Legros, J.; Crousse, B.; Ourévitch, M.; Bonnet-Delpon, D. *Synlett* **2006**, 1899; (b) Spanedda, M. V.; Hoang, V. D.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J.-P. *Tetrahedron Lett.* **2004**, *44*, 219; (c) De, K.; Legros, J.; Crousse, B.; Chandrasekaran, S.; Bonnet-Delpon, D. *Org. Biomol. Chem.* **2011**, *9*, 347.
21. (a) Van Snick, W.; Nulens, W.; Jambon, S.; Dehaen, W. *Synthesis* **2009**, 767; (b) Van Snick, W.; Dehaen, W. *Tetrahedron* **2009**, *65*, 8497.
22. Yang, F.; Zheng, L.; Xiang, J.; Dang, Q.; Bai, X. *J. Comb. Chem.* **2010**, *12*, 476.
23. Yadav, J. S.; Reddy, B. V. S.; Kondaji, G.; Sowjanya, S.; Nagaiah, K. *J. Mol. Catal.* **2006**, *258*, 361.
24. Tomashevskaya, M. M.; Tomashenko, O. A.; Tomashevskii, A. A.; Sokolov, V. V.; Potekhin, A. A. *Russian J. Org. Chem.* **2007**, *43*, 77.
25. Sridharan, V.; Avendaño, C.; Menéndez, J. C. *Tetrahedron* **2007**, *63*, 673.
26. Kamal, A.; Prasad, B. R.; Ramana, A. V.; Babu, A. H.; Reddey, K. S. *Tetrahedron Lett.* **2004**, *45*, 3507.
27. Kamal, A.; Prasad, B. R.; Khan, M. N. *J. Mol. Catal.* **2007**, *274*, 133.