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Reactions of some anellated 2-aminothiophenes with electron poor acetylenes

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Dedicated to the memory of Dr. Emmanuel Nyiondi-Bonguen

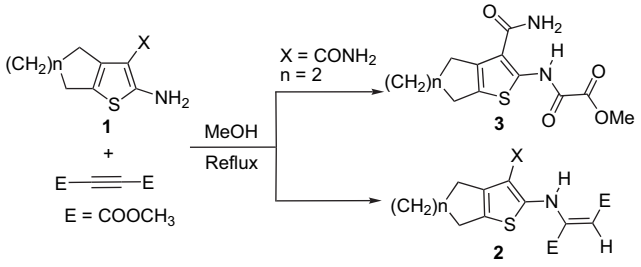
Abstract—The reactivity of 2-aminothiophenes in two different anellations: (a) [*b*]-anellation to a saturated carbocycle and (b) [3,4-*c*]-anellation to benzopyrans, towards typical acetylenic dienophiles has been investigated. Because of the absence of conjugation, the thiophenes of type (a) do not undergo [4+2]-cycloaddition with acetylenic dienophiles. Instead, the *N*-vinylated products **2** and **3** were obtained with dimethyl acetylene dicarboxylate (DMAD). Electron poor alkynes react with the thiophenes of type (b) in three main ways: DMAD reacts in a [4+2]-mode in dioxane to give the products **7**, **8** and **14**; a Michael addition type reaction also takes place at the doubly vinylene homologous carbon atoms (C-1 in the starting materials **4**, **9** and **10**) in dioxane, methanol or ethanol. Methyl propiolate reacts in a similar way. The doubly *N*-vinylated product **26** was obtained from **10** in toluene and the C-1 vinylated products **24B** and **27** were obtained from **9** in dioxane and **10** in methanol. The reaction of **10** with phenyl ethyl propiolate in dimethylformamide gave no addition product, instead a dimer of the acetylenic reagent was the isolated product. The accuracy of the assigned structures **5**, **12** and **13a** could be achieved on the basis of a single-crystal X-ray structure analysis of compound **13a**. The reaction mechanism and the nature of the isolated products are dependent on the nature of the solvent. No addition reaction was observed between **17** and DMAD. The influence of the N-substitution on the nature of the addition (Michael or Diels–Alder) could be settled through the reactions of **18** and **21** with DMAD, which gave **19** and **14** (via **22**), respectively as the only isolable products.

1. Introduction

In previous studies,[1–3a] the reactivity of compound **4** towards a variety of 1,3-dicarbonyl compounds (β-ketoesters and β-diesters) and dienophiles like dimethyl maleate (or dimethyl fumarate) and dimethyl acetylene dicarboxylate (DMAD) was reported. We here report our investigations on the reactivity of 2-aminothiophenes **1a–g**, **4**, **9**, **10**[3b] and **17**[3b] towards electron poor alkynes (DMAD, ethyl propiolate and ethyl phenylpropiolate).

2. Results

The starting compounds were prepared using either the one-pot (**1a–g** and **17**) or the two-step procedures (**4**, **9** and **10**) of the Gewald method. Compounds **1a–d** react with DMAD under reflux in methanol to afford the *N*-vinylated products **2a–d** (Scheme 1). Substrate **1e** under similar reaction conditions gave the product **3**. However, with **1f**,**g**, no product could be obtained under similar reaction conditions.



1,2	a	b	c	d	e	f	g
n	1	2	2	2	2	3	3
X	CO_2CH_3	CN	CO_3CH_3	COC_2H_5	$CONH_2$	CN	$CONH_2$

Scheme 1.

The suggested structures agreed with the analytical and spectroscopic data. The formation of compound **3** can well be attributed to the polyfunctionality of substrate **1e**. The course of the reaction involves the formation of intermediates **3A** and (after addition of water) **3B**. The determining

Keywords: 2-Aminothiophenes; Angular anellation; Diels–Alder addition; Electron poor acetylenes; Michael addition; *retro*-Aldol-reaction.
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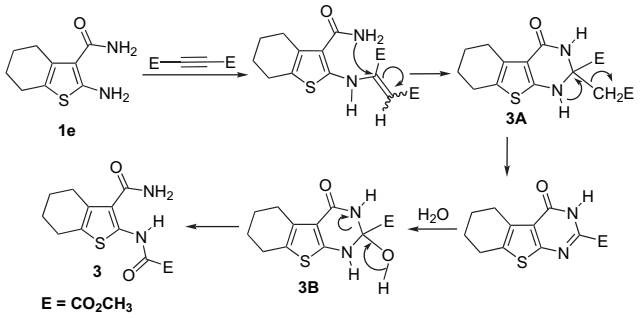
step is a Michael type addition followed by a *retro*-aldol like elimination of methyl acetate (Scheme 2).



Scheme 2.

In refluxing methanol or ethanol, compound **4** reacts with DMAD to give the 1:3 addition product **5** (Scheme 3) as a mixture (1:1) of two stereoisomers in 44% yield.

When compound **4** was treated with excess of DMAD under reflux in dioxane, compound **5** was obtained in 21% yield after cooling in liquid nitrogen. The silica-gel chromatography of the resulting filtrate gave 27% of compound **8**[3b] and 10% of compound **7**. Compound **8** can be quantitatively prepared by reacting **9** with dimethyl maleate (or dimethyl fumarate). Derivative **7** is conceivable from both precursors **6** and **8** (Scheme 3).

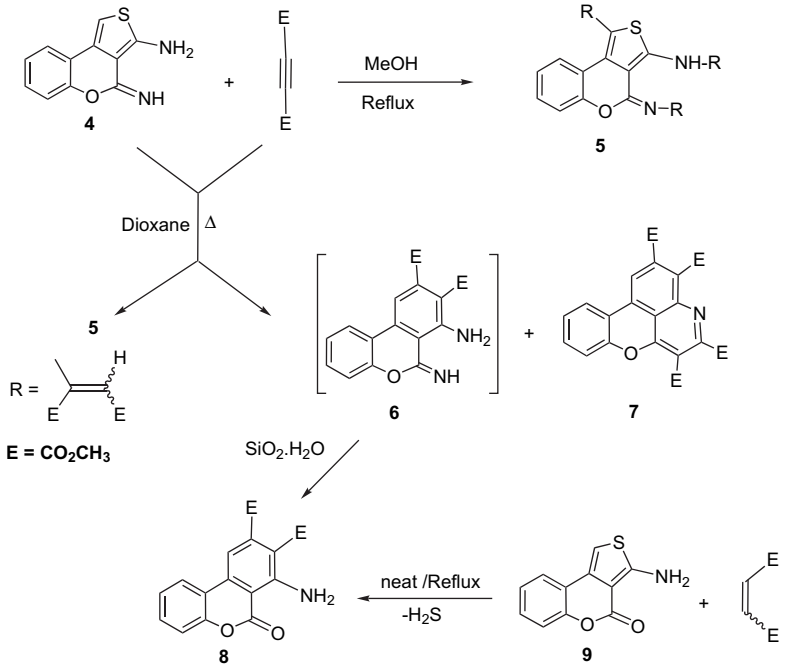
The key steps in both reaction routes could be considered as 6π-electrocyclizations of the intermediate 1:1 Michael adducts. Under the same reaction conditions as with **4**, the substrates **9** and **10**, respectively, react with DMAD to afford compounds **8** and **12** or **13a** and **14**, respectively (Scheme 4).

In the widest sense, the compounds **5**, **12** and **13a** can be considered as Michael addition products. These structures were further supported by a single-crystal X-ray structure analysis of **13a** (Fig. 1). Although the compound exists in a stable helical conformation in the crystal, the existence of stable enantiomers in solution could not be proven (HPLC using various chiral stationary phases). Rotation of the fumarate moiety relative to the thiophene ring may cause rapid interconversion of enantiomers.

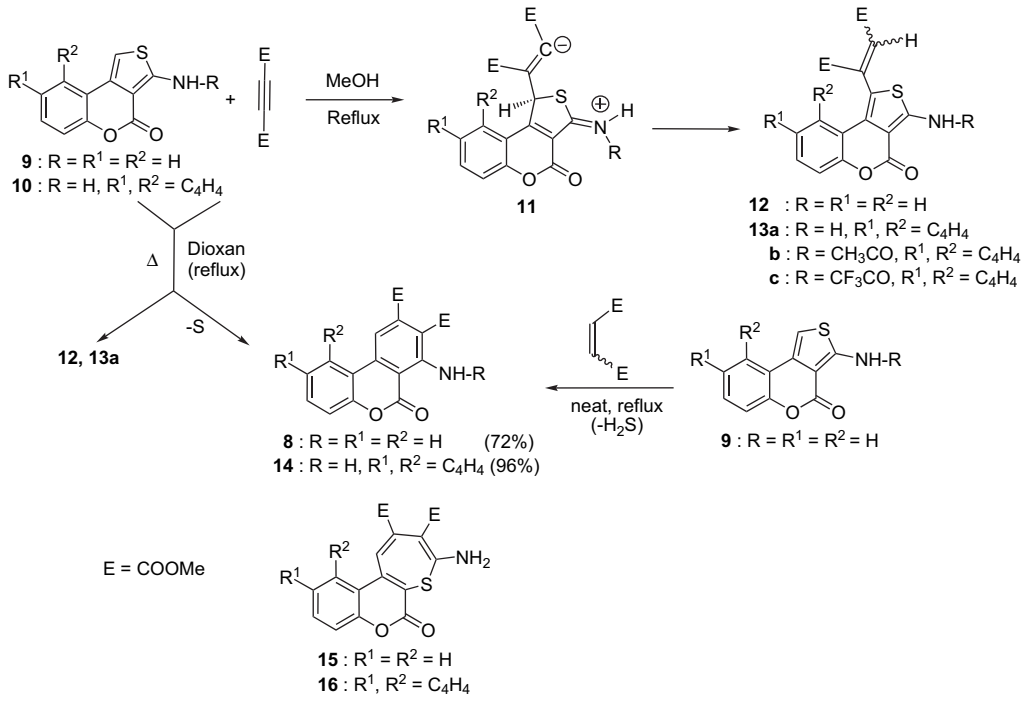
Compound **13a** was further characterized by the preparation of its *N*-acyl derivatives **13b**,**c**. The ^{1}H-NOESY experiment[3b] with **13b** provided more supporting evidence for the suggested structures **5**, **12** and **13a**. The observation of ^{1}H-NOESY cross-peaks between the singlets at δ=3.36 ppm (assigned to $COOCH_3$ at C-3 in the fumarate moiety), the singlet at δ=6.97 ppm (3-H), the doublet at δ=7.86 ppm (6′-H) and the overlapped ddd at 7.46 ppm (9′-H and 10′-H), points to the torsional flexibility of the fumarate 4-methoxy group in solution and to the proximity of the fumarate moiety to C-9′ and C-10′.

On the other hand, only one cross-peak is observed between the singlet at δ=3.52 ppm (assigned to $COOCH_3$ at C-2 in the fumarate moiety) and the singlet at δ=6.97 ppm (3-H). This is in agreement with the apparent remoteness of the carbomethoxy group at C-2 from the naphthalene ring system. Besides a cross-peak between δ=2.41 ppm (s, $COCH_3$) and δ=11.03 ppm (br s, –NH–), another cross-peak is observed between δ=2.41 ppm and δ=6.97 ppm (s, 3-H). This observation suggests a conformation in solution in which the methyl protons are close to 3-H of the fumarate fragment. Similarly all the conceivable isomeric thiepin derivatives (e.g. **15** and **16**) were ruled out on the basis of their ^{1}H and ^{13}C(^{1}H) NMR experimental and simulated spectral data.[3b]

By reacting compound **9** with DMAD under reflux for 4 h, Elnagdi et al.[4] recently isolated a substance to which they



Scheme 3.



Scheme 4.

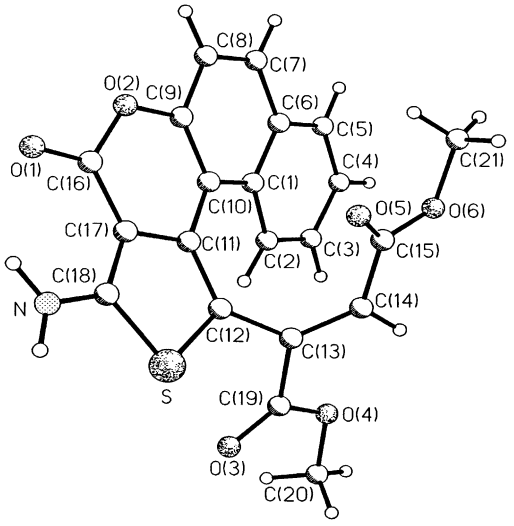
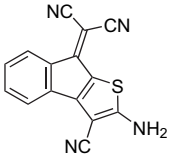


Figure 1. Single-crystal X-ray structure analysis of compound **13a**. The crystallographic numbering does not reflect the systematic IUPAC numbering.

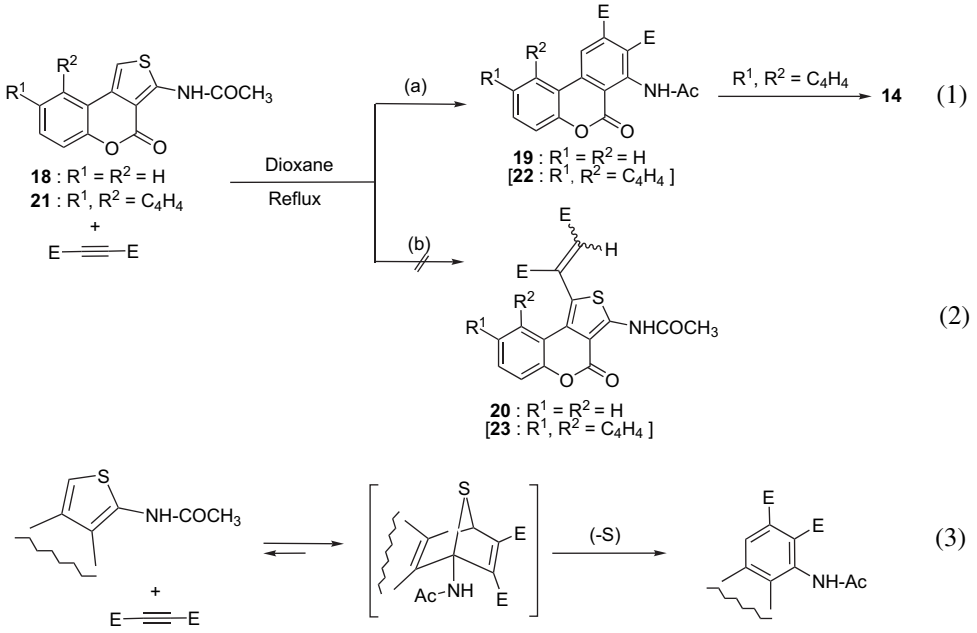
assigned the structure of the thiepin **15**, probably on the basis of former reasoning.[1,2,3a] With a melting point of 162 °C[4] from ethanol (171–173 °C from methanol for **12**) and almost identical analytical and spectroscopic data, we assume that this compound is identical to **12** (Scheme 4). The formation of compound **5** is the most complicated case and the consequence of the polyfunctionality of the starting material **4**: both amino and imino groups can add to the electron poor triple bond. The fastest reaction is obviously the addition of DMAD at the position 1 in **4**, **9** and **10**. It can be rationalized in terms of attack on the doubly vinylene-homologous position to the amino group. The known compounds **8** and **7** are nevertheless products of a Diels–Alder addition of the acetylene diester on the thiophene ring of **4** or **9** (Scheme 3). It is also conceivable that the intermediate **12** cyclizes to give such a [4+2]-adduct. In any case the newly constructed benzene ring results from the extrusion of elemental sulfur from this primary [4+2]-adduct (Scheme 4).



17

Numerous attempts to induce a reaction between compound **17** and DMAD so far remain unsuccessful. The sluggishness of the reaction of substrate **17** compared to other substrates could partly be attributed to the push–pull effect, which leads to the great stability of this substrate, and hence its unreactivity towards dienophiles.

The assumption that the Michael type addition at C-1 in **4**, **9** and **10** is favoured by the free NH_2-group, prompted us to study the reactions of the *N*-acylated products **18** and **21** towards DMAD. As anticipated, no Michael adduct was observed in these reactions in refluxing DMF. The Diels–Alder adducts **19** and **14** (through **22**), respectively, were the only isolable reaction products from substrates **18** and **21** in 42 and 11% yield (Scheme 5). The formation of compound **14** certainly results from subsequent hydrolysis of the acetamido group of the primarily formed but not isolable cycloadduct **22**. The low yields of **14** and **19** (<50% in both cases) observed in these reactions suggests that *N*-acylation as in **18** and **21** drastically decreases the vinylation at C-1 and allows the otherwise less competitive Diels–Alder addition to gain importance.

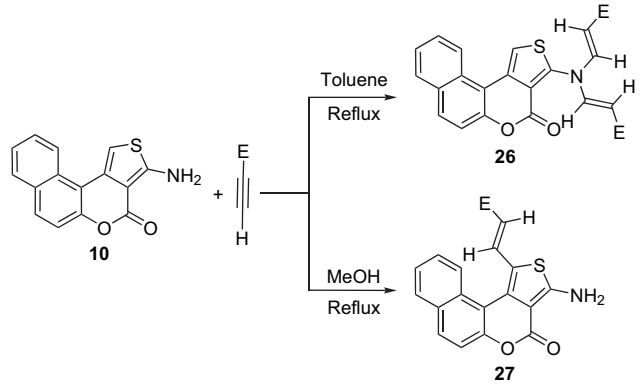


Scheme 5.

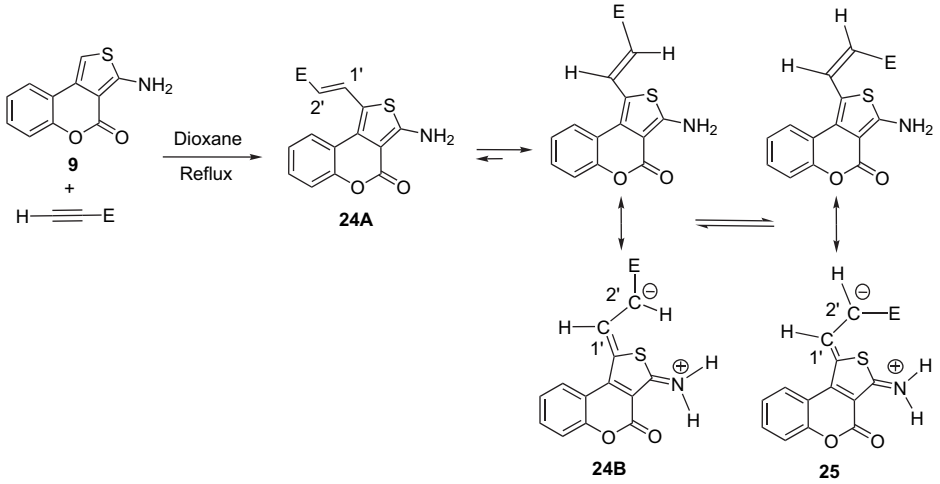
Also the reaction of substrate **9** with methyl propiolate under reflux in dioxane gave 73% yield the Michael type 1:1 adducts **24** and **25** (Scheme 6) as a 13:1 mixture.

By reacting compound **10** with methyl propiolate in refluxing toluene, the *N,N*-divinylation product **26** (Scheme 7) was the isolated product in 70% yield. The structure of **26** resulted from analytical and spectroscopic data.

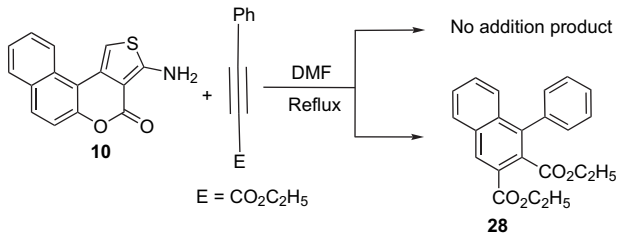
When the reaction was carried out in refluxing methanol, a yellow substance melting at 312–314 °C was isolated, to which structure **27** (Scheme 7) was assigned on the basis of IR- and mass-spectroscopic data. The reaction of **10** with ethyl phenylpropiolate gave neither a cycloaddition, nor a Michael addition product. The dimerization product **28**



Scheme 7.



Scheme 6.

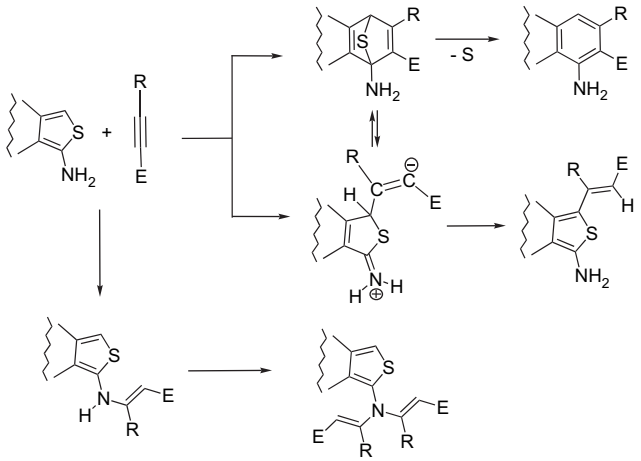


Scheme 8.

(Scheme 8) of the acetylene was instead the isolated compound from this reaction.

3. Conclusions

The reactions of 2-aminothiophenes with electron poor alkynes described in this work are of following types: (i) conjugate additions to the amino- or imino groups; (ii) conjugate additions at C-1 of the thienocoumarin derivatives **4**, **9** and **10**; (iii) formation of an anellated benzene ring across the 3,4-double bond of the coumarin derivative, very probably through a [4+2]-cycloaddition with subsequent desulfuration. One could also, in principle, envisage that the formal [4+2]-cycloaddition can also take place stepwise. The cases found by Elnagdi et al.[4] also fit in Scheme 9. The successful cycloadditions encountered in this work are normal[5] Diels–Alder reactions, in which the diene HOMO/dienophile-LUMO is the predominant interaction. They can therefore be rationalized by perturbation theory.[5,6]



Scheme 9.

4. Experimental

All elemental and spectroscopic analyses were performed in the Chemistry Department Analytical Center of Gerhard-Mercaptor-Universität Duisburg, Duisburg (Germany). All melting points were determined with a Reichert Thermovar microscope and are uncorrected. The IR and the UV spectra were measured with Perkin–Elmer 983 and 554 spectrophotometers, respectively. ^{1}H and ^{13}C(^{1}H) NMR spectra were recorded on Bruker WM 300 and DRX 500 instruments, with TMS as internal standard. Coupling constants J are reported in Hertz. Mass spectra were obtained on Varian MAT 311A and AMD 604 instruments by electron impact ionization (EI) at 18 eV or 70 eV, using a direct inlet system. Combustion analyses were carried out with a CHN+O/S elemental analyzer 'CARLO ERBA' Model 1106. Simulated ^{1}H and ^{13}C(^{1}H) NMR spectra were performed with an ACD NMR spectra simulation programme.

4.1. Gewald synthesis of 2-aminothiophenes

4.1.1. Variant A (one-pot procedure)[7–11] general procedure. To an equimolar (if not otherwise stated) mixture of ketone, nitrile and finely powdered elemental sulfur in ethanol (if not otherwise stated) the indicated amount of diethylamine, piperidine or morpholine is slowly added with magnetic stirring, so that the temperature does not exceed 50 °C. By warming, sulfur progressively dissolves. For a slower reaction one should warm periodically up to 40–50 °C (water bath). Continued warming bears the risk of the formation of the disulfide.[7–11] The reaction lasts for 4–6 h in total. The reaction mixture is kept in the refrigerator for crystallization for several hours, after which the precipitate is collected and worked up as indicated. If not otherwise stated, the given yields are based on the inputs of ketone.

4.1.1.1. Methyl 2-amino-5,6-dihydro-4*H*-cyclopenta-[*b*]thiophene-3-carboxylate (1a). From cyclopentanone (33.60 g, 0.4 mol), methyl cyanoacetate (19.80 g, 0.2 mol), powdered sulfur (3.2 g, 0.1 mol) and piperidine (8.50 g, 0.1 mol), the reaction lasted for 8 h. Crystallization from methanol gave the *title compound* **1a** (13.91 g, 35% based on the nitrile) as yellow powder, mp 181–183 °C [Found: C, 54.73; H, 5.54; N, 7.05; S, 16.45. $C_9H_{11}NO_2S$ requires C, 54.82; H, 5.58; N, 7,11; S, 16.24%]; ν_{max} (potassium bromide) 3410, 3293, 3163, 3076, 2967, 2944, 2857, 1654 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.86 (2H, br s, D_2O-exchangeable, NH_2), 3.78 (3H, s, O*Me*), 2.83–2.77 (2H, m, 4-H_2), 2.74–2.68 (2H, m, 6-H_2), 2.35–2.26 (2H, m, 5-H_2); δ_C (75 MHz, $CDCl_3$) 166.5, 166.1, 142.6, 121.4, 102.8, 50.6, 30.7, 28.8, 27.3; *m*/*z* (EI) 198 (5), 197 (49, M$^+$), 167 (5), 166 (15), 165 (100), 164 (12%).

4.1.1.2. 2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-carbonitrile (1b). From cyclohexanone (29.4 g, 0.3 mol), malononitrile (13.20 g, 0.2 mol), powdered sulfur (6.4 g, 0.2 mol) and diethylamine (7.3 g, 0.1 mol) in ethanol, the reaction was conducted for 2 h. Crystallization from 50% aqueous ethanol gave the *title compound* **1b** (29.94 g, 84%) as yellow powder, mp 144–146 °C (lit.,[10] 147–148 °C from ethanol) [Found: C, 60.68; H, 5.64; N, 15.67; S, 17.96. $C_9H_{10}N_2S$ requires C, 60.67; H, 5.64; N, 15.67; S, 17.96%]; ν_{max} (potassium bromide) 3446, 3330, 3207, 2956, 2932, 2911, 2854, 2838, 2744, 2667, 2649, 2198 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.41 (2H, br s, D_2O-exchangeable, NH_2), 2.55–2.43 (4H, m, 4-H_2 and 7-H_2), 1.86–1.72 (4H, m, 5-H_2 and 6-H_2); δ_C (75 MHz, $CDCl_3$) 160.0, 132.4, 120.7, 115.5, 88.8, 24.6, 24.2, 23.4, 22.2; *m*/*z* (EI) 179 (6), 178 (49, M$^+$), 177 (15), 151(10), 150 (100%).

4.1.1.3. Methyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]-thiophene-3-carboxylate (1c). From cyclohexanone (29.4 g, 0.3 mol), methyl cyanoacetate (19.18 g, 0.2 mol), sulfur (6.40 g, 0.2 mol) and diethylamine (8.50 g, 0.1 mol), the reaction was conducted for 9.5 h. The precipitate was

crystallized from methanol/water (75:25) to give the *title compound* **1c** (29.34 g, 70%) as yellow powder; mp 128–130 °C (lit.,[12] 127–128 °C from methanol) [Found: C, 56.92; H, 6.20; N, 6.62; S, 15.27. $C_{10}H_{13}NO_2S$ requires C, 56.87; H, 6.16; N, 6.64; S, 15.17%]; ν_{max} (potassium bromide) 3421, 3315, 3157, 3013, 2929, 2837, 1653 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.95 (2H, br s, D_2O-exchangeable, NH_2), 3.78 (3H, s, O*Me*), 2.70–2.63 (2H, m, 7-H_2), 2.52–2.46 (2H, m, 4-H_2), 1.81–1.68 (4H, m, 6-H_2 and 5-H_2); δ_C (75 MHz, $CDCl_3$) 166.5, 161.9, 132.5, 117.7, 105.7, 50.6, 26.9, 24.6, 23.3, 22.8; *m/z* (EI) 212 (7), 211 (52, M^+), 183 (3), 181 (6), 180 (16), 179 (100%).

4.1.1.4. Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]-thiophene-3-carboxylate (1d). From cyclohexanone (29.4 g, 0.3 mol) ethylcyanoacetate (11.30 g, 0.1 mol), sulfur (3.20 g, 0.1 mol) and piperidine (4.25 g, 0.05 mol), the reaction lasted for 9 h and the precipitate was crystallized from 50% aqueous ethanol to give the *title compound* **1d** (15.76 g, 70%) as yellow powder, mp 117–118 °C (lit.,[10] 115 °C from methanol) [Found: C, 58.63; H, 6.60; N, 6.30; S, 14.35. $C_{11}H_{15}NO_2S$ requires C, 58.67; H, 6.67; N, 6.22; S, 14.22%]; ν_{max} (potassium bromide) 3405, 3300, 3230, 3167, 3077, 2986, 2939, 2886, 2855, 2841, 1643 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.97 (2H, br s, D_2O-exchangeable, NH_2), 4.24 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 2.71–2.66 (2H, m, 7-H_2), 2.49–2.45 (2H, m, 4-H_2), 1.79–1.67 (4H, m, 6-H_2 and 5-H_2), 1.37 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 166.2, 161.8, 132.5, 117.6, 105.8, 59.4, 27.0, 24.6, 23.32, 22.9, 14.5; *m/z* (EI) 227 (5), 226 (11), 225 (70, M^+), 197 (3), 181(10), 180 (29), 179 (100%).

4.1.1.5. 2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (1e). From cyclohexanone (3.92 g, 40 mmol), cyanoacetamide (3.36 g, 80 mmol), sulfur (1.28 g, 40 mmol) and piperidine (2.92 g, 35 mmol), the reaction was carried out for 7 h and the precipitate was crystallized from 50% aqueous ethanol to give the *title compound* **1e** (3.54 g, 45% based on the nitrile) as yellow powder, mp 180–181 °C (lit.,[10] 189–190 °C from methanol) [Found: C, 55.04; H, 6.08; N, 14.15; S, 16.40. $C_9H_{12}N_2OS$ requires C, 55.10; H, 6.12; N, 14.27; S, 16.34%]; ν_{max} (potassium bromide) 3482, 3387, 3305, 3153, 2939, 1642, 1311, 1281, 1258, 1185 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.55 (4H, br s, D_2O-exchangeable, NH_2), 2.39–2.33 (4H, m, 4-H_2 and 7-H_2), 2.28–2.26 (4H, m, 5-H_2 and 6-H_2); δ_C (75 MHz, $CDCl_3$) 168.4, 160.6, 129.2, 117.7, 107.1, 26.8, 24.4, 22.8, 22.8; *m/z* (EI) 198 (4), 197 (9), 196 (67, M^+), 181 (8), 180 (17), 179 (100%).

4.1.1.6. 2-Amino-5,6,7,8-tetrahydro-4*H*-cyclohepta-[*b*]thiophene-3-carbonitrile (1f). From cycloheptanone (16.8 g, 150 mmol), malononitrile (6.6 g, 100 mmol), sulfur (3.2 g, 100 mmol) and piperidine (4.25 g, 50 mmol) in ethanol, the reaction lasted for 6 h. Crystallization from 50% aqueous ethanol gave the *title compound* **1f** (12.09 g, 67% based on the nitrile) as brown powder, mp 115–117 °C (lit.,[13] 114 °C from ethanol) [Found: C, 62.38; H, 6.21; N, 14.39; S, 16.86. $C_{10}H_{12}N_2S$ requires C, 62.50; H, 6.25; N, 14.58; S, 16.67%]; ν_{max} (potassium bromide) 3445, 3310, 3208, 2927, 2840, 2205 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.57 (2H, br s, D_2O-exchangeable, NH_2), 2.68–2.60 (4H, m, 8-H_2), 2.59–2.51 (2H, m, 4-H_2), 1.86–1.78 (1H, m, 7-H_2), 1.68–1.65 (2H, m, 5-H_2), 1.64–1.60 (2H, m, 6-H_2); δ_C (75 MHz, $CDCl_3$) 158.1, 136.9, 123.8, 115.9, 91.9, 31.9, 29.4, 29.2, 28.1, 27.3; *m/z* (EI) 194 (5), 193 (15), 192 (100%, M^+).

4.1.1.7. 2-Amino-5,6,7,8-tetrahydro-4*H*-cyclohepta-[*b*]thiophene-3-carboxamide (1g). From cycloheptanone (5.60 g, 50 mmol), cyanoacetamide (4.2 g, 50 mmol), sulfur (1.6 g, 50 mmol) and piperidine (4.25 g, 50 mmol) in ethanol, the reaction was conducted for 5 h and the resulting precipitate was crystallized from 50% aqueous ethanol to give the *title compound* **1g** (5.01 g, 48% based on the nitrile) as red powder, mp 154–156 °C (lit.,[14] 183–186 °C from ethanol); ν_{max} (potassium bromide) 3375, 3198, 2915, 2844, 1630 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 6.79 (2H, br s, D_2O-exchangeable, CONH_2), 6.02 (2H, br s, D_2O-exchangeable, NH_2), 2.68–2.48 (4H, m, 4-H_2 and 8-H_2), 1.73–1.50 (6H, m, 5-H_2, 6-H_2 and 7-H_2); δ_C ($CDCl_3$, 75 MHz) 167.9, 153.6, 136.4, 120.1, 113.5, 31.7, 28.6, 28.3, 27.8, 27.2; *m/z* (EI) 210 (44, M^+), 194 (14), 193 (100), 192 (7), 178 (4), 172 (4), 166 (4), 165 (19), 164 (11), 45 (4), 44 (4%).

4.1.1.8. 3-Amino-4*H*-thieno[3,4-*c*](2*H*)chromen-4-one (9). A mixture of *o*-hydroxyacetophenone (27.2 g, 200 mmol), sulfur (6.4 g, 200 mmol) and ethylcyanoacetate (22.6 g, 200 mmol), or methyl cyanoacetate (19.8 g, 200 mmol), respectively in methanol (200 mL) in the presence of morpholine or diethylamine, was stirred for 24 h. The precipitate was crystallized from benzene to give the *title compound* **9** (16 g, 37%) as yellow powder, mp 197–199 °C (lit.,[15a,b] 198–199 °C from benzene) [Found: C, 61.17; H, 3.36; N, 6.49; S, 14.45. $C_{11}H_7NO_2S$ requires C, 60.83; H, 3.23; N, 6.45; S, 14.75%]; ν_{max} (potassium bromide) 3449, 3407, 3343, 3101, 1687 cm^{-1}; δ_H (DMSO-d_6, 300 MHz) 7.86 (6-H, dd, *J* 8.0, 1.5 Hz, 1H), 7.78 (2H, br s, D_2O-exchangeable, NH_2), 7.35 (1H, ddd, *J* 8.0, 7.4, 1.8 Hz, 7-H), 7.21 (1H, d, *J* 7.0 Hz, 9-H), 7.19 (1H, ddd, *J* 8.2, 7.6, 1.2 Hz, 8-H), 6.88 (1H, s, 1-H); δ_C (DMSO-d_6, 75 MHz) 166.6 (C-3), 158.9 (C-2), 151.0, 130.9, 129.3, 124.4, 123.9, 118.1, 117.1, 98.1, 97.54; *m/z* (EI) 219 (6), 218 (13), 217 (100%, M^+).

4.1.1.9. 3-Acetamido-4*H*-thieno[3,4-*c*](2*H*)chromen-4-one (18). From **9** (2.17 g, 10 mmol) and acetic acid anhydride (20 mL) in pyridine at room temperature, the reaction lasted for 48 h and the precipitate was crystallized from pyridine to give the *title compound* **18** (2.21 g, 85%) as yellow crystals, mp 268–270 °C [Found: C, 60.19; H, 3.50; N, 5.57; S, 12.44. $C_{13}H_9NO_3S$ requires C, 60.23; H, 3.47; N, 5.41; S, 12.36%]; ν_{max} (potassium bromide) 3465, 3299, 3100, 1678 cm^{-1}; δ_H (DMSO-d_6, 300 MHz) 10.9 (1H, br s, D_2O-exchangeable, N*H*), 8.03 (1H, dd, *J* 7.7, 1.6 Hz, 6-H), 7.69 (1H, s, 1-H), 7.44 (1H, ddd, *J* 7.0, 6.9, 1.6 Hz, 7-H), 7.34 (1H, dd, *J* 7.9, 1.2 Hz, 9-H), 7.32 (1H, ddd, *J* 7.5, 7.2, 1.4 Hz, 8-H), 2.33 (3H, s, CH_3); δ_C (DMSO-d_6, 75 MHz) 168.8, 158.6, 150.2, 149.9, 130.1, 129.8, 125.1, 124.3, 117.3, 117.1, 108.6, 105.8, 23.2; *m/z* (EI) 260 (4), 259 (25, M^+), 219 (6), 218 (14), 217 (100), 189 (4), 44 (12), 43 (23%).

4.1.1.10. 2-Amino-4-(dicyanomethylene)-4*H*-indeno[2,3-b]thiophene-1-carbonitrile (17). From indan-1,3-dione (1.46 g, 10 mmol), malononitrile (1.32 g, 20 mmol), sulfur (0.32 g, 20 mmol) and diethylamine (1.46 g, 20 mmol) in dioxane, the reaction was conducted for 6 h and the resulting

precipitate was crystallized from dioxane to give the *title compound* **17** (1.84 g, 67%) as deep blue powder, mp>350 °C [Found: C, 65.53; H, 2.24; N, 20.30; S, 11.73. $C_{15}H_6N_4S$ requires C, 65.69; H, 2.19; N, 20.44; S, 11.68%]; ν_{max} (potassium bromide) 3365, 3182, 2951, 2855, 2219 cm^{-1}; λ_{max} (dioxane) (log ε) 240 (4.32), 280 (4.14), 380 (4.14), 540 nm (3.78); δ_H (DMSO-d_6, 300 MHz) 9.24 (2H, br s, D_2O-exchangeable, N*H*$_2$), 7.71 (1H, d, *J* 6.9 Hz, 5-H), 7.35 (1H, ddd, *J* 7.4, 7.3, 1.1 Hz, 6-H), 7.29 (1H, dd, *J* 7.54, 1.25 Hz, 8-H), 7.23 (1H, ddd, *J* 7.7, 7.0, 0.7 Hz, 7-H); δ_C (DMSO-d_6, 75 MHz) 176.2, 154.9, 153.9, 137.6, 134.8, 132.1, 129.5, 123.8, 120.1, 114.9, 114.1, 113.9, 113.0, 80.3, 63.8; *m*/*z* (EI) 275 (35, MH^+), 274 (100%, M^+).

4.1.2. Variant B (two-step procedure)[7–11]. Compounds **4**,[15a,b] **9**[15a,b] and **10** were prepared according to the two-step procedure of the Gewald method, in the reported yields.

4.1.2.1. 3-Amino-4-imino-4*H*-thieno[3,4-*c*](2*H*)chromene (4). Yellowish powder from benzene, mp 158–160 °C, from xylene (lit.,[15a,b] 152 °C from xylene) [Found: C, 61.07; H, 3.74; N, 12.97; S, 14.79. $C_{11}H_8N_2OS$ requires C, 61.09; H, 3.73; N, 12.95; S, 14.83%]; ν_{max} (potassium bromide) 3382, 3276, 3108, 3057, 1630, 1589, 1475, 1355, 1292, 1179, 1099, 932, 877, 792 cm^{-1}; λ_{max} (dioxane) (log ε) 200 (4.88), 228 (5.31), 267 (5.37), 305 nm (4.80); δ_H (DMSO-d_6, 300 MHz) 7.87 (1H, br s, D_2O-exchangeable, =N*H*), 7.77 (1H, dd, *J* 7.7, 1.6 Hz, 9-H), 7.69 (2H, br s, D_2O-exchangeable, N*H*$_2$), 7.26 (1H, ddd, *J* 8.1, 7.0, 1.6 Hz, 7-H), 7.1 (1H, ddd, *J* 14.4, 8.2, 1.3 Hz, 8-H), 7.1 (1H, dd, *J* 8.1, 1.1 Hz, 6-H), 6.8 (1H, s, 1-H); δ_C (DMSO-d_6, 75 MHz) 160.7, 155.1, 150.7, 129.7, 129.0, 123.9, 123.5, 118.3, 116.3, 99.7, 97.2; *m*/*z* (EI) 218 (6), 217 (16), 216 (M^+, 100), 215 (33), 199 (5), 77 (7%).

4.1.2.2. 3-Amino-4*H*-benzo[*f*]thieno[3,4-*c*](2*H*)chromen-4-one (10). Yellow prisms from benzene, mp 235–237 °C [Found: C, 67.36, H, 3.43; N, 5.28; S, 11.90. $C_{15}H_9NO_2S$ requires C, 67.42; H, 3.37; N, 5.24; S, 11.99%]; ν_{max} (potassium bromide) 3439, 3335, 3137, 1690 cm^{-1}; δ_H (DMSO-d_6, 300 MHz) 8.69 (1H, d, *J* 8.5 Hz, 6-H), 8.33 (2H, br dd, *J* 8.1, 1.2 Hz, H-8 and H-11), 7.93 (2H, br s, D_2O-exchangeable, N*H*$_2$), 7.68 (1H, ddd, *J* 8.5, 7.0, 1.5 Hz, 10-H), 7.55 (1H, ddd, *J* 7.5, 7.4, 0.8 Hz, 9-H), 7.40 (1H, d, *J* 8.9 Hz, 7-H), 7.33 (1H, s, 1-H); δ_C (DMSO-d_6, 75 MHz) 165.8, 159.0, 150.4, 130.8, 130.5, 129.6, 129.4, 129.3, 128.3, 125.3, 124.5, 117.9, 111.6, 101.2, 99.4; *m*/*z* (EI) 269 (6, MH_2^+), 268 (17, MH^+), 267 (100%, M^+).

4.1.2.3. 3-Acetamido-4*H*-benzo[*f*]thieno[3,4-*c*](2*H*)-chromen-4-one (21). Compound **10** (0.224 g, 0.84 mmol) was treated with acetic acid anhydride (3.5 mL) in pyridine at room temperature for 48 h and gave the *title compound* **21** after crystallization from pyridine (0.13 g, 85%) as yellow prisms, mp 286–288 °C [Found: C, 66.17; H, 3.62; S, 4.53; S, 10.26. $C_{17}H_{11}NO_3S$ requires C, 66.02; H, 3.56; N, 4.53; S, 10.36%]; ν_{max} (potassium bromide) 3445, 3272, 1696, 1671 cm^{-1}; δ_H (DMSO-d_6, 300 MHz) 10.98 (1H, br s, D_2O-exchangeable, N*H*), 8.82 (1H, d, *J* 8.42 Hz, 6-H), 8.0 (2 H, br d, *J* 8.5 Hz, 8-H and 11-H), 7.75 (1H, dd, *J* 7.8, 7.7 Hz, 10-H), 7.61 (1H, dd, *J* 7.4, 7.3 Hz, 9-H), 7.51 (1H, d, *J* 8.8 Hz, 7-H), 8.09 (1H, s, 1-H), 2.36 (3H, s, CO*Me*); δ_C (DMSO-d_6, 75 MHz) 168.2, 158.3, 149.2, 149.2, 130.8, 130.6, 129.1, 129.0, 128.4, 128.2, 125.3, 124.2, 117.4, 111.2, 110.6, 106.6, 22.9; *m*/*z* (EI) 311 (4), 310 (11), 309 (M^+, 54), 269 (6), 268 (19), 267 (100), 44 (6%).

4.1.3. Reactions of 2-aminothiophenes with acetylenic reagents general procedure. An equimolar amount (1–2.5 mmol, if not specified otherwise) of the 2-aminothiophene and the electron poor acetylene in the given solvent was refluxed with magnetic stirring for 3–10 h (if not specified otherwise). The reaction mixture was worked up as usual and the product was purified as described for each particular substance. The unoptimized yields are based on the amounts of reacted 2-aminothiophene.

4.1.3.1. Dimethyl (*E*,*Z*){*N*-[2-(3-methoxycarbonyl-5,6-dihydro-4*H*-cyclopenta[*b*]thienyl)]amino}butenedioate (2a). From a mixture of **1a** (0.50 g, 2.5 mmol) and DMAD, (1.42 g, 10 mmol) in methanol, the reaction was conducted for 9.5 h and the precipitate was crystallized from methanol to give the *title compound* **2a** (700 mg, 81%) as yellow needles, mp 94–96 °C. The remaining oily fraction was discarded analyzed [Found: C, 53.01; H, 4.90; N, 3.98; S, 9.30. $C_{15}H_{17}NO_6S$ requires C, 53.10; H, 5.01; N, 4.13; S, 9.44%]; ν_{max} (potassium bromide) 3444, 3150, 3023, 2947, 2860, 1731, 1697, 1685 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 11.56 (1H, br s, D_2O-exchangeable, N*H*), 5.44 (1H, s, =C*H*), 3.87 (3H, s, O*Me*), 3.86 (3H, s, O*Me*), 3.78 (3H, s, O*Me*), 2.91–2.81 (2H, m, 4′-H_2), 2.79–2.76 (2H, m, 6′-H_2), 2.39–2.29 (2H, m, 5′-H_2); δ_C ($CDCl_3$, 75 MHz) 168.3, 164.8, 164.1, 154.8, 144.6, 143.4, 128.4, 110.1, 96.8, 53.2, 51.6, 51.5, 30.6, 29.1, 27.4; *m*/*z* (EI) 342 (7), 340 (18), 339 (100, M^+), 44 (3%).

4.1.3.2. Dimethyl (*E*,*Z*)-2{*N*-[2-(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thienyl)]amino}butenedioate (2b). From **1b** (450 mg, 2.5 mmol) and DMAD (1.42 g, 10 mmol) in methanol, the reaction was carried out for 9 h. The reaction mixture was concentrated in vacuo and the resulting oily residue was kept in the refrigerator for few days. Crystallization of the solid from methanol gave the *title compound* **2b** (273 mg, 34%) as yellow needles, mp 117–118 °C. The mother liquor was discarded [Found: C, 56.14; H, 4.92; N, 8.67; S, 10.25. $C_{15}H_{16}N_2O_4S$ requires C, 56.25; H, 5.00; N, 8.75; S, 10.00%]; ν_{max} (potassium bromide) 3447, 3187, 3095, 2950, 2935, 2859, 2212, 1734, 1672 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 9.90 (1H, br s, D_2O-exchangeable, N*H*), 5.69 (1H, s, (COOMe)C*H*=), 3.83 (3H, s, COO*Me*), 3.77 (3H, s, COO*Me*), 2.63–2.57 (4H, m, 4′-H_2 and 7′-H_2), 1.87–1.78 (4H, m, 5′-H_2 and 6′-H_2); δ_C ($CDCl_3$, 75 MHz): 169.5, 162.8, 150.3, 146.1, 133.8, 130.2, 102.0, 97.5, 53.2, 51.7, 24.5, 24.4, 23.0, 22.0; *m*/*z* (EI) 322 (4), 321 (9), 320 (51, M^+), 289 (10), 288 (44), 262 (10), 261 (37), 260 (100), 59 (5), 45 (3), 32 (46%).

4.1.3.3. Dimethyl (*E*,*Z*)-2-{*N*-[2-(3-methoxycarbonyl-4,5,6,7-tetrahydrobenzo[*l*]thienyl)]amino}butenedioate (2c). From a mixture of **1c** (0.53 g, 2.5 mmol) and DMAD (1.42 g, 10 mmol) in methanol, the reaction lasted for 10 h and the resulting precipitate was crystallized from aqueous methanol to afford the *title compound* **2c** (742 mg, 84%) as yellow needles, mp 107–109 °C. The mother liquor was discarded. [Found: C, 54.35; H, 5.42; N, 3.95; S, 9.34. $C_{10}H_{13}NO_2S$ requires C, 54.39; H, 5.38; N, 3.97; S,

9.07%]; ν_{max} (potassium bromide) 3450, 3269, 3130, 3034, 3000, 2948, 2844, 1735, 1681 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 11.62 (1H, br s, D_2O-exchangeable, N*H*), 5.43 (1H, s, 3-H), 3.88 (3H, s, O*Me*), 3.87 (3H, s, O*Me*), 3.78 (3H, s, O*Me*), 2.77–2.63 (2H, m, 7′-H_2), 2.59–2.55 (2H, m, 4′-H_2), 1.83–1.71 (4H, m, 6′-H_2 and 5′-H_2); δ_C ($CDCl_3$, 75 MHz) 168.3, 165.0, 164.3, 150.4, 145.0, 133.4, 124.5, 113.2, 97.1, 53.3, 51.6, 51.4, 26.6, 24.7, 23.0, 22.6; *m/z* (EI) 353 (64, M^+), 321 (32), 293 (21), 234 (100), 44 (4%).

4.1.3.4. (*E* or *Z*) Dimethyl 2-{*N*-[2-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[*b*]thienyl)]amino}butenedioate (2d). A mixture of **1d** (0.56 g, 2.5 mmol) and DMAD (1.42 g, 10 mmol) in methanol gave after 10 h of reaction a precipitate, which was crystallized from methanol to give the *title compound* **2d** (3.43 g, 38%) as yellow needles, mp 82–84 °C. The oily mother liquor was discarded. [Found: C, 55.60; H, 5.60; N, 3.84; S, 9.07. $C_{17}H_{21}NO_6S$ requires C, 55.59; H, 5.72; N, 3.80; S, 8.72%]; ν_{max} (potassium bromide) 3450, 3232, 3029–2843, 1736, 1673 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 11.56 (1H, br s, D_2O-exchangeable, N*H*), 5.41 (1H, s, =C*H*), 4.35 (2H, q, *J* 7.1 Hz, OC$H_2$$CH_3$), 3.84 (3H, s, O*Me*), 3.75 (3H, s, O*Me*), 2.75–2.57 (2H, m, 7′-H_2), 2.56–2.53 (2H, m, 4′-H_2), 1.80–1.71 (4H, m, 6′-H_2 and 5′-H_2), 1.35 (3H, t, *J* 7.1 Hz, $OCH_2C$$H_3$); δ_C ($CDCl_3$, 75 MHz) 168.2, 164.6, 164.2, 150.3, 144.9, 133.3, 124.5, 113.5, 97.1, 60.3, 53.2, 51.5, 26.6, 24.6, 22.9, 22.6, 14.3; *m/z* (EI) 367 (95, M^+), 335 (37), 307 (25), 276 (15), 262 (100%).

4.1.3.5. Methyl {*N*-[2-(3-aminocarbonyl-4,5,6,7-tetrahydrobenzo[*b*]thienyl)]}oxamate (3). From a mixture of **1e** (0.50 g, 2.5 mmol) and DMAD (1.42 g, 10 mmol) in methanol, the reaction was carried out for 9 h and the resulting precipitate was crystallized from methanol to give the *title compound* **3** (95 mg, 13%) as yellowish powder, mp 218–220 °C. The remaining oilish mixture was not further analyzed [Found: C, 51.12; H, 4.98; N, 9.83; S, 11.50. $C_{12}H_{14}N_2O_4S$ requires C, 51.06; H, 4.96; N, 9.93; S, 11.35%]; ν_{max} (potassium bromide) 3499, 3331, 3265, 3211, 2953, 2836, 1729, 1693 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 12.81 (1H, br s, D_2O-exchangeable, N*H*), 7.65 (1H, br s, D_2O-exchangeable, N*H*), 7.05 (1H, br s, D_2O-exchangeable, N*H*), 3.84 (3H, s, COO*Me*), 2.72 (2H, m, 8′-H_2), 2.64 (2H, m, 5′-H_2), 1.73 (4H, m, 6′-H_2 and 7′-H_2); δ_C ($CDCl_3$, 75 MHz) 167.2, 167.2, 159.7, 152.6, 140.9, 129.7, 128.1, 118.1, 53.7, 25.3, 24.1, 22.5, 22.4; *m/z* (EI) 283 (6, MH^+), 282 (43, M^+), 266 (9), 265 (61), 59 (6%).

4.1.4. Reactions with 1f,g. From 2.5 mmol of **1f** (or **1g**, respectively) and 1.42 g (10 mmol) of DMAD, the reactions in methanol gave after 9 h no new products.

4.1.4.1. Dimethyl 2-{3-[1,2-di(methoxycarbonyl)vinyl]-amino-4-[1,2-di(methoxycarbonyl)vinyl]imino-4*H*-thieno-[3,4-*c*](2*H*)chromen-1-yl}butenedioate (5, *E*,*Z*-mixture). From a mixture of **4** (0.54 g, 2.5 mmol) and DMAD (3 mL, excess) in methanol, the reaction was conducted for 9 h. The solvent was evaporated in vacuo to give a crude material, which was kept in the freezer for few days. The resulting precipitate was crystallized from methanol to give the *title compound* **5** (704 mg, 44%) as orange powder, mp 165–167 °C [Found: C, 54.20; H, 4.01; N, 4.38; S, 5.04. $C_{29}H_{26}N_2O_{13}S$ requires C, 54.21; H, 4.05; N, 4.36; S, 4.98%]; ν_{max} (potassium bromide) 3433, 2953, 1725, 1661 cm^{-1}; λ_{max} (THF) (log ε) 252 (3.28), 292 (3.19), 322 (3.11), 368 (3.06), 400 nm (3.01); δ_H (500 MHz, $CDCl_3$) 12.16 (1H, br s, N*H*, D_2O-exchangeable), 11.81 (1H, br s, N*H*, D_2O-exchangeable), 7.46 (1H, dd, *J* 7.9, 1.3 Hz, 9-H), 7.40 (1H, ddd, *J* 8.0, 7.9, 1.5 Hz, 7-H), 7.35 (1H, s, olefinic H), 7.29 (1H, ddd, *J* 11.7, 8.9, 1.4 Hz, 8-H), 7.28 (1H, s, olefinic H), 7.25 (1H, dd, *J* 7.8, 1.1 Hz, 6-H), 7.12 (1H, ddd, *J* 7.7, 7.6, 1.0 Hz, 7-H), 7.08 (1H, dd, *J* 6.9, 1.0 Hz, 9-H), 7.05 (1H, dd, *J* 9.2, 2.1 Hz, 6H), 7.06 (1H, ddd, *J* 7.0, 6.2, 1.8 Hz, 8-H), 6.45 (1H, s, olefinic H), 6.35 (1H, s, olefinic H), 5.83 (1H, s, olefinic H), 5.66 (1H, s, olefinic H), 3.95 (3H, s, O*Me*), 3.90 (3H, s, O*Me*), 3.84 (3H, s, O*Me*), 3.75 (3H, s, O*Me*), 3.73 (s, 3H, OMe), 3.71 (3H, s, O*Me*), 3.70 (3H, s, O*Me*), 3.692 (3H, s, O*Me*), 3.689 (3H, s, O*Me*), 3.65 (3H, s, O*Me*); δ_C (125 MHz, $CDCl_3$) 166.7, 166.3, 165.6, 165.5, 165.4, 164.7, 164.5, 164.3, 164.2, 163.8, 151.7, 150.5, 150.4, 150.3, 150.1, 148.9, 144.9, 144.6, 143.3, 142.2, 136.4, 136.3, 134.2, 133.6, 129.7, 129.3, 124.6, 124.5, 124.2, 116.9, 116.8, 112.8, 112.1, 101.8, 97.2, 128.1, 127.7, 117.9, 117.6, 112.4, 111.7, 107.9, 107.8, 53.6, 53.5, 53.3, 53.3, 52.9, 52.9, 52.5, 52.3, 51.7, 51.6, 51.5, 51.4; *m/z* (EI) 642 (27, M^+), 585 (28), 583 (70), 552 (17), 551 (26), 425 (89), 366 (49), 334 (12), 307 (26), 248 (10), 154 (100), 59 (67), 44 (16%).

4.1.4.2. Tetramethyl 4-aza-7-oxabenz[*m*,*n*]anthracene-2,3,5,6-tetracarboxylate (7). The reaction of **4** (0.54 g, 2.5 mmol) and DMAD (3 mL, excess) in dioxane for 10 h, gave a mixture from which compound **5** (325 mg, 21%) gently separated on ice-cooling (freezer), for few days. The mother liquor residue was subjected to plc (solvent: hexane/ethyl acetate 7:3) to afford compound **8** (220 mg, 27%) as red needles (mp 201–203 °C from methanol); the *title compound* **7** (110 mg, 10%) as yellow needles (mp 268–270 °C, from aqueous DMF); compound **9** as yellow powder (mp 197–199 °C, from benzene) and the non-reacted DMAD [Found: C, 62.09; H, 4.13; N, 4.30. $C_{23}H_{17}NO_9$ requires C, 62.39; H, 3.98; N, 4.28%]; ν_{max} (potassium bromide) 3005, 2953, 1746, 1726 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 8.48 (1H, s, 1-H), 8.33 (1H, dd, *J* 8.5, 1.6 Hz, 8-H), 7.61 (1H, ddd, *J* 8.3, 7.3, 1.5 Hz, 9-H), 7.43 (1H, ddd, *J* 7.4, 7.3, 1.0 Hz, 10-H), 7.42 (1H, dd, *J* 9.4, 1.1 Hz, 11-H), 3.97 (3H, s, COO*Me*), 3.96 (3H, s, COO*Me*), 3.93 (3H, s, COO*Me*), 3.92 (3H, s, COO*Me*); δ_C (125 MHz, DMSO-d_6) 166.1, 164.7, 164.6, 163.3, 156.3, 151.0, 149.8, 144.8, 132.2, 132.0, 131.0, 128.7, 125.8, 124.1, 118.4, 117.9, 117.6, 115.8, 109.7, 53.0, 52.9, 52.6, 52.3; *m/z* (EI) 451 (83, M^+), 421 (10), 420 (39), 406 (8), 393 (4), 392 (13), 374 (6), 335 (100%).

4.1.4.3. Dimethyl 7-amino-6-oxo-6*H*-benzo[*c*](2*H*)-chromen-8,9-dicarboxylate (8). [Found: C, 62.02; H, 3.98; N, 4.22. $C_{17}H_{13}NO_6$ requires C, 62.39; H, 3.98; N, 4.28%]; ν_{max} (potassium bromide) 3415, 3311, 2958, 1740, 1710 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 8.30 (1H, dd, *J* 8.1, 1.5 Hz, 4-H), 8.19 (2H, br s, D_2O-exchangeable, NH_2), 7.60 (1H, ddd, *J* 9.5, 8.0, 1.5 Hz, 3-H), 7.59 (1H, dd, *J* 6.9, 1.8 Hz, 1-H), 7.39 (s, 1H, 10-H), 7.37 (1H, ddd, *J* 7.9, 7.2, 1.1 Hz, 2-H), 3.86 (3H, s, COO*Me*), 3.80 (3H, s,

COO*Me*); δ_C (75 MHz, DMSO-d_6) 168.1, 166.6, 161.4, 152.1, 151.3, 141.1, 139.8, 132.4, 125.2, 124.9, 117.2, 117.1, 110.0, 107.4, 104.9, 53.0, 52.8; *m/z* (EI) 328 (19), 327 (100, M^+), 238 (22), 44 (5%).

4.1.4.4. Dimethyl 2-(3-amino-4-oxo-4*H*-thieno[3,4-*c*](2*H*)chromen-1-yl)butenedioate (12). Reacting **9** (0.54 g, 2.5 mmol) with DMAD (4 mL, excess) in methanol for 5 h, gave after concentration in vacuo, a crude material, which was crystallized from methanol to afford the *title compound* **12** (570 mg, 64%) as red prisms, mp 154–156 °C. When the same reaction was conducted with the same inputs of starting materials in dioxane for 8 h, compound **12** separated from the reaction concentrate on ice-cooling (freezer), to give the *title compound* **12** (159 mg, 21%) as red prisms, mp 155–157 °C (from ethanol). [Found: C, 56.73; H, 3.68; N, 3.88; S, 8.93. $C_{17}H_{13}NO_6S$ requires C, 56.82; H, 3.62; N, 3.90; S, 8.91%]; ν_{max} (potassium bromide) 3438, 3331, 2956, 1722, 1704, 1617, 1584, 1482, 1384, 1264, 1129, 943, 888, 793 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.98 (2H, br s, D_2O-exchangeable, N*H*$_2$), 7.38 (1H, dd, *J* 8.03, 1.69 Hz, 6′-H), 7.37 (1H, ddd, *J* 7.2, 6.4, 1.7 Hz, 7′-H), 7.25 (1H, dd, *J* 8.6, 1.3 Hz, 9′-H), 7.16 (1H, ddd, *J* 8.2, 6.9, 1.5 Hz, 8′-H), 7.16 (1H, s, 3-H), 3.68 (3H, s, COO*Me*), 3.56 (3H, s, COO*Me*); δ_C (75 MHz, DMSO-d_6) 166.3, 165.5, 158.8, 151.4, 136.1, 133.2, 129.7, 128.7, 124.5, 124.4, 118.1, 117.5, 105.1, 98.8, 53.5, 52.3; *m/z* (EI) 361 (7, MH_2^+), 359 (33, M^+), 301 (14), 300 (60), 299 (100), 285 (8), 268 (20), 257 (12), 242 (14), 241 (81), 240 (13), 186 (19), 59 (9), 44 (5%). On further cooling of the mother liquor in liquid nitrogen a precipitate was collected and crystallized from methanol to afford compound **8** (see above, 354 mg, 44%).

4.1.4.5. Dimethyl 2-(3-amino-4-oxo-4*H*-benzo[*f*]-thieno[3,4-*c*](2*H*)chromen-1-yl)fumarate (13a). On reacting **10** (0.814 g, 3 mmol) with DMAD (5 mL, excess) in methanol for 10 h, a precipitate was obtained from the reaction concentrate after ice-cooling (freezer) for several days. Recrystallization from methanol gave the *title compound* **13a** (777 mg, 62%) as red prisms, mp 171–173 °C. When the same quantities of **10** and DMAD were reacted for 8 hours in dioxane, compound **13a** crystallized on cooling (upon storage in a freezer) the reaction concentrate after a few days. This crop was crystallited from ethanol to give 108 mg (26%) of red prisms, mp 174–176 °C [Found: C, 61.43; H, 3.75; N, 3.34; S, 7.84. $C_{21}H_{15}NO_6S$ requires C, 61.61; H, 3.67; N, 3.42; S, 7.82%]; ν_{max} (potassium bromide) 3440, 3334, 3055, 2939, 1723, 1705, 1592, 1427, 1332, 1263, 1113, 1079, 942, 874, 792 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 8.20 (2H, br s, D_2O-exchangeable, NH_2), 7.99 (1H, d, *J* 8.84 Hz, 6′-H), 7.93 (1H, dd, *J* 7.5, 1.9 Hz, 11′-H), 7.88 (1H, dd, *J* 8.3, 1.4 Hz, 8′-H), 7.46 (2H, br ddd, *J* 9.6, 6.9, 2.1 Hz, 9′-H and 10′-H), 7.43 (1H, dd, *J* 8.8, 1.3 Hz, 7′-H), 6.61 (1H, s, 3-H), 3.38 (3H, s, COO*Me*), 3.26 (3H, s, COO*Me*); δ_C (75 MHz, DMSO-d_6) 167.2, 165.4, 164.9, 158.7, 150.3, 137.0, 132.4, 131.0, 130.6, 128.4, 128.1, 126.7, 126.5, 125.8, 125.4, 117.2, 112.6, 106.6, 101.1, 52.9, 51.6; *m/z* (EI) 409 (14, M^+), 377 (17), 351 (15), 350 (53), 349 (100), 335 (11), 318 (18), 292 (19), 291 (90), 175 (18), 44 (9%). Further cooling of the mother liquor in liquid nitrogen and crystallization of the precipitate from ethanol gave 220 mg (58%) of compound **14** (see below) as yellow prisms, mp 187–189 °C. Analytical HPLC of **13a** using a Merck-Hitachi chromatograph, column length 250 mm, column diameter 5 mm, flow rate 1 mL/min, on chiral stationary phases Merck Chiraspher NT (5 μm) with heptane/THF 50:50, 70:30, and 80:20 as well as Merck Whelk-01 (5 μm) with hexane/2-propanol 95:5, 80:20 and 70:30, gave no separation.

Crystal structure analysis of **13a**: The crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 602732. Details will be published separately.

4.2. Acylations of 13a

4.2.1. Reaction with acetic acid anhydride.

4.2.1.1. Dimethyl 2-(3-acetamino-4-oxo-4*H*-benzo[*f*]-thieno[3,4-*c*](2*H*)chromen-1-yl)fumarate (13b). A mixture of **13a** (52 mg, 0.13 mmol) and acetic acid anhydride (3 mL) was treated with pyridine (4 mL) for 48 h at room temperature. Evaporation of the solvent in vacuo gave a crude material, which was crystallized from ethyl acetate to afford the *title compound* **13b** (56 mg, 98%) as yellow powder, mp 241–243 °C [Found: C, 60.98; H, 3.85; N, 3.10; S, 7.33. $C_{23}H_{17}NO_7S$ requires C, 61.20; H, 3.77; N, 3.10; S, 7.10%]; ν_{max} (potassium bromide) 3436, 3267, 2953, 1723, 1708, 1682 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.03 (1H, br s, D_2O-exchangeable, N*H*), 8.10 (1H, dd, *J* 7.4, 1.5 Hz, 11′-H), 7.86 (1H, d, *J* 8.7 Hz, 6′-H), 7.83 (1H, dd, *J* 7.3, 2.2 Hz, 8′-H), 7.46 (2H, br ddd, *J* 9.8, 7.7, 1.0 Hz, 9′-H and 10′-H), 7.43 (1H, d, *J* 8.8 Hz, 7′-H), 6.97 (1H, s, 3-H), 3.52 (3H, s, COO*Me*), 3.36 (3H, s, COO*Me*), 2.41 (3H, s, CO*Me*); δ_C (125 MHz, DMSO-d_6) 167.7, 165.0, 164.9, 160.2, 151.1, 149.5, 137.9, 130.9, 130.8, 130.3, 128.7, 128.4, 128.1, 126.6, 126.1, 125.6, 117.8, 117.2, 112.9, 108.8, 52.8, 52.0, 23.4; *m/z* (EI) 452 (4), 451 (17, M^+), 421 (3), 420 (8), 419 (27), 409 (14), 378 (5), 377 (17), 393 (40), 391(86), 352 (6), 349 (100), 290 (17), 44 (6%).

4.2.2. Reaction with trifluoroacetanhydride.

4.2.2.1. Dimethyl 2-(3-trifluoroacetylamino-4-oxo-4*H*-benzo[*f*]thieno[3,4-*c*](2*H*)chromen-1-yl)fumarate (13c). A stirred mixture of **13a** (52 mg, 0.13 mmol) and trifluoroacetic acid anhydride (3 mL) was heated to reflux for 24 h. After evaporating the solvent to dryness in vacuo, the resulting crude material was purified by plc (hexane/ethyl acetate 7:3) and crystallized from ethyl acetate to yield the *title compound* **13c** (52 mg, 83%) as yellow powder, mp 154–156 °C [Found: C, 54.50; H, 2.70; N, 2.76; S, 6.41. $C_{23}H_{14}NO_7SF_3$ requires C, 54.65; H, 2.77; N, 2.77; S, 6.34%]; ν_{max} (potassium bromide) 3438, 1727, 1700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 11.91 (1H, br s, D_2O-exchangeable, N*H*COCF$_3$), 8.05 (1H, dd, *J* 9.2, 1.0 Hz, 11′-H), 7.91 (1H, d, *J* 8.8 Hz, 6′-H), 7.86 (1H, dd, *J* 8.8, 1.2 Hz, 8′-H), 7.49 (2H, br ddd, *J* 8.4, 7.0, 1.3 Hz, 9′-H and 10′-H), 7.47 (1H, d, *J* 8.9 Hz, 7′-H), 7.04 (1H, s, 3-H), 3.52 (3H, s, COO*Me*), 3.41 (3H, s, COO*Me*); δ_C (125 MHz, $CDCl_3$) 165.0, 164.8, 160.0, 149.9, 147.6, 137.5, 131.6, 131.2, 131.2, 129.7, 128.7, 128.5, 127.1, 126.3, 126.1, 120.5, 117.4, 112.7, 112.0, 53.3, 52.3; *m/z* (EI) 505 (6, M^+), 473 (11), 447(10), 446 (31), 445 (100), 387(30), 377 (17), 393 (40), 69 (6), 59 (4%).

4.2.3. Attempted reaction of 2-amino-4-(dicyanomethylene)-4*H*-indeno[2,3-*b*]thiophen-1-carbonitrile (17) with DMAD in methanol, ethanol or dioxane. Stirred mixtures of compound **17** (0.28 g, 1 mmol) and DMAD (3 mL) were successively heated to reflux in methanol, ethanol and dioxane for 9 h. Concentration in vacuo and subsequent crystallization of the resulting precipitates from dioxane gave deep blue powders (mp>350 °C), which were identified to be the starting material **17**.

4.2.3.1. Dimethyl 7-(acetylamino)-5-oxobenz[*c*](2*H*)-chromen-8,9-dicarboxylate (19). From a mixture of compound **18** (0.26 g, 1 mmol) and DMAD (3 mL) in dioxane, the reaction was carried out for 8.5 h. On cooling, the precipitate was crystallized from ethanol to afford the *title compound* **19** (155 mg, 42%) as yellow needles, mp 204–206 °C [Found: C, 61.61; H, 4.15; N, 3.72. $C_{19}H_{15}NO_7$ requires C, 61.79; H, 4.07; N, 3.79%]; ν_{max} (potassium bromide) 3431, 3273, 3066, 2953, 1740, 1725, 1671 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 10.50 (1H, br s, D_2O-exchangeable, N*H*), 8.55 (1H, s, 10-H), 8.43 (1H, dd, *J* 8.6, 1.4 Hz, 4-H), 7.63 (1H, ddd, *J* 8.0, 7.5, 1.3 Hz, 3-H), 7.44 (1H, dd, *J* 8.1, 1.2 Hz, 1-H), 7.31 (1H, ddd, *J* 7.4, 7.3, 1.2 Hz, 2-H), 3.90 (3H, s, O*Me*), 3.75 (3H, s, O*Me*), 2.09 (3H, s, CO*Me*); δ_C (75 MHz, DMSO-d_6) 169.4, 158.6, 166.3, 158.5, 151.0, 138.6, 137.5, 132.3, 129.1, 125.3, 125.0, 124.7, 117.3, 119.6, 117.1, 116.7, 108.5, 53.4, 52.7, 23.6; *m/z* (EI) 369 (26, M^+), 338 (18), 327 (100), 311 (16), 310 (80), 43 (13%).

4.2.3.2. Dimethyl 4-amino-5-oxo-5*H*-dibenzo[*c*,*f*]-(2*H*)chromen-2,3-dicarboxylate (14). From a mixture of compound **21** (0.31 g, 1 mmol) and DMAD (3 mL) in dioxane, the reaction was conducted for 8.5 h. Cooling to room temperature and subsequent crystallization of the resulting solid material from benzene afforded yellow crystals (160 mg), mp 284–286 °C, identified in all respects to the starting compound **21**. The resulting mother liquor was diluted with acetone and separated by plc using hexane/ethyl acetate 3:2 to afford the unreacted excess of DMAD and a brown amorphous substance, which was crystallized from ethanol to give 43 mg (11%) of yellow prisms (mp 180–182 °C), identified in all respects to the *title compound* **14**, mp 183–185 °C from ethanol [Found: C, 66.65; H, 4.02; N, 3.69. $C_{21}H_{15}NO_6$ requires C, 66.84; H, 3.98; N, 3.71%]; ν_{max} (potassium bromide): 3443, 3339, 2953, 1735, 1709 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 8.58 (1H, d, *J* 8.59 Hz, 12-H), 8.16 (1H, dd, *J* 8.8 Hz, 7-H), 8.11 (2H, br s, D_2O-exchangeable, NH_2), 8.09 (1H, br dd, *J* 8.1, 1.2 Hz, 9-H), 7.74 (1H, ddd, *J* 8.6, 7.1, 1.5 Hz, 11-H), 7.76 (1H, d, *J* 0.5 Hz, 1-H), 7.62 (1H, ddd, *J* 7.9, 7.0, 0.9 Hz, 10-H), 7.52 (1H, d, *J* 8.83 Hz, 8-H), 3.85 (3H, s, COO*Me*), 3.82 (3H, s, COO*Me*); δ_C (125 MHz, DMSO-d_6) 167.7, 166.5, 160.9, 151.3, 150.6, 139.6, 139.6, 133.5, 131.3, 129.6, 128.7, 128.4, 125.8, 124.4, 116.8, 111.8, 111.5, 110.2, 105.8, 53.1, 52.7; *m/z* (EI) 378 (24), 377 (100, M^+), 346 (24), 288 (12).

4.2.3.3. (*E*,*Z*) Methyl 3-[1-(3-amino-4-oxo-4*H*-thieno-[3,4-*c*](2*H*)chromenyl]propoate (24). From **9** (0.54 g, 2.5 mmol) and methyl propiolate (3 mL) in dioxane, the reaction was carried out for 5.5 h. Concentration in vacuo of the resulting solution to half of its volume gave a precipitate, which was crystallized from dioxane/ethyl acetate to afford the *title compound* **24** (550 mg, 73%) as yellow powder, mp 302–304 °C [Found: C, 59.67; H, 3.72; N, 4.68; S, 10.67. $C_{15}H_{11}NO_4S$ requires C, 59.80; H, 3.65; N, 4.65; S, 10.63%]; ν_{max} (potassium bromide) 3387, 3281, 1717, 1696 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 8.37 (2H, br s, D_2O-exchangeable, NH_2), 8.21 (1H, dd, *J* 15.0, 3.3 Hz, 2-H), 7.91 (1H, d, *J* 8.1 Hz, 6′-H), 7.48 (1H, dd, *J* 7.9, 7.6 Hz, 7′-H), 7.36 (1H, d, *J* 7.9 Hz, 9′-H), 7.29 (1H, dd, *J* 8.2, 7.7 Hz, 8′-H), 5.87 (1H, dd, *J* 15.0, 3.1 Hz, 3-H), 3.72 (3H, s, O*Me*); δ_C (75 MHz, DMSO-d_6) 166.4, 166.1, 158.3, 151.9, 135.4, 133.0, 130.4, 125.4, 124.8, 117.8, 117.6, 113.4, 111.6, 100.4, 51.2; *m/z* (EI) 303 (8), 302 (21), 301 (100, M^+), 270 (32), 243 (22), 242 (96), 241 (87%).

4.2.3.4. Dimethyl 3,3′-[3-(4-oxo-4*H*-benzo[*f*]thieno-[3,4-*c*](2*H*)chromenyl)]aminodipropoate (*E*,*Z*-mixture) (26). The reaction in dioxane of a mixture of **10** (0.67 g, 2.5 mmol) with methyl propiolate (3 mL) gave after 7 h refluxing no new product. The starting compound was instead recovered after the usual work-up. From a mixture of **10** (0.54 g, 2 mmol) and methyl propiolate (3 mL) in toluene, the reaction was carried out for 8 h. Cooling to room temperature and subsequent crystallization of the solid from 10% aqueous DMF afforded the *title compound* **26** (617 mg, 70%) as yellow powder, mp 291–293 °C [Found: C, 63.45; H, 3.91; N, 3.22; S, 7.36. $C_{23}H_{17}NO_6S$ requires C, 63.44; H, 3.94; N, 3.22; S, 7.36%]; ν_{max} (potassium bromide) 3445, 3061, 2957, 1727, 1661 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 8.97 (1H, s, 1″-H), 8.88 (1H, d, *J* 8.31 Hz, 6″-H), 8.20 (2H, d, *J* 13.5 Hz, 3-H and 3′-H), 8.09 (2H, br d, 8″-H and 11″-H); 7.82 (1H, ddd, 10″-H, *J* 8.5, 6.9, 1.4 Hz), 7.65 (1H, dd, *J* 8.7, 7.2, 7.1 Hz, 9″-H), 7.53 (1H, d, *J* 8.9 Hz, 7″-H), 4.84 (2H, d, *J* 13.5 Hz, 2-H and 2′-H), 3.59 (6H, s, 2×COO*Me*); δ_C (75 MHz, DMSO-d_6) 166.4, 153.7, 149.9, 148.6, 143.8, 133.1, 131.1, 130.8, 129.3, 128.9, 128.6, 125.5, 124.1, 121.8, 121.6, 117.4, 110.5, 98.7, 50.7; *m/z* (EI) 437 (9), 436 (27), 435 (100, M^+), 404 (11), 403 (12), 376 (27), 44 (7%).

4.2.3.5. (*E* or *Z*) Methyl 3-[1-(3-amino-4-oxo-4*H*-benzo[*f*]thieno[3,4-*c*](2*H*)chromenyl)]propenoate (27). From a mixture of **10** (401 g, 1.5 mmol) and methyl propiolate (3 mL) in methanol, the reaction was conducted for 7 h. Cooling at room temperature followed by crystallization of the precipitate from ethyl acetate gave the *title compound* **27** (35 mg, 7%) as yellow powder, mp 312–314 °C. The compound was not soluble enough in DMSO-d_6 to afford exploitable information from the NMR experiments. ν_{max} (potassium bromide) 3406, 3289, 2957, 1710, 1681 cm^{-1}; *m/z* (EI) 351 (49, M^+), 320 (6), 318 (4), 297 (7), 293 (21), 292 (100), 291 (36), 290 (3%).

4.2.3.6. Dimethyl 1-phenylnaphthalene-2,3-dicarboxylate (ethyl phenylethynecarboxylate dimer″) (28). The reaction in methanol of a mixture of **10** (401 mg, 1.5 mmol) and ethyl phenylethynecarboxylate (3 mL) was successively conducted for 54 and 48 h, respectively, in methanol and toluene and gave no new product, but rather the starting material **10**. From a mixture of **10** (270 mg, 1 mmol) and ethyl phenylpropiolate (2 mL) in DMF, the reaction was carried out for 7 h. The reaction mixture was then concentrated in vacuo to half of its volume. The resulting precipitate was crystallized from 10% aqueous DMF to

afford the *title compound* **28** (103 mg, 30%) as green-yellowish powder, mp 124–126 °C (lit.,[16–18] 127–128 °C from petroleum ether). The mother liquor was discarded; ν_{max} (potassium bromide) 3064, 2977, 2929, 2903, 1715, 1661 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.60 (1H, s, 7-H), 8.01–7.26 (9H, m, aromatic H), 4.42 (2H, q, *J* 7.1 Hz, OCH_2), 4.06 (2H, q, OCH_2, *J* 7.2 Hz), 1.42 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 0.97 (3H, t, OCH_2CH_3, *J* 7.1 Hz); δ_C (75 MHz, $CDCl_3$) 168.8, 166.0, 138.6, 136.8, 134.1, 132.4, 131.4, 131.3, 130.4, 129.3, 128.9, 128.0, 127.4, 127.0, 61.6, 61.1, 14.3, 13.7; *m/z* (EI) 348 (97, M^+), 320 (6), 304 (9), 290 (4), 277 (3), 276 (24), 275 (100, M–COOEt), 274 (4).

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