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An efficient synthetic route towards novel thienobenzothiazoles, thienobenzothiazepines, and thienobenzothiazines

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ABSTRACT

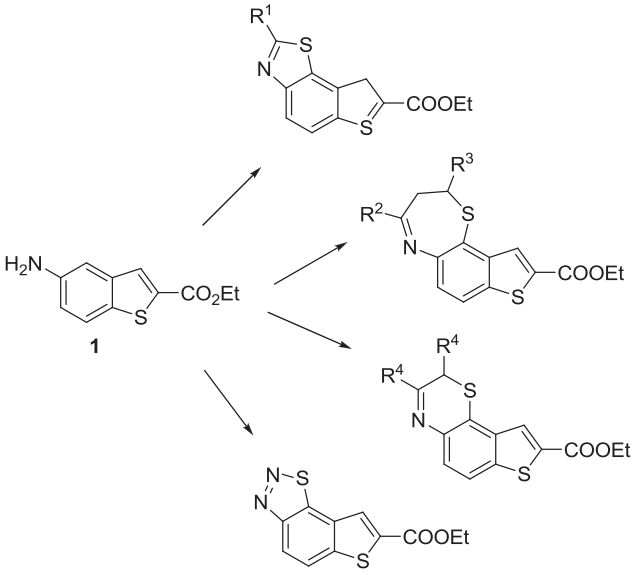
Efficient methods for the synthesis of novel nitrogen- and sulfur-containing heterocycles, annulated in the 4,5-position of benzothiophene, are described. Applying the Herz reaction, 3*H*-thienobenzodithiazole 2-oxide was prepared. This compound served as *o*-aminothiophenol precursor in the synthesis of a variety of thienobenzothiazoles, thienobenzothiazepines, thienobenzothiazines, and thienothiadiazole.

1. Introduction

Sulfur-containing heterocyclic ring systems, such as benzothiazoles, benzothiazepines, and benzothiazines, have shown a great potential in pharmaceutical research and serve as versatile scaffolds in experimental drug design.[1–4] These heterocycles are generally synthesized via condensation of an *o*-aminothiophenol with substituted aromatic aldehydes, acid chlorides, acetophenones, α,β-unsaturated ketones or substituted α-bromoacetophenones.

Our general point of interest goes to the synthesis of 4,5-annulated benzothiophenes with *N*-containing heterocycles, thus providing easy strategies towards the synthesis of novel benzothiophene fused structures. Therefore, we use the 5-aminobenzothio phene scaffold as starting material. In our preceding work we described the synthesis of ethyl 5-aminobenzothiophene-2-carboxy late (**1**),[5] the latter 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 novel thienobenzothiazoles, thienobenzothiazepines, thienobenzothiazines, and thienobenzothiadiazole in moderate to high yields, all based on our 5-aminobenzothiophene scaffold **1** (Scheme 1). It was therefore necessary to introduce an extra sulfur atom into the 4-position of this 5-aminobenzothiophene **1**, in order to obtain an *o*-aminothiophenol derivative.



Scheme 1. Synthesis of novel thienobenzothiazoles, thienobenzothiazepines, thienobenzothiazines, and thienobenzothiadiazole.

One of the most commonly used pathways for the synthesis of *o*-aminothiophenol derivatives takes place via the synthesis of a 2-aminobenzothiazole. This 2-aminobenzothiazole is easily formed by reaction of the corresponding aniline with potassium

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thiocyanate (or ammonium thiocyanate), followed by the oxidative cyclization of the formed thiourea with bromine.[6,7] The next step involves the hydrolytic cleavage of the formed benzothiazole, to yield the expected 2-aminothiophenol. However, the necessity of hydroxide base under refluxing conditions forms an obstacle, as the benzothiophene ester function, present in the starting material **1**, will be hydrolyzed too.

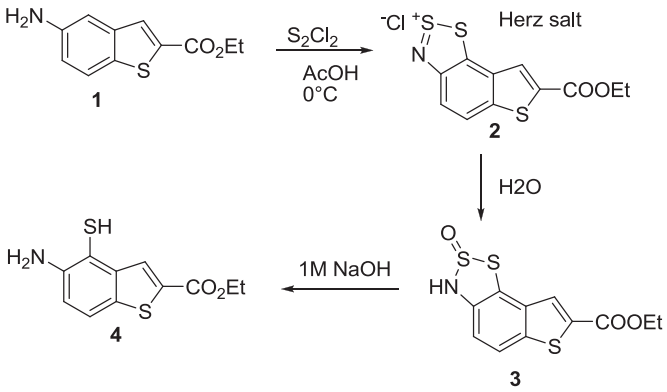
Another pathway towards our 2-aminothiophenol precursor is the Herz reaction.[8,9] This reaction involves the condensation of a primary aniline with sulfur monochloride to give the corresponding, benzodithiazolium chloride (Herz salt). Since the discovery of Herz salts, a number of reports have appeared using this method.[10–16] This method was found very popular for the synthesis of substituted *o*-aminothiophenols, as the salt can be easily hydrolyzed with sodium hydroxide. In his review, W.K. Warburton[11] described this Herz reaction and the subsequent hydrolysis of the condensation product towards *o*-aminothiophenols. Of course, 2-aminothiophenols readily undergo oxidation, forming the more stable and in this case synthetically less useful disulfides. On the other hand, the Herz salt can readily be hydrolyzed in water to give the fairly stable 3*H*-benzodithiazole 2-oxide derivative. This was reported by Herz,[9] Warburton,[11] Blomquist et al.,[12] Huestis et al.,[13] and Belica et al.[14]

We thus report herein the synthesis of a 5-amino-4-mercapto benzothiophene precursor, being the corresponding 3*H*-thienobenzodithiazole 2-oxide **3**, using the Herz reaction, and optimized methods for the synthesis of five-, six-, and seven-membered heterocyclic rings, starting from this benzodithiazole 2-oxide precursor.

2. Results and discussion

Conforming these literature procedures, we synthesized the corresponding Herz salt **2** by reaction of the starting compound 5-aminobenzothiophene **1** with S_2Cl_2 in acetic acid. This Herz compound **2** was readily hydrolyzed in water to give the 3*H*-thienobenzodithiazole 2-oxide **3** (Scheme 2). We have also tried to hydrolyze compound **3**, by treatment with a 1 M sodium hydroxide solution (Scheme 2).[11] Although the smell of sulfide was readily observed, we were not able to isolate the desired 5-amino-4-mercaptobenzothiophene derivative **4**, due to the quick oxidation of the free thiophenol function to disulfides. Moreover, ^{1}H NMR analysis also indicated hydrolysis of the ester function, as the specific signals (a quartet at 4.45 ppm and a triplet at 1.45 ppm) were no longer present in the ^{1}H NMR spectrum.

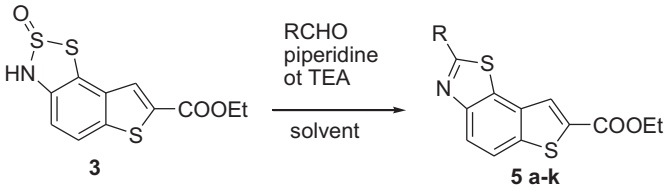
It is worth noting that brief heating of this dithiazole-oxide **3** causes decomposition, which is observed by the presence of sulfur dioxide.[15] In order to purify the compound, we generally followed



Scheme 2. Synthesis of 3*H*-thienobenzodithiazole 2-oxide **3**.

literature procedures. The crude reaction product needed to be dissolved in a large amount of methanol (about 150 mL per gram of product), followed by precipitation of the product on addition of water.[13,15] In larger scale reactions (more than 10 g of product), the workup of compound **3** seemed to become problematic. The exothermic reaction, upon mixing both liquids, was difficult to control and led to a drastic decrease of the yield with about 50%. Moreover, this purification method turned out to be less efficient on large scale, as the compound still contained impurities, which was indicated by ^{1}H NMR spectral analysis. We finally found that simply washing the compound **3** with toluene removed these impurities. Using this optimized procedure, we were able to synthesize **3** in an overall yield of 78%.

The synthesized 3*H*-thienobenzodithiazole 2-oxide **3** serves as a more stable and convenient alternative for the corresponding oxidation-sensitive *o*-aminothiophenol, as we have noticed before. Sawhney et al.[16] have reported that 3*H*-benzodithiazole 2-oxide can be reacted with benzaldehyde to afford 2-phenylbenzothia zole. We applied this reaction procedure, using benzaldehyde and triethylamine as base, at room temperature and in refluxing ethanol (Scheme 3 and Table 1, entry 1–2). In both cases we obtained the expected 2-phenylthienobenzothiazole **5a** in low to fair yields (27% and 44% resp.).



Scheme 3. Thienobenzothiazole synthesis from **3** and aromatic aldehydes.

Table 1
Optimization of thienobenzothiazole synthesis (R=phenyl)

Entry	Benzaldehyde	Solvent	Temperature	Yield **5a** [%][b]
1	1.2 equiv	EtOH[a]	25 °C	27
2	1.2 equiv	EtOH[a]	Reflux	44
3	1.2 equiv	DMSO	25 °C+120 °C	48
4	2.2 equiv	DMSO	25 °C+120 °C	77

[a] Et_3N is used as base.
[b] Yields refer to isolated products.

The mechanism of the general benzothiazole synthesis starting from 2-aminothiophenol is described in literature to go via formation of a benzothiazoline intermediate,[17] which is then oxidized to the benzothiazole. We therefore used DMSO as solvent (Table 1, entry 3). After completion of the reaction at room temperature, as indicated by TLC, we increased the reaction temperature to 120 °C and observed the formation of the final benzothiazole **5a**. We assume that the solvent DMSO acts as oxidant, because of the strong odor of dimethylsulfide, which was observed after reaction. Besides the oxidation by DMSO, it is also possible that part of the aldehyde present in the reaction is used as oxidant or hydride acceptor. In support of this the yield strikingly increased (77%) on adding more benzaldehyde to the reaction mixture (Table 1, entry 4).

We next explored this benzothiazole synthesis using a variety of aldehydes to establish optimized reaction conditions, being an excess of aldehyde in DMSO with piperidine as base (Scheme 3 & Table 2). We obtained moderate to good yields (39–77%). No specific influence from the electronic effects of the substituents was observed, except in one case, **5e** (Table 2, entry 5). Thus, an electron-donating substituent, such as the dimethylamino group, has a negative effect on the reaction, by making the aldehyde and the imine

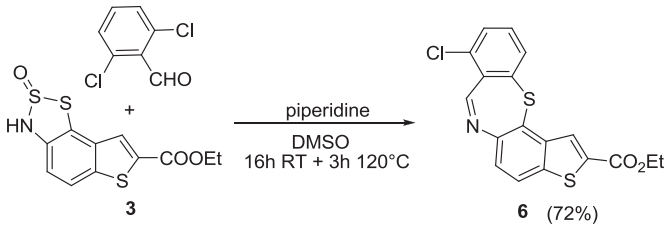
Table 2
Benzothiazole synthesis by reaction of **3** with different aldehydes

Entry	Substituent R[a]	Yield [%][b]
1	Phenyl	**5a**, 77
2	2-Thienyl	**5b**, 64
3	4-Fluorophenyl	**5c**, 62
4	2-Methoxyphenyl	**5d**, 69
5	4-Dimethylaminophenyl	**5e**, 39
6	4-Cyanophenyl	**5f**, 76
7	4-(4-Fluorobenzyloxy)phenyl	**5g**, 60
8	*o*-Tolyl	**5h**, 55
9	2-Hydroxyphenyl	**5i**, 65
10	2-Chloro-4-fluorophenyl	**5k**, 55

[a] Procedure: **3** (1 equiv), aldehyde (2.2 equiv), DMSO, piperidine (1 equiv) stirred overnight at 25 °C, then 2–3 h at 120 °C.
[b] Yields refer to isolated products.

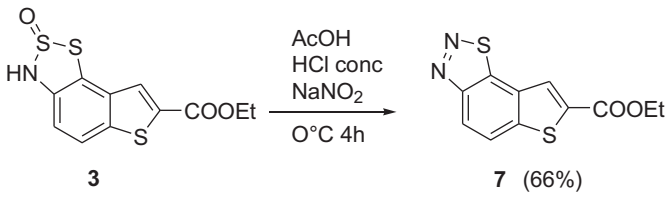
intermediate electron rich and thus less activated for a nucleophilic attack. This results in a slower reaction with decreased yield.

In contrast, while performing the described reaction of 3*H*-thienobenzodithiazole 2-oxide **3** with 2,6-dichlorobenzaldehyde, we obtained a different compound, namely the thienobenzothiazepine derivative **6** (Scheme 4), instead of the desired benzothiazole. In this case, an intramolecular nucleophilic aromatic substitution reaction of the sulfur atom to the 2-position of the intermediate imine has occurred. On the contrary, this intramolecular substitution reaction was not observed in the reaction with 2-chloro-4-fluorobenzal dehyde (Table 2, entry 10). Here, the 2-(2-chloro-4-fluorophenyl) thienobenzothiazole **5j** was formed as the sole compound. Such an intramolecular nucleophilic aromatic substitution has been reported for the reaction of 2-aminothiophenol with 2-chloro-5-nitrobenzal dehyde.[18]



Scheme 4. Synthesis of thienobenzothiazepine **6**, via an intramolecular nucleophilic aromatic substitution reaction.

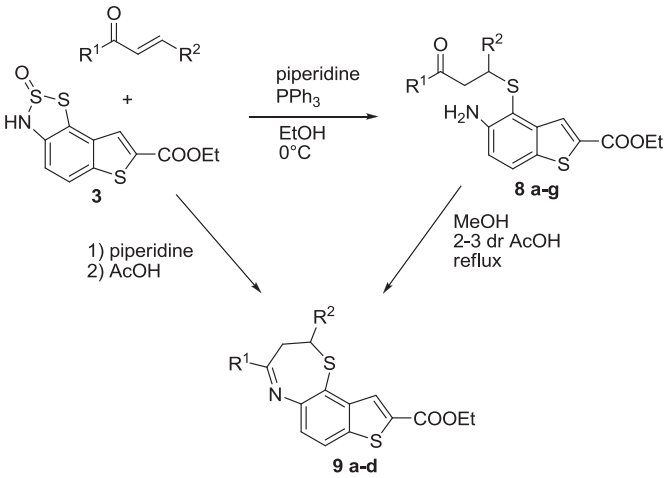
As a last part in the synthesis of nitrogen- and sulfur-containing five-membered ring structures, we finally synthesized the thienobenzothiadiazole-**7** (Scheme 5). This thiadiazole derivative was obtained in a yield of 66%, by treatment of the sulfoxide **3** with sodium nitrite.



Scheme 5. Synthesis of thienobenzothiadiazole-**7**.

The synthesis of 1,5-benzothiazepines has been extensively described in literature, due to the broad applicability of the benzothiazepine scaffold as pharmacophore.[3,19] Generally, 1,5-benzothiazepines are synthesized via condensation of 2-aminothiophenols with α,β-unsaturated ketones (chalcones).[20,21] In literature, several catalytic systems have been reported to promote this reaction, such as HCl,[19] piperidine/acetic acid,[22] amino acids,[23] SiO_2,[24] $Ga(OTf)_3$,[25] HBF_4/SiO_2,[26] NH_4Cl,[27] or sodium dodecyl sulfate in water.[28] Mechanistically, this method has been reported to proceed via a thia-Michael addition of the sulfhydryl group of the 2-aminothiophenol on the α,β-unsaturated ketone ([1,4]-addition), followed by an intramolecular nucleophilic attack of the NH_2 group on the carbonyl carbon with subsequent dehydration ([1,2]-addition).[26,29] An alternative pathway was also described, primarily forming an imine (or azadiene) followed by intramolecular conjugate addition by the sulfhydryl.[26]

Inspired by the previously reported benzothiazepine syntheses using *o*-aminothiophenols, we herein report a method for the synthesis of novel thienobenzothiazepines. This method comprises the reaction of the 3*H*-thienobenzodithiazole 2-oxide **3** with chalcones (Scheme 6). While optimizing this reaction, we found that initially the thia-Michael adduct **8a** was formed under basic



Scheme 6. Synthesis of thia-Michael adducts **8** and benzothiazepines **9**, from 3*H*-thienobenzodithiazole 2-oxide **3** and chalcones.

conditions (Table 3). In a next step, this compound **8a** was annulated using acetic acid, resulting in the expected dihydrothienoben zothiazepine **9a** (Scheme 6 & Table 4). The formation of this thia-Michael adduct shows evidence for the first mechanistic pathway. Moreover, we were able to form the benzothiazepine **9a** in one step, by altering the reaction conditions. Thus, by adding an excess of acetic acid to the reaction mixture, after formation of **8a**, we obtained the desired benzothiazepine **9a** in an one-pot reaction (Scheme 6). The yield of this one-pot reaction (44%) was lower than

Table 3
Optimization of the reaction of **3** with chalcone (R^1=R^2=Ph)

Entry	Base[a]/acid	Solvent	Temp	Time	Yield **8a** [%]
1	Piperidine	EtOH/H_2O	Reflux	20 h	—
2	HCl (2dr)	MeOH	Reflux	16 h	—
3	Et_3N	EtOH	60 °C	16 h	—
4	NH_4Cl	H_2O	RT	19 h	—
5	Et_3N	MeOH	0 °C	19 h	38
6	Piperidine	MeOH	0 °C to RT	18 h	49
7	Piperidine	EtOH	0 °C to RT	19 h	76
8	Piperidine	EtOH/H_2O	0 °C to RT	17 h	—
9	Piperidine	Toluene	0 °C	3 h	57
10	Piperidine	MeCN	0 °C	1 h	32
11	Piperidine	MeCN	0 °C to RT	17 h	—
12	Piperidine	MeCN	−15 °C	20 min	47
13	Piperidine+PPh_3[b]	EtOH	0 °C to RT	17 h	76

[a] Excess of base used.
[b] 0.5 equiv of PPh_3 used.

Table 4
Thia-Michael addition in the presence of PPh_3 and subsequent annulation reaction

Entry	α,β-unsaturated ketone		Yield [%]
	R^1	R^2	
1	Phenyl	Phenyl	**8a**, 76
2	4-Methoxyphenyl	4-Fluorophenyl	**8b**, 45
3	4-Chlorophenyl	4-Fluorophenyl	**8c**, 59
4	2-Hydroxyphenyl	2-Chlorophenyl	**8d**, 53
5	4-Methoxyphenyl	4-Cyanophenyl	**8e**, —[a]
6	4-Nitrophenyl	2,6-Dichlorophenyl	**8f**, —
7	4-Chlorophenyl	2-Methoxyphenyl	**8g**, —
8	Phenyl	Phenyl	**9a**, 86 (44[b])
9	4-Methoxyphenyl	4-Fluorophenyl	**9b**, 90
10	4-Chlorophenyl	4-Fluorophenyl	**9c**, 90
11	2-Hydroxyphenyl	2-Chlorophenyl	**9d**, 85

[a] The corresponding thienobenzothiazepine **9e** was formed (16% yield).
[b] Tandem reaction: (1) piperidine; (2) excess AcOH.

the overall yield in two steps (66%). The compounds **9** were easily purified by filtration, as the products precipitated from the reaction solvent.

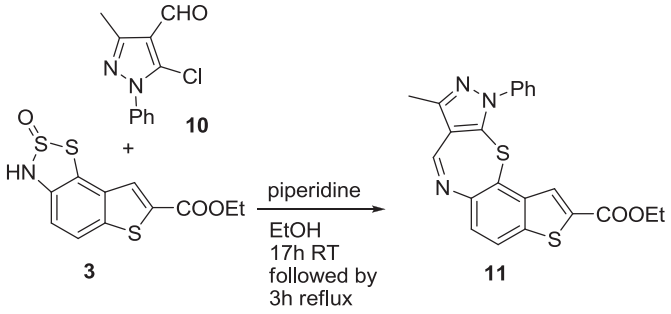
The results in Table 3 clearly show the need for low temperature (0 °C) in the reaction. Heating the reaction mixture from the start is detrimental for the 3*H*-benzodithiazole 2-oxide moiety. Piperidine, instead of triethylamine as base, was found to give slightly better results (Table 3, entry 5–6). Furthermore, addition of water to the reaction mixture breaks down the formed product, when left for a longer period of time (entry 8). The same remark holds for the use of acetonitrile as solvent (entry 10–12). The addition of PPh_3 to the reaction mixture seemed to have no effect on the formation of **8a** (entry 13). However, while applying the highest yielding reaction condition (Table 3, entry 7: compound **3**, chalcone and piperidine in EtOH at 0 °C in an overnight reaction) on a small series of substituted chalcones, we observed a drastic decrease in the obtained yields (7–15%). In these cases, we found that the addition of PPh_3 to the reaction mixture resulted in higher and acceptable yields (Table 4, entry 8–11).

The necessity for PPh_3 in the thia-Michael addition reaction can be explained by its reducing effect on disulfides. In literature, the condensation reaction of chalcones with *o*-aminothiophenols, in situ formed by reductive cleavage of disulfides using PPh_3, was reported.[30] In our case, the PPh_3 actually prevents the formation of disulfides, making it possible for the sulfur nucleophile to attack the chalcone. Other reported methods use Zn,[31] $SnCl_2$,[32] or SmI_2[33] as reducing agents for the in situ cleavage of disulfides.

Furthermore, compounds **8e**–**g** were not formed (Table 4, entry 5–7). Reasons can be found in the poor solubility of the cyano- and nitro-substituted chalcones, the steric hindrance of the dichlorophenyl group, and the electron-donating effect of the methoxy group (Table 4, entry 7), which deactivates the α,β-unsaturated ketone towards nucleophilic attack. However, in the reaction of precursor **3** with the cyano-substituted chalcone (Table 4, entry 5), we observed the formation of the corresponding thienobenzothiazepine **9e** in a low yield (16%).

An alternative way for benzothiazepines is effected by the condensation of 2-aminothiophenols with *o*-chlorobenzaldehyde derivatives. Inspired by the reaction of **3** with 2,6-dichlorobenzal dehyde, yielding compound **6** (Scheme 4), we have performed another reaction of this type, using the chloroformylpyrazole **10**. Employing a literature procedure,[34] we performed the reaction of **3** with **10** in ethanol using piperidine as base (Scheme 8). We obtained the pyrazole fused thiazepine **11** without the need for further purification in a yield of 37% (Scheme 7).

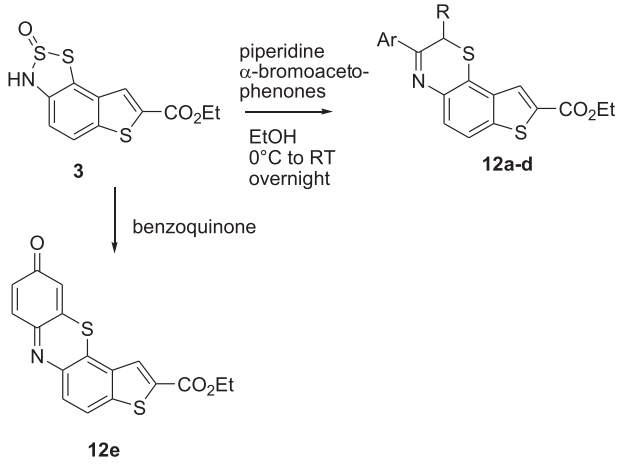
In the last part, we looked at the synthesis of 2*H*-thienobenzothiazines. Generally, 1,4-benzothiazines are synthesized by condensation of *o*-aminothiophenols with α-bromoacetophenones.[35,36]



Scheme 7. Synthesis of pyrazole fused thienobenzothiazepine **11**.

Other methods have been reported using different precursors. For instance, benzothiazines are also synthesized by reaction of bis(*o*-nitrophenyl)disulfide with α-bromoacetophenones promoted by SmI_2,[33] or by ring expansion of benzothiazolines or benzothiazoles.[35,36] In 1994, Sawhney et al.[37] also reported the synthesis of benzothiazine, by use of a dithiazole 2-oxide precursor. The benzodithiazole 2-oxide precursor was also reported in the synthesis of benzothiazinones.[38]

In agreement with the previously introduced methods for the synthesis of thienobenzothiazoles, -benzothiazepines, and -benzothiadiazole, we have developed a method for the synthesis of thienobenzothiazines, starting from our precursor, 3*H*-thienobenzodithiazole 2-oxide **3**. We have focused on the reaction of **3** with different α-bromoacetophenones. In analogy with the thiazepine synthesis, we have obtained compounds **12a**–**d** in good yields (52–75%), using piperidine in ethanol at 0 °C with slow warming up to room temperature overnight (Scheme 8 & Table 5). All reaction products were easily obtained by filtration of the precipitated product and purified by recrystallization from ethanol. Similarly, condensation of **3** with an excess of benzoquinone led to a good yield of the intensively red dibenzothiazinone **12e** after chromatographic separation.

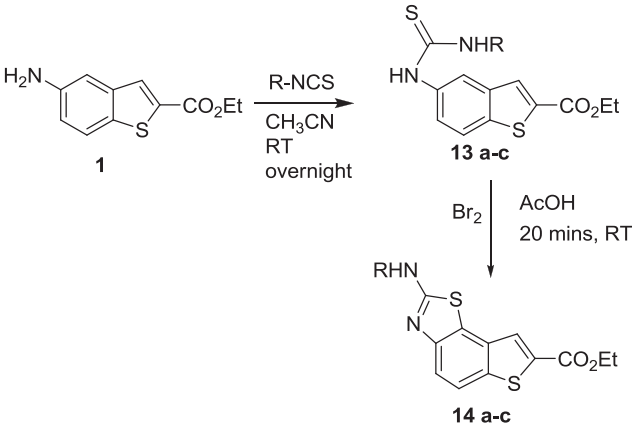


Scheme 8. General method for the synthesis of 2*H*-thienobenzothiazines **12a**–**d** and **12e**.

Table 5
Fused thiazine formation from **3** and bromoacetophenones

Entry	α-Bromoacetophenone		Yield [%]
	Aryl	R	
1	4-Bromophenyl	H	**12a**, 75
2	Phenyl	H	**12b**, 74
3	Phenyl	CH_3	**12c**, 70
4	Phenyl	Phenyl	**12d**, 52

Finally, we have tested the alternative route to thienobenzothiazoles, using the condensation reaction of amine **1** with organic isothiocyanates, and bromine-mediated oxidative cyclization of the intermediate thiourea derivatives **13a**–**c**. The 2-(*R*) aminothienobenzothiazoles **14a**–**c** were thus obtained in good overall yield (Scheme 9). This method is complementary to the previously mentioned one, leading to **5a**–**k** (Table 6).



Scheme 9. General method for the synthesis of 5-aminothienobenzothiazoles.

Table 6
Thienobenzothiazoles formation from **1** and different isothiocyanates

Entry	Substituent R	Yield [%]	Yield [%]
1	Butyl	**13a**, 63	**14a**, 74
2	Phenyl	**13b**, 82	**14b**, 80
3	Benzyl	**13c**, 86	**14c**, 91

3. Conclusions

We have synthesized sulfur and nitrogen containing heterocycles, fused in the 4,5-position of the benzothiophene scaffold. Therefore, we firstly needed to derive a stable 5-amino-4-mercaptobenzothiophene precursor. Using the Herz reaction, we were able to introduce a sulfur atom in the 4-position of the benzothiophene scaffold. The Herz salt was readily hydrolyzed in water to the 3*H*-thienobenzodithiazole 2-oxide derivative, which was used as *o*-aminothiophenol precursor. We have optimized the reaction conditions for the synthesis of thienobenzothiazoles, -thiazepines, -thiazines, and thienobenzothiadiazole, all starting from this precursor. The reaction of the latter with 2,6-dichlorobenzaldehyde did not result in the usual thienobenzothiazole, but gave rise to a thiazepine, due to an intramolecular nucleophilic substitution reaction. We introduced a new reaction procedure for the synthesis of thienobenzothiazepines. In the condensation reaction with substituted chalcones, we found that low temperature and the addition of PPh_3 to the reaction mixture were crucial for this thienobenzothiazepine synthesis.

4. Experimental section

4.1. General methods

Melting points (not corrected) were determined using a Reichert Thermovar apparatus. IR spectra were recorded using a Bruker ALPHA-P spectrometer. IR measurements were based the ATR technique instead of the normal transmission method using KBr pellets. ^1H and ^{13}C NMR spectra were measured 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.[5]

*4.1.1. Ethyl 3H-thieno[3′,2′:3,4]benzo[1,2-d][1,2,3]dithiazole-7-carboxylate 2-oxide (**3**).* A solution of ethyl 5-aminobenzo[*b*]thiophene-2-carboxylate **1** (2.21 g, 10.0 mmol) in acetic acid (25 mL) was slowly added to S_2Cl_2 (6 mL) at 0 °C, whereupon a thick red-orange slurry formed. The reaction mixture was then stirred for 2 h at 40 °C and diluted with toluene and filtered. The precipitate was washed with toluene and finally with diethyl ether, and dried to yield 7-(ethoxycarbonyl)thieno[3′,2′:3,4]benzo[1,2-*d*][1,2,3]dithiazol-2-ium chloride (**2**) as a dark orange solid. This dithiazolium chloride (Herz salt) was next stirred in water (100 mL) overnight. The reaction mixture was filtered and the residue was dissolved in MeOH (400 mL) and precipitated by adding cold water (150 mL). The precipitate was filtered and dried, triturated with toluene and filtered off to yield ethyl 3*H*-thieno-[3′,2′:3,4]benzo[1,2-*d*][1,2,3]dithiazole-7-carboxylate 2-oxide **3** as yellow solid (2.36 g, 78%). Mp 138–139 °C; IR: 3129, 2971, 1706, 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.44 (t, J=7.1 Hz, 3H, CH_3), 4.43 (q, J=7.1 Hz, 2H, CO_2CH_2), 7.18 (d, J=8.6 Hz, 1H), 7.62 (m, 2H), 7.92 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 62.1, 114.0, 115.5, 121.2, 127.5, 133.6, 136.6, 137.7, 138.5, 162.5; HRMS (EI): *m*/*z* calcd for $C_{11}H_9NO_3S_3$ (M^+): 298.9745; found: 298.9761.

*4.1.2. Preparation of thienobenzothiazoles (**5**).* To a mixture of ethyl 3*H*-thieno[3′,2′:3,4]benzo[1,2-*d*][1,2,3]dithiazole-7-carboxylate 2-oxide **3** (150 mg, 0.50 mmol) and aldehyde (1.10 mmol) in DMSO (4 mL) was added piperidine (0.05 mL, 0.50 mmol). The reaction mixture was first stirred overnight at room temperature, and then for 1.5–3 h at 120 °C. After cooling, water was added, the precipitate was filtered and dried. The product was purified by recrystallization from ethanol or by column chromatography on silica gel using CH_2Cl_2 as eluent to afford pure **5**.

*4.1.3. Ethyl 2-phenylthieno[3′,2′:3,4]benzo[1,2-d]thiazole-7-carboxylate (**5a**).* Mp 163–163.5 °C; IR: 3075, 2972, 1703, 1259 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.45 (t, J=7.2 Hz, 3H, CH_3), 4.44 (q, J=7.2 Hz, 2H, CO_2CH_2), 7.51 (m, 3H), 7.89 (d, J=8.7 Hz, 1H), 8.11 (m, 3H), 8.20 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 62.0, 121.0, 122.4, 127.5, 128.5, 129.3, 130.8, 131.1, 132.1, 133.5, 135.6, 139.9, 152.5, 162.5, 167.1; HRMS (EI): *m*/*z* calcd for $C_{18}H_{13}NO_2S_2$ (M^+): 339.0388; found: 339.0396.

*4.1.4. Ethyl 2-(thien-2-yl)thieno[3′,2′:3,4]benzo[1,2-d]thiazole-7-carboxylate (**5b**).* Mp 177–178 °C; IR: 3078, 1697, 1283 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.45 (t, J=7.2 Hz, 3H, CH_3), 4.44 (q, J=7.2 Hz, 2H, CO_2CH_2), 7.16 (t, J=4.5 Hz, 1H), 7.52 (d, J=4.7 Hz, 1H), 7.68 (d, J=3.2 Hz, 1H), 7.88 (d, J=8.9 Hz, 1H), 8.06 (d, J=8.6 Hz, 1H), 8.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 62.0, 121.1, 122.1, 128.2, 128.3, 128.6, 129.5, 130.4, 132.0, 135.7, 137.1, 139.9, 152.0, 160.5, 162.5; HRMS (EI): *m*/*z* calcd for $C_{16}H_{11}NO_2S_3$ (M^+): 344.9952; found: 344.9962.

*4.1.5. Ethyl 2-(4-fluorophenyl)thieno[3′,2′:3,4]benzo[1,2-d]thiazole-7-carboxylate (**5c**).* Mp 215–217 °C; IR: 3076, 2983, 1706, 1263,

1223 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.45 (t, J=7.2 Hz, 3H, CH_3), 4.44 (q, J=7.2 Hz, 2H, CO_2CH_2), 7.21 (t, J=8.7 Hz, 2H), 7.90 (d, J=8.9 Hz, 1H), 8.10 (m, 3H), 8.20 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 62.0, 116.3, 116.6, 121.1, 122.3, 128.5, 129.5, 129.6, 129.8, 130.8, 132.1, 135.7, 139.9, 152.5, 162.5, 162.9, 165.8, 166.3; HRMS (EI): m/z calcd for $C_{18}H_{12}NO_2S_2F$ (M^+): 357.0293; found: 357.0278.

*4.1.6. Ethyl 2-(2-methoxyphenyl)thieno[3′,2′:3,4]benzo[1,2-d]thiazole-7-carboxylate (**5d**).* Mp 185–186 °C; IR: 3084, 2978, 1715, 1261, 1246 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.45 (t, J=7.1 Hz, 3H, CH_3), 4, 12 (s, CH_3O), 4.44 (q, J=7.1 Hz, 2H, CO_2CH_2), 7.13 (m, 2H), 7.49 (t, J=8.1 Hz, 1H), 7.89 (d, J=8.7 Hz, 1H), 8.13 (d, J=8.9 Hz, 1H), 8.28 (s, 1H), 8.56 (d, J=7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 55.9, 61.9, 111.7, 120.5, 121.4, 122.1, 122.2, 128.6, 129.4, 131.9, 132.1, 135.1, 139.4, 150.5, 157.1, 161.9, 162.7; HRMS (EI): m/z calcd for $C_{19}H_{15}NO_3S_2$ (M^+): 369.0493; found: 369.0487.

*4.1.7. Ethyl 2-(4-(dimethylamino)phenyl)thieno[3′,2′:3,4]benzo[1,2-d]thiazole-7-carboxylate (**5e**).* Mp 214–216 °C; IR: 2898, 1702, 1603, 1283, 1184, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.44 (t, J=7.2 Hz, 3H, CH_3), 3.07 (s, 6H, $N(CH_3)_2$), 4.44 (q, J=7.2 Hz, 2H, CO_2CH_2), 6.75 (d, J=8.9 Hz, 2H), 7.85 (d, J=8.9 Hz, 1H), 7.96 (d, J=8.9 Hz, 2H), 8.04 (d, J=8.9 Hz, 1H), 8.18 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 40.3, 61.9, 111.8, 120.5, 121.1, 121.8, 128.6, 128.8, 130.1, 132.2, 135.2, 139.0, 152.3, 152.7, 162.7, 168.0; HRMS (EI): m/z calcd for $C_{20}H_{18}N_2O_2S_2$ (M^+): 382.0810; found: 382.0816.

*4.1.8. Ethyl 2-(4-cyanophenyl)thieno[3′,2′:3,4]benzo[1,2-d]thiazole-7-carboxylate (**5f**).* Mp 268–270 °C; IR: 3077, 2987, 2226, 1708, 1246 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2): δ 1.44 (t, J=7.2 Hz, 3H, CH_3), 4.44 (q, J=7.2 Hz, 2H, CO_2CH_2), 7.83 (d, J=8.1 Hz, 2H), 7.99 (d, J=9.0 Hz, 1H), 8.14 (d, J=9.0 Hz, 1H), 8.25 (m, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 14.2, 62.0, 114.2, 118.3, 121.5, 122.5, 127.8, 128.3, 131.3, 132.1, 133.0, 136.1, 137.3, 140.4, 152.5, 162.2, 164.4; HRMS (EI): m/z calcd for $C_{19}H_{12}N_2O_2S_2$ (M^+): 364.0340; found: 364.0360.

*4.1.9. Ethyl 2-(4-((4-fluorobenzyl)oxy)phenyl)thieno[3′,2′:3,4]-benzo-[1,2-d]thiazole-7-carboxylate (**5g**).* Mp 196–196.5 °C; IR: 3057, 1704, 1264, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.44 (t, J=7.0 Hz, 3H, CH_3), 4.44 (q, J=7.0 Hz, 2H, CO_2CH_2), 5.12 (s, 2H, CH_2O), 7.09 (m, 4H), 7.43 (m, 2H), 7.87 (d, J=8.9 Hz, 1H), 8.05 (m, 3H), 8.18 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 62.0, 69.6, 115.5, 115.6, 115.7, 115.9, 120.9, 122.2, 126.6, 128.5, 129.2, 129.5, 129.6, 130.6, 132.2, 135.5, 139.6, 145.4, 152.6, 161.0, 162.6, 166.8; HRMS (EI): m/z calcd for $C_{25}H_{18}NO_3S_2F$ (M^+): 463.0712; found: 463.0719.

*4.1.10. Ethyl 2-(o-tolyl)thieno[3′,2′:3,4]benzo[1,2-d]thiazole-7-carboxylate (**5h**).* Mp 146–147 °C; IR: 3076, 2977, 1704, 1258 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.45 (t, J=7.2 Hz, 3H, CH_3), 2.69 (s, 3H, CH_3), 4.44 (q, J=7.1 Hz, 2H, CO_2CH_2), 7.37 (m, 3H), 7.80 (d, J=7.3 Hz, 1H), 7.92 (d, J=8.6 Hz, 1H), 8.15 (d, J=8.9 Hz, 1H), 8.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 21.6, 62.0, 120.8, 122.6, 126.4, 128.6, 130.2, 130.7, 131.4, 131.8, 132.0, 132.8, 135.5, 137.4, 139.8, 152.1, 162.6, 166.9; HRMS (EI): m/z calcd for $C_{19}H_{15}NO_2S_2$ (M^+): 353.0544; found: 353.0535.

*4.1.11. Ethyl 2-(2-hydroxyphenyl)thieno[3′,2′:3,4]benzo[1,2-d]thiazole-7-carboxylate (**5i**).* Mp 184–185 °C; IR: 2984, 1705, 1285 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (t, J=7.2 Hz, 3H, CH_3), 4.44 (q, J=7.1 Hz, 2H, CO_2CH_2), 6.99 (t, J=7.4 Hz, 3H), 7.12 (d, J=8.3 Hz, 1H), 7.41 (t, J=7.1 Hz, 1H), 7.73 (d, J=7.0 Hz, 1H), 7.92 (d, J=8.9 Hz, 1H), 8.04 (d, J=8.7 Hz, 1H), 8.21 (s, 1H), 12.30 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 62.1, 116.7, 118.1, 119.8, 121.2, 121.4, 128.2, 128.3, 128.4, 131.9, 132.9, 136.1, 140.1, 150.2, 157.9, 162.4, 168.2; HRMS (EI): m/z calcd for $C_{18}H_{13}NO_3S_2$ (M^+): 355.0337; found: 355.0341.

*4.1.12. Ethyl 2-(2-chloro-4-fluorophenyl)thieno[3′,2′:3,4]benzo[1,2-d]thiazole-7-carboxylate (**5j**).* Mp 215–216 °C; IR: 3079, 2990, 1715, 1254, 1232 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.44 (t, J=7.1 Hz, 3H, CH_3), 4.44 (q, J=7.1 Hz, 2H, CO_2CH_2), 7.15 (td, J=2.6, 8.6 Hz, 1H), 7.30 (dd, J=8.3, 2.6 Hz, 1H), 7.92 (d, J=8.6 Hz, 1H), 8.14 (d, J=9.0 Hz, 1H), 8.25 (s, 1H), 8.33 (dd, J=8.6, 2.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.5, 62.0, 100.2, 115.0, 115.2, 118.2, 118.4, 121.2, 122.6, 128.4, 128.7, 128.8, 132.0, 132.1, 133.5, 133.6, 133.8, 133.9, 136.1, 140.3, 151.0, 161.9, 162.5, 162.7, 164.4; HRMS (EI): m/z calcd for $C_{18}H_{11}NO_2S_2ClF$ (M^+): 390.9904; found: 390.9896.

*4.1.13. Ethyl 8-chlorobenzo[f]thieno[2′,3′:5,6]benzo[1,2-b][1,4]-thiazepine-2-carboxylate (**6**).* To a mixture of ethyl 3*H*-thieno[3′,2′:3,4]benzo[1,2-*d*][1,2,3]dithiazole-7-carboxylate 2-oxide **3** (150 mg, 0.50 mmol) and 2,6-dichlorobenzaldehyde (193 mg, 1.10 mmol) in DMSO (4 mL) was added piperidine (0.05 mL, 0.50 mmol). The reaction mixture was first stirred overnight at room temperature, and then for 3 h at 120 °C. After cooling, water was added, the precipitate was filtered and dried. The product was purified by recrystallization from ethanol to afford pure ethyl 8-chlorobenzo[*f*]thieno[2′,3′:5,6]benzo[1,2-*b*][1,4]thiazepine-2-carboxylate **6** as bright yellow needles (135 mg, 72%). Mp 200–201 °C; IR: 3085, 2979, 2912, 1712, 1251, 1066 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.44 (t, J=7.1 Hz, 3H, CH_3), 4.44 (q, J=7.1 Hz, 2H, CO_2CH_2), 7.34 (m, 2H), 7.42 (m, 2H), 7.78 (d, J=8.7 Hz, 1H), 8.46 (s, 1H), 9.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 62.0, 123.1, 123.4, 125.8, 130.1, 130.2, 130.5, 132.4, 134.0, 134.9, 135.1, 140.5, 142.4, 146.3, 160.6, 160.6, 162.7; HRMS (EI): m/z calcd for $C_{18}H_{12}NO_2S_2Cl$ (M^+): 372.9998; found: 373.0016.

*4.1.14. Ethyl thieno[3′,2′:3,4]benzo[1,2-d][1,2,3]thiadiazole-7-carboxylate (**7**).* A mixture of ethyl 3*H*-thieno[3′,2′:3,4]benzo[1,2-*d*][1,2,3]dithiazole-7-carboxylate 2-oxide **3** (150 mg, 0.50 mmol), concentrated HCl (1 mL), and water (1 mL) in acetic acid (6.5 mL) was stirred at room temperature for 30 min, and then cooled to 0 °C. A solution of $NaNO_2$ (34.5 mg, 0.5 mmol) in water (1 mL) was slowly added. The reaction mixture was stirred for 4 h, and then filtered. The precipitate was washed with a $NaHCO_3$ solution, and then with water and dried to afford pure ethyl thieno[3′,2′:3,4]benzo[1,2-*d*][1,2,3]thiadiazole-7-carboxylate **7** (87.1 mg, 66%). Mp 156.5–157.5 °C; IR: 3078, 2979, 1714, 1288, 1244 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.45 (t, J=7.1 Hz, 3H, CH_3), 4.45 (q, J=7.1 Hz, 2H, CO_2CH_2), 8.04 (d, J=8.9 Hz, 1H), 8.31 (s, 1H), 8.61 (d, J=9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 62.3, 121.6, 122.2, 129.1, 130.0, 136.9, 138.7, 143.3, 157.5, 162.0; HRMS (EI): m/z calcd for $C_{11}H_8N_2O_2S_2$ (M^+): 264.0027; found: 264.0029.

*4.1.15. Thia-Michael addition: general procedure (**8**).* A mixture of ethyl 3*H*-thieno[3′,2′:3,4]benzo[1,2-*d*][1,2,3]dithiazole-7-carboxylate-2-oxide **3** (150 mg, 0.50 mmol), PPh_3 (65.6 mg, 0.25 mmol), and α,β-unsaturated ketone (0.50 mmol) in EtOH (4 mL) was cooled to 0 °C and piperidine (0.1 mL, 1.00 mmol) was added. The reaction mixture was stirred at 0 °C, and allowed to slowly warm up to room temperature overnight. The precipitated reaction product was filtered and washed with cold ethanol. The product was purified by recrystallization from ethanol to afford pure **8**.

*4.1.16. Ethyl 5-amino-4-((3-oxo-1,3-diphenylpropyl)sulfanyl)benzothiophene-2-carboxylate (**8a**).* Mp 173–175 °C; IR: 3468, 3365, 2977, 1716, 1675, 1595, 1245 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.41 (t, J=7.1 Hz, 3H, CH_3), 3.58 (dd, J=6.2, 17.7 Hz, 1H, CH_2), 3.76 (dd, J=7.9, 17.5 Hz, 1H, CH_2), 4.36 (q, J=7.1 Hz, 2H, CO_2CH_2), 4.62 (s, 2H, NH_2), 4.77 (dd, J=6.2, 7.9 Hz, 1H, CH), 6.89 (d, J=8.7 Hz, 1H),

7.15 (m, 5H), 7.44 (m, 2H), 7.55 (m, 2H), 7.83 (s, 1H), 7.88 (d, J=7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 38.2, 61.8, 63.1, 119.3, 123.5, 125.5, 126.2, 127.6, 127.7, 128.2, 128.5, 128.8, 129.0, 129.1, 130.3, 130.8, 131.6, 134.3, 135.1, 137.5, 139.1, 142.4, 144.0, 150.1, 162.8; HRMS (EI): m/z calcd for $C_{26}H_{23}NO_3S_2$ (M^+): 461.1119; M^+ not found.

*4.1.17. Ethyl 5-amino-4-((1-(4-fluorophenyl)-3-(4-methoxyphenyl)-3-oxopropyl)sulfanyl)benzo[b]thiophene-2-carboxylate (**8b**).* Mp 128–129 °C; IR: 3476, 3370, 2990, 1712, 1665, 1596, 1248, 1226 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (t, J=7.2 Hz, 3H, CH_3), 3.49 (dd, J=6.4, 17.5 Hz, 1H, CH_2), 3.69 (dd, J=7.9, 17.3 Hz, 1H, CH_2), 3.87 (s, 3H, CH_3O), 4.37 (q, J=7.2 Hz, 2H, CO_2CH_2), 4.62 (br s, 2H, NH_2), 4.74 (dd, J=6.4, 7.9 Hz, 1H, CH), 6.83 (m, 2H), 6.89 (d, J=8.7 Hz, 1H), 6.91 (d, J=8.9 Hz, 2H), 7.11 (m, 2H), 7.33 (m, 4H), 7.54 (d, J=8.7 Hz, 1H), 7.75 (s, 1H), 7.88 (d, J=8.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 43.4, 46.8, 55.7, 61.6, 109.1, 113.9, 114.3, 115.2, 115.4, 115.7, 117.2, 124.7, 128.6, 128.7, 129.1, 129.2, 129.4, 129.7, 130.1, 130.5, 131.9, 132.1, 132.1, 132.2, 132.3, 133.3, 134.3, 137.5, 137.5, 142.4, 144.5, 148.2, 162.9, 163.7, 163.9, 195.3; HRMS (EI): m/z calcd for $C_{27}H_{24}NO_4S_2F$ (M^+): 509.1131; found 509.1170.

*4.1.18. Ethyl 5-amino-4-((3-(4-chlorophenyl)-1-(4-fluorophenyl)-3-oxopropyl)sulfanyl)benzo[b]thiophene-2-carboxylate (**8c**).* Mp 149–150 °C; IR: 3476, 3371, 2974, 1710, 1679, 1590, 1249, 1226 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (t, J=7.2 Hz, 3H, CH_3), 3.49 (dd, J=6.0, 17.7 Hz, 1H, CH_2), 3.70 (dd, J=7.5, 17.3 Hz, 1H, CH_2), 4.38 (q, J=7.2 Hz, 2H, CO_2CH_2), 4.62 (s, 2H, NH_2), 4.75 (t, J=6.4 Hz, 1H, CH), 6.87 (m, 3H), 7.12 (m, 2H), 7.41 (d, J=7.5 Hz, 2H), 7.55 (d, J=8.5 Hz, 1H), 7.80 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 43.8, 46.5, 61.6, 108.9, 115.3, 115.6, 117.2, 124.9, 129.1, 129.2, 129.6, 130.0, 132.4, 134.5, 134.9, 137.2, 140.0, 144.5, 148.2, 160.5, 162.9, 163.8, 195.6; HRMS (EI): m/z calcd for $C_{26}H_{21}NO_3S_2ClF$ (M^+): 513.0635; found: 495.0529 [M^+-H_2O].

*4.1.19. Ethyl 5-amino-4-((1-(2-chlorophenyl)-3-(2-hydroxyphenyl)-3-oxopropyl)sulfanyl)benzo[b]thiophene-2-carboxylate (**8d**).* Mp 145–146 °C; IR: 3470, 3368, 2980, 1702, 1638, 1289 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (t, J=7.1 Hz, 3H, CH_3), 3.59 (dd, J=6.5, 17.5 Hz, 1H, CH_2), 3.80 (dd, J=7.5, 17.5 Hz, 1H, CH_2), 4.38 (q, J=7.2 Hz, 2H, CO_2CH_2), 4.67 (s, 2H, NH_2), 5.41 (t, J=7.0 Hz, 1H, CH), 6.83 (t, J=7.7 Hz, 1H), 6.90 (m, 2H), 7.14 (m, 2H), 7.29 (m, 2H), 7.44 (t, J=7.7 Hz, 1H), 7.55 (d, J=8.6 Hz, 1H), 7.60 (d, J=8.1 Hz, 1H), 7.98 (s, 1H), 11.92 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 43.2, 43.4, 61.6, 108.3, 117.2, 118.7, 119.0, 119.1, 125.1, 127.2, 128.6, 128.8, 129.7, 130.0, 132.5, 133.9, 134.6, 136.7, 138.1, 144.6, 148.5, 162.5, 162.9, 202.3; HRMS (EI): m/z calcd for $C_{26}H_{22}NO_4S_2Cl$ (M^+): 511.0679; found: 511.0680.

*4.1.20. Preparation of thienobenzothiazepines **9**. General procedure*: To the 3-oxopropylsulfanylbenzo[*b*]thiophene derivative (thia-Michael adduct) **8** (0.50 mmol) in MeOH (6 mL) was added 2–3 drops of acetic acid. This reaction mixture was refluxed until TLC-analysis (eluent: CH_2Cl_2) indicated completion of the reaction (5–24 h). After cooling, the precipitated product was filtered, washed with MeOH, and dried to afford pure thienobenzothiazepine **9**.

*4.1.20.1. Ethyl 2,4-diphenyl-2,3-dihydrothieno[2′,3′:5,6]benzo[1,2-b][1,4]thiazepine-9-carboxylate (**9a**).* Mp 206–207 °C; IR: 2974, 1709, 1245 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, J=7.1 Hz, 3H, CH_3), 3.14 (t, J=12.6 Hz, 1H, CH_2), 3.36 (dd, J=4.5, 12.8 Hz, 1H, CH_2), 4.39 (q, J=7.1 Hz, 2H, CO_2CH_2), 5.19 (dd, J=4.5, 12.4 Hz, 1H, CH), 7.26 (m, 4H), 7.44 (d, J=8.5 Hz, 1H), 7.52 (m, 4H), 7.89 (d, J=8.7 Hz, 1H), 8.08 (m, 2H), 8.31 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 38.1, 61.8, 63.1, 119.1, 123.4, 125.5, 126.2, 127.6, 128.2, 128.9, 129.0, 130.7, 131.4, 135.0, 137.6, 138.8, 142.4, 144.0, 150.4, 162.8, 169.6; HRMS (EI): m/z calcd for $C_{26}H_{21}NO_2S_2$ (M^+): 443.1014; found: 443.1013.

*4.1.20.2. Ethyl 2-(4-fluorophenyl)-4-(4-methoxyphenyl)-2,3-dihydro-thieno[2′,3′:5,6]benzo[1,2-b][1,4]thiazepine-9-carboxylate (**9b**).* Mp 178–179 °C; IR: 2903, 1702, 1286, 1179 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, J=7.1 Hz, 3H, CH_3), 3.07 (t, J=12.6 Hz, 1H, CH_2), 3.29 (dd, J=4.7, 13.0 Hz, 1H, CH_2), 3.90 (s, 3H, CH_3O), 4.40 (q, J=7.1 Hz, 2H, CO_2CH_2), 5.15 (dd, J=4.4, 12.2 Hz, 1H, CH), 6.98 (m, 4H), 7.21 (m, 2H), 7.42 (d, J=8.6 Hz, 1H), 7.89 (d, J=8.5 Hz, 1H), 8.03 (d, J=8.8 Hz, 2H), 8.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 37.8, 55.6, 61.8, 62.1, 114.3, 115.7, 116.0, 118.6, 123.5, 125.6, 127.8, 127.9, 129.4, 130.6, 135.0, 138.6, 139.9, 140.0, 142.4, 150.7, 160.7, 162.4, 162.8, 164.0, 168.6; HRMS (EI): m/z calcd for $C_{27}H_{22}NO_3S_2F$ (M^+): 491.1025; found: 491.1047.

*4.1.20.3. Ethyl 4-(4-chlorophenyl)-2-(4-fluorophenyl)-2,3-dihydro-thieno-[2′,3′:5,6]benzo[1,2-b][1,4]thiazepine-9-carboxylate (**9c**).* Mp 197–198 °C; IR: 2983, 1703, 1286 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, J=7.1 Hz, 3H, CH_3), 3.08 (t, J=12.5 Hz, 1H, CH_2), 3.27 (dd, J=4.7, 13.0 Hz, 1H, CH_2), 4.40 (q, J=7.1 Hz, 2H, CO_2CH_2), 5.15 (dd, J=4.7, 12.1 Hz, 1H, CH), 6.97 (t, J=8.5 Hz, 2H), 7.21 (m, 2H), 7.42 (d, J=8.6 Hz, 1H), 7.47 (d, J=8.5 Hz, 2H), 7.90 (d, J=8.6 Hz, 1H), 7.99 (d, J=8.5 Hz, 2H), 8.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 37.9, 61.9, 62.3, 115.8, 116.0, 118.7, 123.6, 125.4, 127.8, 127.9, 128.9, 129.2, 130.5, 135.3, 136.0, 137.7, 139.0, 139.6, 139.7, 142.4, 150.2, 160.8, 162.7, 164.1, 168.2; HRMS (EI): m/z calcd for $C_{26}H_{19}NO_2S_2ClF$ (M^+): 495.0530; found: 495.0555.

*4.1.20.4. Ethyl 2-(2-chlorophenyl)-4-(2-hydroxyphenyl)-2,3-dihydro-thieno[2′,3′:5,6]benzo[1,2-b][1,4]thiazepine-9-carboxylate (**9d**).* Mp 226–227 °C; IR: 2976, 1712, 1251 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (t, J=7.0 Hz, 3H, CH_3), 2.97 (t, J=12.8 Hz, 1H, CH_2), 3.49 (m, 1H, CH_2), 4.41 (q, J=7.1 Hz, 2H, CO_2CH_2), 5.84 (m, 1H, CH), 6.96 (m, 1H), 7.08 (d, J=8.1 Hz, 1H), 7.20 (m, 2H), 7.42 (m, 4H), 7.81 (d, J=7.3 Hz, 1H), 7.93 (d, J=8.5 Hz, 1H), 8.38 (s, 1H), 14.3 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 36.3, 58.1, 62.0, 118.5, 118.7, 119.0, 120.4, 123.9, 125.4, 127.9, 128.3, 128.8, 129.4, 129.7, 130.3, 131.2, 134.0, 135.8, 139.8, 140.7, 142.3, 147.0, 162.6, 162.7, 173.5; HRMS (EI): m/z calcd for $C_{26}H_{20}NO_3S_2Cl$ (M^+): 493.0573; found: 493.0550.

*4.1.20.5. Ethyl 2-(4-cyanophenyl)-4-(2-methoxyphenyl)-2,3-dihydro-thieno[2′,3′:5,6]benzo[1,2-b][1,4]thiazepine-9-carboxylate (**9e**).* This compound was obtained as sole product in the thia-Michael addition reaction, conforming the general procedure for the synthesis of compounds (**8**). IR: 2978, 2226, 1705, 1241, 1173 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.33 (t, J=7.0 Hz, 3H, CH_3), 3.05 (t, J=12.8 Hz, 1H, CH_2), 3.48 (dd, J=4.8, 12.8 Hz, 1H, CH_2), 3.88 (s, 3H, CH_3O), 4.35 (q, J=7.0 Hz, 2H, CO_2CH_2), 5.53 (dd, J=4.8, 12.8 Hz, 1H, CH), 7.10 (d, J=8.8 Hz, 2H), 7.47 (d, J=8.8 Hz, 1H), 7.49 (d, J=8.5 Hz, 2H), 7.79 (d, J=8.0 Hz, 2H), 7.95 (s, 1H), 8.15 (d, J=8.8 Hz, 2H), 8.21 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.1, 35.6, 55.5, 60.9, 61.6, 110.3, 114.1, 116.9, 118.6, 124.3, 125.4, 127.1, 129.3, 129.4, 129.5, 132.7, 134.5, 137.5, 141.6, 149.0, 150.8, 161.7, 162.0, 173.5; HRMS (EI): m/z calcd for $C_{28}H_{22}N_2O_3S_2$ (M^+): 498.1072; found: 498.1089.

*4.1.21. Ethyl 8-methyl-10-phenyl-10H-pyrazolo[4,3-f]thieno[2′,3′:5,6]-benzo[1,2-b][1,4]thiazepine-2-carboxylate (**11**).* A mixture of ethyl 3*H*-thieno[3′,2′:3,4]benzo[1,2-*d*][1,2,3]dithiazole-7-carboxylate 2-oxide **3** (150 mg, 0.50 mmol) and 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (121 mg, 0.55 mmol) in EtOH (4 mL) was cooled to 0 °C and piperidine (0.1 mL, 1.00 mmol) was added. The reaction mixture was stirred at 0 °C, and allowed to slowly warm up to room temperature overnight. The precipitated reaction product was filtered and washed with cold ethanol to afford pure

ethyl 8-methyl-10-phenyl-10*H*-pyrazolo[4,3-*f*]thieno[2′,3′:5,6]benzo[1,2-*b*]-[1,4]thiazepine-2-carboxylate **11** (77 mg, 37%). Mp 145.5–146.5 °C; IR: 3089, 2972, 1714, 1247 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.42 (t, J=7.1 Hz, 3H, CH_3), 2.40 (s, 1H, CH_3), 4.41 (q, J=7.1 Hz, 2H, CO_2CH_2), 7.40 (d, J=8.7 Hz, 1H), 7.54 (m, 5H), 7.82 (d, J=8.6 Hz, 1H), 8.28 (s, 1H), 8.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.4, 14.4, 62.0, 119.7, 120.0, 123.7, 124.9, 125.3, 128.2, 128.7, 129.2, 129.3, 129.4, 135.2, 137.3, 137.9, 140.6, 141.0, 148.7, 149.0, 155.4, 162.5; HRMS (EI): m/z calcd for $C_{22}H_{17}N_3O_2S_2$ (M^+): 419.0762; found: 419.0760.

4.1.22. Preparation of 2H-thienobenzothiazines ***12****. General procedure*: A mixture of ethyl 3*H*-thieno[3′,2′:3,4]benzo[1,2-*d*][1,2,3]dithiazole-7-carboxylate-2-oxide **3** (150 mg, 0.50 mmol) and α-bromoketone (0.50 mmol) in EtOH (4 mL) was cooled to 0 °C and piperidine (0.05 mL, 0.50 mmol) was added. The reaction mixture was stirred at 0 °C, and allowed to slowly warm up to room temperature overnight. The precipitated reaction product was filtered and washed with cold ethanol. The product was purified by recrystallization from ethanol to afford pure 2*H*-thienobenzothiazine **12**.

*4.1.22.1. Ethyl 3-(4-bromophenyl)-2H-thieno[2′,3′:5,6]benzo[1,2-b][1,4]-thiazine-8-carboxylate (****12a****).* Mp 155–156 °C; IR: 2993, 2903, 1706, 1244 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (t, J=7.0 Hz, 3H, CH_3), 3.67 (s, 2H, CH_2), 4.42 (q, J=7.0 Hz, 2H, CO_2CH_2), 7.64 (m, 4H), 7.92 (d, J=8.3 Hz, 2H), 8.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 23.0, 61.9, 119.5, 120.1, 125.8, 127.7, 129.0, 129.2, 132.1, 132.2, 135.0, 136.2, 136.3, 141.1, 153.5, 162.7; HRMS (EI): m/z calcd for $C_{19}H_{14}NO_2S_2Br$ (M^+): 432.9629; found: 432.9669.

*4.1.22.2. Ethyl 3-phenyl-2H-thieno[2′,3′:5,6]benzo[1,2-b][1,4]thiazine-8-carboxylate (****12b****).* Mp 143–144 °C; IR: 3068, 2979, 2903, 1708, 1258 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2): δ 1.40 (t, J=7.0 Hz, 3H, CH_3), 3.71 (s, 2H, CH_2), 4.38 (q, J=7.0 Hz, 2H, CO_2CH_2), 7.50 (m, 3H), 7.57 (d, J=8.5 Hz, 1H), 7.69 (d, J=8.5 Hz, 1H), 8.04 (m, 2H), 8.12 (s, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 14.2, 23.1, 61.8, 119.7, 119.9, 127.6, 127.7, 128.4, 128.9, 131.0, 135.0, 136.2, 137.3, 140.6, 141.3, 155.0, 162.4; HRMS (EI): m/z calcd for $C_{19}H_{15}NO_2S_2$ (M^+): 353.0544; found: 353.0553.

*4.1.22.3. Ethyl 2-methyl-3-phenyl-2H-thieno[2′,3′:5,6]benzo[1,2-b]-[1,4]thiazine-8-carboxylate (****12c****).* Mp 110–111 °C; IR: 3048, 2974, 2923, 1703, 1259 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 (d, J=6.8 Hz, 3H, CH_3), 1.43 (t, J=7.1 Hz, 3H, CH_3), 4.30 (q, J=6.8 Hz, 1H, CH), 4.42 (q, J=7.1 Hz, 2H, CO_2CH_2), 7.51 (m, 3H), 7.64 (d, J=8.5 Hz, 1H), 7.71 (d, J=8.7 Hz, 1H), 8.07 (m, 2H), 8.18 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 17.6, 29.8, 61.8, 116.3, 119.8, 127.4, 127.6, 128.9, 129.0, 131.0, 134.7, 137.0, 139.8, 141.1, 158.3, 162.7; HRMS (EI): m/z calcd for $C_{20}H_{17}NO_2S_2$ (M^+): 367.0701; found: 367.0702.

*4.1.22.4. Ethyl 2,3-diphenyl-2H-thieno[2′,3′:5,6]benzo[1,2-b][1,4]-thiazine-8-carboxylate (****12d****).* Mp 147–148 °C; IR: 2982, 1697, 1252 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.39 (t, J=7.0 Hz, 3H, CH_3), 4.38 (q, J=7.0 Hz, 2H, CO_2CH_2), 7.20 (m, 5H), 7.46 (m, 3H), 7.64 (d, J=8.7 Hz, 1H), 7.70 (d, J=8.7 Hz, 1H), 8.02 (m, 2H), 8.07 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 38.5, 62.0, 116.3, 120.1, 127.6, 127.7, 128.6, 128.9, 129.0, 129.3, 130.3, 133.5, 134.7, 135.6, 136.6, 137.1, 138.1, 141.3, 155.6, 162.7; HRMS (EI): m/z calcd for $C_{25}H_{19}NO_2S_2$ (M^+): 429.0857; found: 429.0858.

*4.1.22.5. Ethyl 9-oxo-9H-thieno[2,3-c]phenothiazine-2-carboxylate (****12e****).* A solution of benzoquinone (105 mg, 0.975 mmol) in MeOH (2 mL) was added slowly to a solution of ethyl 3*H*-thieno-[3′,2′:3,4]benzo[1,2-*d*][1,2,3]dithiazole-7-carboxylate 2-oxide **3** (100 mg, 0.325 mmol) in MeOH (2 mL) at room temperature. After stirring the resulting mixture for another 12 h, the reaction mixture was added to a 1:1 mixture of water and methanol (10 mL) and the precipitate formed was filtered off and dried in vacuum. Purification by column chromatography (silica, eluent CH_2Cl_2/EtOAc 95:5) afforded pure **12e** (70 mg, 63%) as a deep red solid. Mp 159–160 °C; IR: 3062, 1700, 1622, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.45 (t, J=7.15 Hz, 3H, CH_3), 4.46 (q, J=7.10 Hz, 2H, CO_2CH_2), 6.86 (s, 1H), 6.99 (d, J=9.79 Hz 1H), 7.66 (d, J=9.88 Hz, 1H); 7.89 (s, 2H), 8.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 29.8, 120.5, 120.9, 122.0, 126.6, 131.7, 133.5, 133.6, 135.4, 136.9, 137.0, 139.7, 144.5, 145.9, 161.9, 182.5; HRMS (EI): m/z calcd for $C_{17}H_{12}NO_3S_2$ (M+H): 342.0258; found: 342.0252.

*4.1.23. Ethyl 5-(3-butylthioureido)benzo[b]thiophene-2-carboxylate (****13a****).* To a solution of ethyl 5-aminobenzo[*b*]thiophene-2-carboxylate **1** (208 mg, 0.941 mmol) in acetonitrile (3 mL) was added butyl isothiocyanate (400 mg, 3.5 mmol). After stirring the resulting mixture for another 12 h, the reaction mixture was added to a 1:1 mixture of water and methanol (10 mL) and the precipitate formed was filtered off and dried in vacuum to afford analytically pure product **13a** as an off-white solid (198 mg, 63%). Mp 152–153 °C; IR: 2958, 1712, 1542, 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, J=7.09 Hz, 3H, CH_3), 1.33 (q, J=7.36 Hz, 2H, CH_2), 1.43 (t, J=7.10 Hz, 3H, CH_3), 1.56 (t, J=7.06 Hz, 2H, CH_2), 3.64 (d, J=6.17 Hz, 2H, CH_2), 4.42 (q, J=7.10 Hz, 2H, CH_2), 5.99 (s, 1H), 7.31 (d, J=8.58 Hz, 1H), 7.72 (s, 1H), 7.91 (d, J=8.50 Hz, 1H), 7.97 (br s, 1H), 8.03 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 14.4, 20.2, 31.2, 45.5, 62.1, 122.1, 124.7, 124.8, 129.9, 133.5, 136.4, 139.9, 140.9, 162.4, 180.9; HRMS (EI): m/z calcd for $C_{16}H_{21}N_2O_2S_2$ (M+H); 337.1044; found: 337.1037.

*4.1.24. Ethyl 5-(3-phenylthioureido)benzo[b]thiophene-2-carboxylate (****13b****).* Similarly, starting from ethyl 5-aminobenzo[*b*]-thiophene-2-carboxylate **1** (214 mg, 0.967 mmol) and phenyl isothiocyanate (261 mg, 1.9 mmol), product **13b** was obtained as an off-white solid (279 mg, 82%). Mp 183–184 °C; IR: 3307, 1701, 1245, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.42 (t, J=7.12 Hz, 3H, CH_3), 4.41 (q, J=7.23 Hz, 2H, CO_2CH_2), 7.43 (m, 5H), 7.85 (m, 2H), 7.92 (s, 1H), 8.02 (s, 1H); ^{13}C NMR δ 14.4, 31.1, 121.9, 123.7, 125.1, 125.5, 127.7, 130.1, 134.8, 135.9, 136.7, 139.4, 140.7, 162.6, 180.5; HRMS (EI): m/z calcd for $C_{18}H_{17}N_2O_2S_2$ (M+H): 357.0731; found 357.0722.

*4.1.25. Ethyl 5-(3-benzylthioureido)benzo[b]thiophene-2-carboxylate (****13c****).* Similarly, starting from ethyl 5-aminobenzo[*b*]thio-phene-2-carboxylate **1** (199 mg, 0.9 mmol) and benzylisothiocyanate (201 mg, 1.35 mmol), product **13c** was obtained as an off-white solid (285 mg, 86%). Mp 164–165 °C; IR: 3328, 1693, 1512, 1269, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.41 (t, J=7.12 Hz, 3H, CH_3), 4.39 (q, J=7.02 Hz, 2H, CO_2CH_2), 4.88 (d, J=4.76 Hz, 2H, CH_2), 6.29 (s, 1H), 7.30 (br s, 6H), 7.72 (s, 1H), 7.86 (d, J=8.56 Hz, 1H) 7.97 (s, 1H), 8.17 (s, 1H); ^{13}C NMR δ 14.4, 49.6, 62.0, 122.1, 124.7, 127.8, 127.9, 128.9, 129.1, 129.8, 133.3, 136.4, 137.2, 139.8, 141.0, 162.4, 181.3; HRMS (EI): m/z calcd for $C_{19}H_{19}N_2O_2S_2$ (M^++H): 371.0888; found: 371.0881.

*4.1.26. Ethyl-2-butylaminothieno[3′,2′:3,4]benzo[1,2-d]thiazole-7-carboxylate (****14a****).* A solution of Br_2 (51 mg, 0.321 mmol) in acetic acid (1 mL) was added to precursor **13a** (108 mg, 0.321 mmol) in acetic acid (3 mL) at rt After stirring the resulting mixture for another 20 min, the reaction mixture was added to a 1:1 mixture of water and methanol (15 mL) and the precipitate formed was filtered off and dried in vacuum to afford analytically pure product **14a** as an off-white solid (79 mg, 74%). Mp 158–159 °C; IR: 3359, 2929, 1691, 1511, 1265, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, J=7.26 Hz, 3H, CH_3), 1.47 (m, 5H), 1.71 (m, 2H), 3.44 (t, J=6.93 Hz, 2H, CH_2), 4.42 (q, J=7.08 Hz, 2H, CH_2), 5.67 (s, 1H), 7.65 (d, J=8.69 Hz, 1H), 7.74 (d, J=8.78 Hz, 1H), 7.99 (s, 1H); ^{13}C NMR δ 13.9, 14.5, 20.2, 31.7, 45.8, 61.8, 119.3, 120.4, 127.7, 132.1, 135.1, 136.5,

150.3, 162.8, 167.6; HRMS (EI): *m*/*z* calcd for $C_{16}H_{19}N_2O_2S_2$ (M+H): 335.0888; found: 335.0869.

*4.1.27. Ethyl-2-phenylaminothieno[3′,2′:3,4]benzo[1,2-d]thiazole-7-carboxylate (**14b**).* Similarly, from Br_2 (76 mg, 0.477 mmol) and precursor **13b** (170 mg, 0.477 mmol) was prepared product **14b** as an off-white solid (134 mg, 80%). Mp 164–165 °C; IR: 3330, 1691, 1514, 1268 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 1.36 (t, *J*=6.71 Hz, 3H, CH_3), 4.38 (q, *J*=6.56 Hz, 2H, CH_2), 7.04 (t, *J*=7.05 Hz, 1H), 7.38 (t, *J*=7.39 Hz, 2H), 7.82 (d, *J*=8.49 Hz, 3H), 8.00 (d, *J*=8.62, 1H), 8.29 (s, 1H), 10.65 (s, 1H); ^{13}C NMR δ 14.2, 30.7, 41.7, 61.6, 104.7, 117.7, 119.8, 120.5, 122.1, 128.5, 129.1, 131.5, 134.4, 136.1, 140.6, 150.2, 161.5, 161.8; HRMS (EI): *m*/*z* calcd for $C_{18}H_{15}N_2O_2S_2$ (M+H): 355.0574; found: 355.0562.

*4.1.28. Ethyl-2-benzylthieno[3′,2′:3,4]benzo[1,2-d]thiazole-7-carboxylate (**14c**).* Similarly, from Br_2 (88 mg, 0.55 mmol) and precursor **13c** (204 mg, 0.55 mmol) was prepared product **14c** as an off-white solid (183 mg, 91%). Mp 175–176 °C; IR: 3328, 1693, 1512, 1269, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.41 (t, *J*=7.06 Hz, 3H, CH_3), 4.39 (q, *J*=7.06 Hz, 2H, CO_2CH_2), 4.63 (s, 2H), 7.37 (m, 5H), 7.55 (d, 1H), 7.70 (d, 1H), 7.96 (s, 1H); ^{13}C NMR δ 14.5, 49.8, 61.8, 119.1, 120.4, 124.5, 126.9, 127.6, 127.8, 128.1, 128.9, 129.1, 132.0, 135.2, 136.6, 137.2, 149.7, 162.7, 167.8; HRMS (EI): *m*/*z* calcd for $C_{19}H_{16}N_2O_2S_2$ (M+H): 369.0731; found: 369.0721.

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