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Tandem transformations of tetrahydrobenzothieno[2,3-*c*]pyridines in the presence of activated alkynes

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ABSTRACT

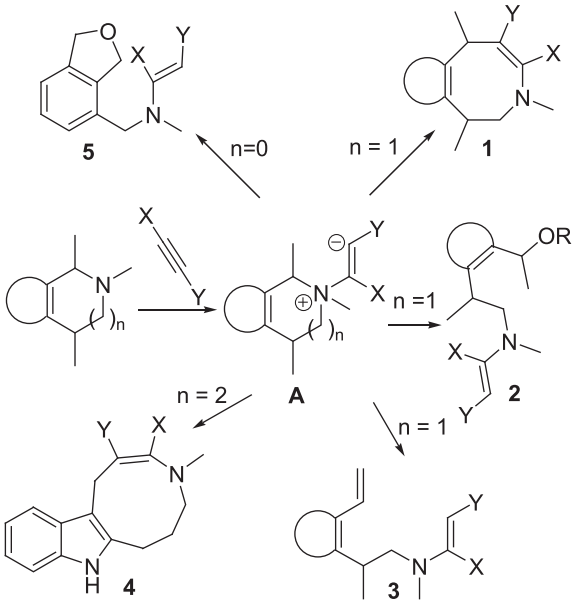
The reactivity of some new tetrahydrothienopyridines towards activated alkynes was investigated. A novel cascade cleavage-spiroannulation process, leading to the formation of previously unreported derivatives of 1′*H*-spiro[1-benzothiophene-3,4′-pyridine] was discovered and studied.

1. Introduction

Domino reactions have emerged as powerful tools to allow the rapid increase of molecular complexity. These processes avoid the excessive handling and isolation of synthetic intermediates, generating less waste and thus, contribute towards 'Green Chemistry'.[1] Domino reactions (also known as cascade or tandem) in which multiple reactions are combined into one synthetic operation, have been reported extensively in the literature and have already become 'state-of-the-art' in synthetic organic chemistry.[2]

Our own research efforts have focused on developing a new tandem reaction involving the Michael addition of the tertiary *N*-atom in (hetero)annulated pyrrolidines,[3] piperidines[4] or azepines[5] to the triple bond of activated alkyne, followed by the nucleophilic substitution (S_N) reaction in the zwitter-ionic intermediate A (Scheme 1).

The pathways for the further nucleophilic transformations of the zwitter-ion **A** are presumably defined by the reactivity of the anionic centre, the electronic effects of the substituent or the fused aromatic system and the nature of the solvent. In aprotic solvents tetrahydropyrrolopyridines produce pyrrolo[2,3-*c*]azocines **1**, but



Scheme 1.

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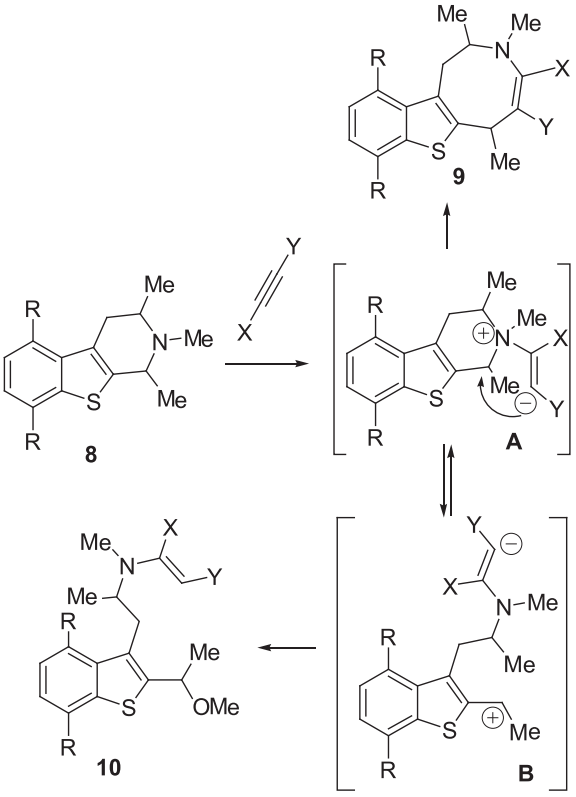
in the case of methyl-substituted tetrahydropyridine fragment the mixture of azocines and 3-vinylpyrroles **3** (the product of Hoffmann degradation) is formed; tetrahydrocarbolines under the same conditions smoothly form azocino[4,5-*b*] and [5,4-*b*]indoles **1**. If the reaction is carried out in methanol, the tandem transformation of the tetrahydropyridine ring takes place and the formation of alkoxyalkyl substituted pyrroles and indoles **2** occurs (Scheme 1). Tetrahydroazepino[4,3-*b*]indoles under the action of activated alkynes give azonino[5,6-*b*]indoles **4** in high yields both in acetonitrile and in methanol. In the case of 4-hydroxymethyl dihydroisoindoles, a new recyclization takes place, providing access towards phthalane derivatives **5**.

The analysis of the data obtained earlier enabled us to consider the transformation of the tetrahydropyridine ring as a domino Michael addition-S_N process. Based on this presumption we think that electron effects and the annulation pattern of the fused fragment would change the partial positive charge $+\delta^1$ appearing on C_1 atom in the intermediate zwitter-ion **A** and would influence the cleavage of C_1–N bond thus determining the reaction pathway. It is obvious that the steric effects of the substituents at C_1- and N-atoms would also affect the formation of the intermediate zwitter-ion **A**.

Thus, the elucidation of the reaction pathways requires taking into account many parameters and makes the investigation of other piperidine-containing substrates reactivity a justified task.

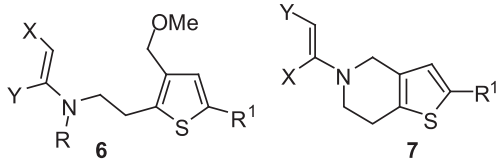
To get more information on the reaction scope and limitations, we studied the transformations of tetrahydrothieno[2,3-*c*]pyridines, condensed with benzene or oxopyrimidine rings under the action of methyl propiolate (MP), acetyl acetylene, and dimethyl acetylenedicarboxylate (DMAD).



Scheme 3.

2. Results and discussion

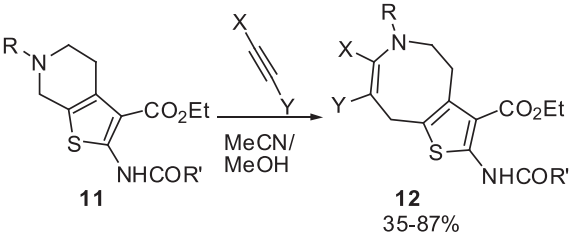
We have reported, that tetrahydrothieno[3,2-*c*]pyridines reacted with dimethyl acetylenedicarboxylate (DMAD) or ethyl propiolate in methanol or *iso*-propanol only under rather forcing conditions (reflux, 4 days). Even so the target azocine derivatives were not isolated. Two concurrent processes took place: the cleavage of the tetrahydropyridine ring, leading to the formation of 3-methoxy(hydroxy) substituted thiophenes (**6**), or the elimination of the benzyl fragment, producing *N*-dimethoxycarbonyl(ethoxycarbonyl)vinyl tetrahydrothieno[3,2-*c*]pyridines (**7**)[6] (Scheme 2).



Scheme 2.

Unlike tetrahydrothieno[3,2-*c*]pyridines 1,2,3-trimethylbenzo[*b*]thieno[2,3-*c*]pyridines **8** reacted with activated alkynes (methyl or ethyl propiolates, acetyl acetylene, DMAD) in methanol at rt giving multi-component mixtures. The target tetrahydrobenzo[*b*]thieno[3,2-*d*]azocines **9** were isolated in 2–9% yield, whereas the main products of the reactions were 2-methoxyethyl substituted benzo[*b*]thiophenes **10** resulting from the tandem cleavage of the tetrahydropyridine ring under the action of methanol[7] (Scheme 3).

At the same time 2-acetylaminotetrahydrothieno[2,3-*c*]pyridines **11** are effectively converted into the target azocine derivatives **12** under the action of activated alkynes both in methanol or acetonitrile[8] (Scheme 4).



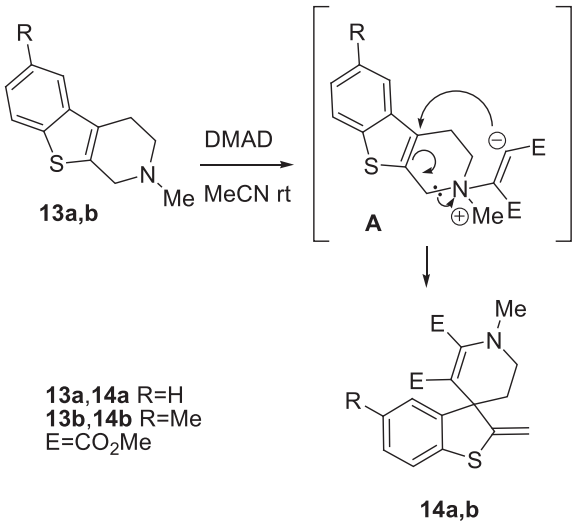
Scheme 4.

The present paper reports on new results of the tandem transformations of tricyclic analogues of **11** in the reaction with activated alkynes.

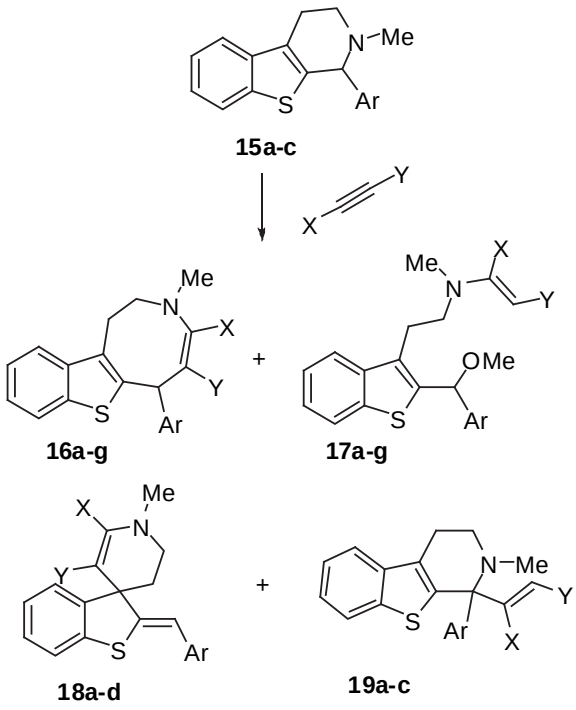
The annulation of a benzene ring to the thiophene moiety also decreases the reactivity of thienopyridines in this reaction. Tetrahydrobenzothieno[2,3-*c*]pyridines **13a**,**b** do not react with activated alkynes in methanol even under rather forcing reaction conditions (several days at reflux). The use of aprotic solvents (THF, nitromethane, acetonitrile) in the case of methyl propiolate or acetyl acetylene did not allowed to isolate any product as well. However in the case of the reaction of **13a**,**b** with DMAD in acetonitrile a really surprising product—spirotetrahydropyridyl annulated benzothiophenes—**14a**, **b** were obtained[9] (Scheme 5).

We presume, that the reaction proceeds via the intermediacy of the zwitter-ion A, followed by the cleavage-recyclization sequence to yield spiro compounds **14a**, **b**. The structures were confirmed by a complex of spectral data, including ^{1}H, ^{13}C NMR spectra (COSY, HMBC experiments), mass- and IR-spectra.

The ^{1}H NMR spectra of compounds **14a**, **b** show characteristic signals (doublets with ^2J=1.7 Hz) at 4–5 ppm fitting with the resonance of =CH_2 protons. The formation of spiropyridyl products in the reaction of isosteric β-carbolines with DMAD was reported earlier by González-Gómez et al.[10]



Scheme 5.



Scheme 6.

The implementation of an aryl substituent in 1-position of the benzothieno[2,3-*c*]pyridine skeleton changed both the activity and transformation pathways of the thienopyridine system under the action of alkynes. Compounds **15a**–**c** smoothly react with activated acetylenes in methanol or acetonitrile (Scheme 6, Table 1).

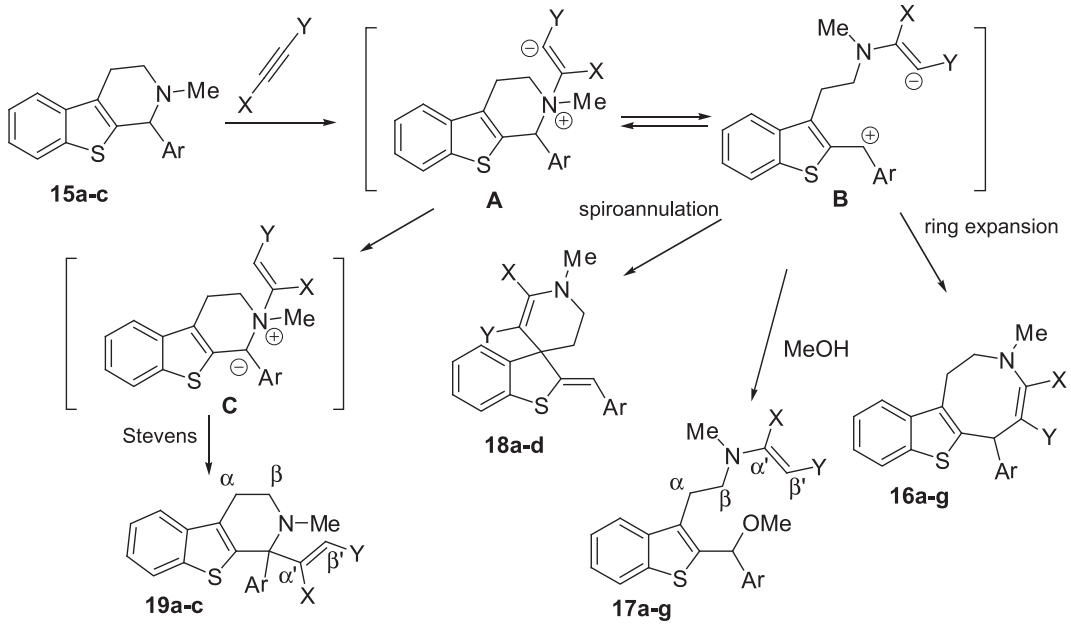
Reactions of 1-phenyl- and 1-*p*-methoxyphenyl-derivatives **15a**, **b** with methyl propiolate in methanol proceed much faster compared with the same reaction in the case of 1-*p*-nitrophenyl derivative **15c**. The reactions of **15a**–**c** with acetyl acetylene and methyl propiolate lead to the formation of spiro[benzothieno-3′,4′-piperidines] **18a**–**d**. In the case of methyl propiolate this transformation is accompanied by the alternative reaction through the intermediate ylide **C**, yielding the Stevens rearrangement products—1-aryl-1-vinyl-benzothienopyridines **19a**–**c** (Scheme 7).

The initially formed zwitter-ion **A**, most likely, partially exists in the 'opened' form **B**, containing a benzhydryl-like cation, that facilitates ring expansion and spiroannulation processes, providing compounds **16** and **18**, respectively. The addition of a methanol molecule to **B** yields substituted benzo[*b*]thiophenes **17a**–**g**. The ability of a 1-Ar radical to delocalize the negative charge on C-1 allows the formation of the ylide intermediate **C** that undergoes the Stevens rearrangement to give compounds **19a**–**c**. The spiro compounds **18a**–**d** are formed only as the (*Z*)-isomer. The structures of compounds **18a** (Fig. 1) and **16a** (Fig. 2) were unambiguously elucidated by means of X-ray analysis of their single crystals obtained by slow evaporation of their methanol solution. Crystallographic data (excluding structure factors) for compounds **18a** and **16a** have been deposited with the Cambridge Crystallographic Data Centre [12, Union Road, Cambridge CB2 1EZ, UK; tel.: +44 1223 336 408; e-mail: deposit@ccdc.cam.ac.uk] as supplementary publication numbers CCDC 770393 and 770394, respectively. Those data can be obtained free of charge at www.ccdc.cam.ac.uk/cont/retrieving.html.

As mentioned above, compounds **18a**, **b** were isolated solely as the (*Z*)-isomers, however, in the case of 1-*p*-nitrophenyl-tetrahydrobenzothieno[2,3-*c*]pyridine **15c**, during the column chromatography purification of the reaction mixtures (Al_2O_3, EtOAc/

Table 1

Compound	Alkyne	Solvent, temperature	Time of reaction	Product of reaction, yield, %			
15a	X=Y=CO_2Me	MeOH, rt	25 h		**17e**, 90%	—	—
Ar=Ph	X=H, Y=CO_2Me	MeOH, rt	20 h	**16a**, 81%	**17a**, 11%	**18a**, 5%	—
	X=H, Y=COMe	MeOH, rt	5 min	**16d**, 30%	**17b**, 11%	—	—
	X=Y=CO_2Me	MeCN, reflux	147 h	Multi-component mixture			
	X=H, Y=CO_2Me	MeCN, rt	175 h	**16a**, 63%	—	**18a**, 22%	trace
	X=H, Y=COMe	MeCN, rt	7 days	**16d**, 82%	—	**18b**, 15%	—
	X=H, Y=CO_2Me	CH_2Cl_2, rt	30 days	**16a**, 62%	—	**18a**, 19%	**19a**, 7%
15b	X=Y=CO_2Me	MeOH, rt	26 h	—	**17f**, 94%	—	—
Ar=*p*-OMe–C_6H_4	X=H, Y=CO_2Me	MeOH, rt	24 h	**16b**, 83%	Trace	—	—
	X=H, Y=COMe	MeOH, rt	5 min	**16e**, 43%	**17c**, 48%	—	—
	X=Y=CO_2Me	MeCN, reflux	45 h	**16g**, 32%	—	—	—
	X=H, Y=CO_2Me	MeCN, reflux	11 h	**16b**, 78%	—	—	—
	X=H, Y=COMe	MeCN, rt	11 days	**16e**, 89%	—	—	—
	X=H, Y=CO_2Me	CH_2Cl_2, rt	20 days	**16b**, 68%	—	—	**19b**, 15%
15c	X=Y=CO_2Me	MeOH, 45 °C	10 days	—	**17 g**, 93%	—	—
Ar=*p*-NO_2-C_6H_4	X=H, Y=CO_2Me	MeOH, 45 °C	3 days	**16c**, 80%	—	**18c**, 9%	—
	X=H, Y=COMe	MeOH, 45 °C	16 h	**16f**, 53%	**17d**, 19%	**18d**, 16%	—
	X=Y=CO_2Me	MeCN, reflux	257 h	Multi-component mixture			
	X=H, Y=CO_2Me	MeCN, reflux	158 h	**16c**, 39%	—	**18c**, 22%	**19c**, 20%
	X=H, Y=COMe	MeCN, reflux	92 h	**16f**, 56%	—	**18d**, 29%	—



Scheme 7.

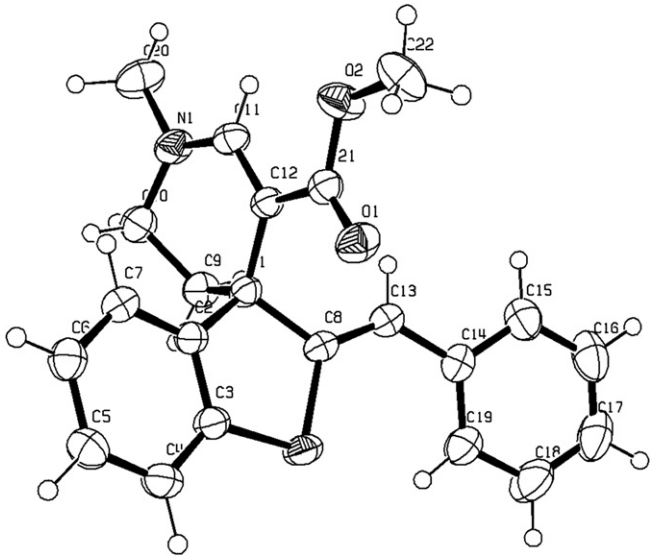


Fig. 1. ORTEP plot of **18a** with 50% probability ellipsoid.

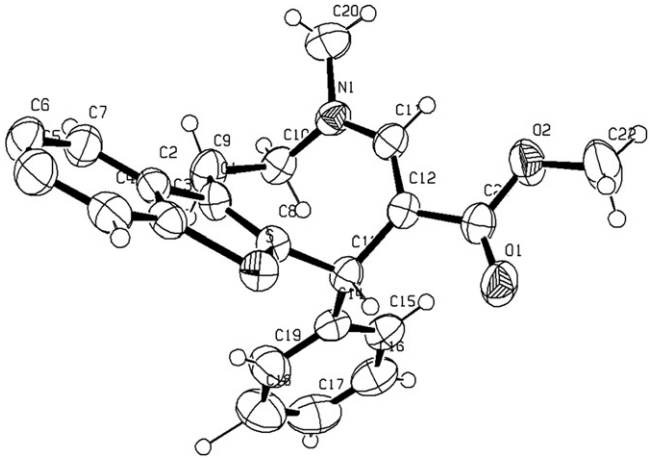
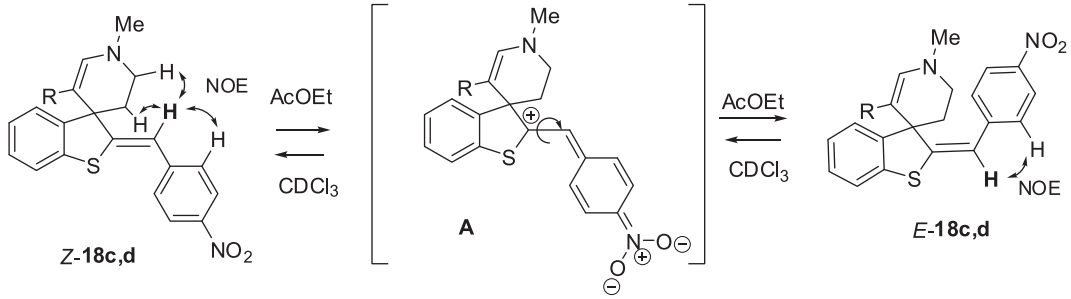


Fig. 2. ORTEP plot of **16a** with 50% probability ellipsoid.

hexanes) *Z*–*E* isomerisation was observed and the corresponding (*E*)-**18c**, **d** were isolated as well. The structures of both isomers were elucidated based on 2D NOESY NMR experiments. We presume, that this isomerisation occurs via the intermediacy of the quinoid structure **A** (Scheme 8). It was demonstrated, that the isomerisation process is solvent-dependant, whereas the dissolution of (*Z*)-**18c**, **d** in ethyl acetate within 24 h leads to a 1:1 (*E*)/(*Z*) **18c**, **d** mixture; however, the use of chloroform does not cause any transformation. In contrast, (*E*)-**18c**, **d**, upon dissolution in $CDCl_3$ are completely transformed into (*Z*)-**18c**, **d** within 2 weeks. The latter was confirmed by the dynamic ^1H NMR experiment (See Supplementary data for details).



Scheme 8.

3. Conclusion

In summary, we have investigated the reactivity of some new tetrahydrothienopyridines towards activated alkynes. A novel cascade cleavage-spiroannulation process, leading to the formation of previously unreported derivatives of 1′*H*-spiro[1-benzothiophene-3,4′-pyridine] was found. The work, aimed at the reaction conditions optimization as well as at establishing its scope and limitations is underway and will be reported in due course.

4. Experimental section

4.1. General

All solvents were distilled and dried before use, DMAD, acetyl acetylene and methyl propiolate were purchased from Acros ORGANICS and were used without any additional purification. Column chromatography was performed with aluminium oxide, activated, neutral, Brockmann I purchased from ACROS ORGANIC or Silicagel, 40–60 μm, 60A. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions, at 25°C, using a 600 MHz NMR spectrometer, peak positions are given in parts per million (δ) with tetramethylsilane used as the internal standard. Mass-spectra were registered using ESI or EI techniques. IR spectra were recorded with a Perkin–Elmer Spectrum One instrument. Only noteworthy IR absorptions [cm^{-1}] are listed. Vario Micro cube element analyzer was used to perform C, H, N analyses. Melting points were determined in capillary tube and are uncorrected. 2-Methyl-1,2,3,4-tetrahydrobenzothieno[2,3-*c*]pyridines **13a**,**b** and 1-aryl-2-methyl-1,2,3,4-tetrahydrobenzothieno [2,3-*c*]pyridines **15a**–**c** were prepared according to Ref. 11,12.

4.2. Experimental procedure for the synthesis of benzothienoazocine 16c and spiro compound 18c in methanol

Methyl propiolate (0.083 mL, 0.9 mmol) was added to a stirred solution of benzothienopyridine **15c** (250 mg, 0.8 mmol) in methanol (25 mL) at 45 °C. The temperature was maintained and the stirring was continued for 3 days (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography to give benzothienoazocine **16c** (251 mg, 80%) as a yellow solid and spiro compound **18c** (28 mg, 9%) as a yellow oil.

*4.2.1. Methyl 3-methyl-6-(4-nitrophenyl)-1,2,3,6-tetrahydro[1]benzothieno[3,2-d]azocine-5-carboxylate (**16c**).* Purified by column chromatography (SiO_2, chloroform/hexane, 1:4), yield 251 mg, (80%) as a yellow solid, mp 213–214 °C (ethyl acetate/hexane); [found: C, 64.6; H, 5.0; N, 6.7. $C_{22}H_{20}N_2O_4S$ requires C, 64.69; H, 4.94; N, 6.86%]; R_f (sorbfil, 1:3, ethyl acetate/hexane) 0.53; ν_{max} (KBr) 1671, 1617 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.12 (2H, d, *J* 8.9 Hz, *m*-C_6H_4–NO_2), 7.82 (dd, 1H, *J* 7.2, 1.3 Hz, 8-H), 7.74 (1H, s, 4-H), 7.64 (1H, dd, *J* 7.2, 1.3 Hz, 11-H), 7.43–7.33 (4H, m, 9-H, 10-H, *o*-C_6H_4–NO_2), 6.17 (1H, s, 6-H), 3.78 (3H, s, CO_2Me), 3.72–3.64 (1H, m, 2-CH_2), 3.34 (1H, ddd, *J* 17.5, 13.6, 4.4 Hz, 1-CH_2), 3.03 (3H, s, N–CH_3), 2.88 (1H, ddd, *J* 15.1, 4.4, 2.8 Hz, 2-CH_2), 2.74 (1H, td, *J* 17.5, 2.8 Hz, 1-CH_2); δ_C (100 MHz, $CDCl_3$) 170.3, 154.3, 152.3, 146.2, 141.7, 138.5, 138.1, 127.2 (2C), 127.1, 124.4, 124.2, 124.0 (2C), 122.2, 121.3, 95.2, 51.6, 48.6, 44.2, 41.9, 28.2; *m*/*z* (LCMS) 409 $[M+H]^+$.

*4.2.2. Methyl (2Z)-1′-methyl-2-(4-nitrobenzylidene)-5′,6′-dihydro-1′H-spiro[1-benzothiophene-3,4′-pyridine]-3′-carboxylate (**18c**).* Purified by column chromatography (SiO_2, chloroform/hexane, 1:2), yield 28 mg (9%) as a yellow oil; [found: C, 64.8; H, 4.9; N, 6.8. $C_{22}H_{20}N_2O_4S$ requires C, 64.69; H, 4.94; N, 6.86%]; R_f (sorbfil, 1:2, ethyl acetate/hexane) 0.45; ν_{max} (KBr) 1679, 1614 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.20 (2H, d, *J* 8.9 Hz, *m*-C_6H_4–NO_2), 7.83 (1H, s, 2′-H), 7.54 (2H, d, *J* 8.9 Hz, *o*-C_6H_4–NO_2), 7.30 (d, 1H, *J* 7.4 Hz, 7-H), 7.20 (1H, dt, *J* 7.4, 1.1 Hz, 6-H), 7.12 (1H, dt, *J* 7.4, 1.1 Hz, 5-H), 7.02 (1H, dd, *J* 7.4, 1.1 Hz, 4-H), 6.46 (1H, s, *CH*–Ar–NO_2), 3.40 (3H, s, CO_2Me), 3.30–3.37 (1H, m, 6′-CH_2), 3.09–3.15 (4H, m, 6′-CH_2, N–CH_3), 2.08 (1H, ddd, *J* 13.7, 5.6, 3.9 Hz, 5′-CH_2), 1.95 (1H, ddd, *J* 13.7, 4.2, 9.4 Hz, 5′-CH_2); δ_C (100 MHz, $CDCl_3$) 166.6, 155.2, 148.9, 145.9, 143.5, 136.0, 129.7, 128.6 (2C), 127.7, 125.4, 123.7 (2C), 123.0, 121.6, 117.0, 97.1, 56.4, 50.4, 43.3, 43.0, 38.1; *m*/*z* (LCMS) 409 $[M+H]^+$.

4.3. Experimental procedure for the synthesis of benzothienoazocine 16c, spiro compound 18c and benzothienopyridine 19c in acetonitrile

Methyl propiolate (0.711 mL, 8.0 mmol) was added to a solution of benzothienopyridine **15c** (250 mg, 0.8 mmol) in acetonitrile (25 mL). The reaction mixture was heated at reflux for 158 h (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 1:30) to give benzothienoazocine **16c** (123 mg, 39%) as a yellow solid, spiro compound **18c** (69 mg, 22%) a yellow oil, and benzothienopyridine **19c** (63 mg, 20%) as a white solid.

*4.3.1. Methyl 3-methyl-6-(4-nitrophenyl)-1,2,3,6-tetrahydro[1]benzothieno[3,2-d]azocine-5-carboxylate (**16c**).* Purified by column chromatography (SiO_2, chloroform/hexane, 1:4), yield 123 mg (39%).

*4.3.2. Methyl (2Z)-1′-methyl-2-(4-nitrobenzylidene)-5′,6′-dihydro-1′H-spiro[1-benzothiophene-3,4′-pyridine]-3′-carboxylate (**18c**).* Purified by column chromatography (SiO_2, chloroform/hexane, 1:2), yield 69 mg (22%).

*4.3.3. Methyl (2E)-3[2-methyl-1-(4-nitrophenyl)-1,2,3,4-tetrahydro[1]benzothieno[2,3-c]pyridine-1-yl]acrylate (**19c**).* Purified by column chromatography (SiO_2, chloroform/hexane, 1:6), yield 63 mg, (20%) as a white solid, mp 148–150 °C (ethyl acetate/hexane); [found: C, 64.7; H, 5.0; N, 6.8. $C_{22}H_{20}N_2O_4S$ requires C, 64.69; H, 4.94; N, 6.86%]; R_f (sorbfil, 1:3, ethyl acetate/hexane) 0.70; ν_{max} (KBr) 1722, 1640 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.21 (2H, d, *J* 8.7 Hz, *m*-C_6H_4–NO_2), 7.74 (2H, d, 7.8 Hz, 5-H, 8-H), 7.64 (2H, d, *J* 8.7 Hz, *o*-C_6H_4–NO_2), 7.44 (1H, d, *J* 15.7 Hz, CH=*CH*–CO_2Me), 7.37 (1H, t, *J* 7.8 Hz, 7-H), 7.29 (1H, t, *J* 7.8 Hz, 6-H), 5.85 (1H, d, *J* 15.7 Hz, *CH*=CH–CO_2Me), 3.77 (3H, s, OCH_3), 3.11–3.00 (2H, m, 4-CH_2), 2.97–2.89 (2H, m, 3-CH_2), 2.34 (3H, s, N–CH_3); δ_C (100 MHz, $CDCl_3$) 166.0, 147.8, 145.7, 145.5, 140.0, 138.2, 130.0, 128.7, 127.5, 124.9, 124.4, 123.8 (3C), 122.4 (2C), 121.5, 61.3, 51.9, 46.8, 38.9, 24.3; *m*/*z* (EI, 70 eV) 408 (27, M^+), 392 (8), 377 (9), 340 (9), 323 (44), 306 (13), 286 (78), 267 (25), 258 (25), 223 (16), 213 (17) 188 (24), 160 (13), 128 (34), 117 (26), 103 (18), 76 (35), 59 (100), 42 (91).

4.4. Experimental procedure for the synthesis of benzothiophene 17g in methanol

DMAD (0.147 mL, 1.2 mmol) was added to a stirred solution of benzothienopyridine **15c** (200 mg, 0.6 mmol) in methanol (20 mL) at 45 °C. The temperature was maintained and the stirring was continued for 10 days (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:13) to give benzothiophene **17g** (267 mg, 93%) as a yellow oil.

*4.4.1. Dimethyl (2E)-2-[(2-{2-[methoxy(4-nitrophenyl)methyl]-1-benzothien-3-yl}ethyl)(methyl)amino]but-2-enedioate (**17g**).* Yield 267 mg (93%) as a yellow oil; [found: C, 60.3; H, 5.3; N, 5.7. $C_{25}H_{26}N_2O_7S$ requires C, 60.23; H, 5.26; N, 5.62%]; R_f (sorbfil, 1:3, ethyl acetate/hexane) 0.54; ν_{max} (KBr) 1739, 1693, 1578 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 8.20 (2H, d, *J* 8.8 Hz, *m*-C_6H_4–NO_2), 7.81 (1H, d, *J*

7.7 Hz, 7-H), 7.70–7.65 (3H, m, 4-H, *o*-C_6H_4–NO_2), 7.41 (1H, d, *J* 7.7 Hz, 6-H), 7.35 (1H, d, *J* 7.7 Hz, 5-H), 5.79 (1H, s, *CH*–OCH_3), 4.63 (1H, s, β′-CH), 3.89 (3H, s, CO_2CH_3), 3.67 (3H, s, CO_2CH_3), 3.47 (3H, s, CH–O*CH*$_3$), 3.42–3.37 (2H, m, α-CH_2), 3.20–3.11 (2H, m, β-CH_2), 2.71 (3H, s, N–CH_3); δ_C (100 MHz, $CDCl_3$) 167.9, 166.1, 154.2, 147.7, 140.9, 139.4, 139.2, 129.6, 127.8 (2C), 127.3, 125.0, 124.6, 123.8 (2C), 122.9, 121.3, 85.3, 78.6, 57.4, 53.1, 53.0, 50.8, 38.1, 26.0; *m*/*z* (LCMS) 499 $[M+H]^+$.

4.5. Experimental procedure for the synthesis of benzothienoazicine 16f, spiro compound 18d and benzothiophene 17d in methanol

Acetyl acetylene (0.057 mL, 0.7 mmol) was added to a stirred solution of benzothienopyridine **15c** (200 mg, 0.6 mmol) in methanol (20 mL) at 45 °C. The temperature was maintained and the stirring was continued for 16 h (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography to give benzothienoazocine **16f** (128 mg, 53%) as a white solid, spiro compound **18d** (39 mg, 16%) as a yellow oil and benzothiophene **17d** (50 mg, 19%) as a yellow oil.

*4.5.1. 1-[3-Methyl-6-(4-nitrophenyl)-1,2,3,6-tetrahydro[1]benzothieno[3,2-d]azocin-5-yl]ethanone (**16f**).* Purified by column chromatography (SiO_2, chloroform), yield 128 mg, (53%) as a white solid, mp 216–218 °C (ethyl acetate/hexane); [found: C, 67.4; H, 5.2; N, 7.1. $C_{22}H_{20}N_2O_3S$ requires C, 67.33; H, 5.14; N, 7.14%]; R_f (sorbfil, 1:1, ethyl acetate/hexane) 0.40; ν_{max} (KBr) 1635, 1572 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.10 (2H, d, *J* 8.9 Hz, *m*-C_6H_4–NO_2), 7.81 (1H, d, *J* 7.4 Hz, 8-H), 7.64 (1H, d, *J* 7.4 Hz, 11-H), 7.54 (1H, s, 4-H), 7.41 (1H, dt, *J* 7.4, 1.2 Hz, 9-H), 7,37 (1H, dt, 7.4, *J* 1.2 Hz, 10-H), 7.24 (2H, dd, *J* 8.9, 1.2 Hz, *o*-C_6H_4–NO_2), 6.54 (1H, s, 6-H), 3.79–3.71 (1H, m, 2-CH), 3.38 (1H, ddd, *J* 17.5, 13.7, 4.5 Hz, 1-CH), 3.10 (3H, s, N–CH_3), 2.92 (1H, ddd, *J* 15.0, 4.5, 2.7 Hz, 2-CH), 2.77 (1H, td, *J* 17.5, 2.7 Hz, 1-CH), 2.38 (3H, s, COMe); δ_C (100 MHz, $CDCl_3$) 193.9, 154.3, 154.2, 146.2, 141.6, 138.7, 138.3, 127.1 (2C), 124.4, 124.2, 124.0 (3C), 122.2, 121.2, 110.4, 48.8, 44.5, 39.6, 27.9, 24.8; *m*/*z* (LCMS) 393 $[M+H]^+$.

*4.5.2. (3E)-4-[(2-{2-[Methoxy(4-nitrophenyl)methyl]-1-benzothien-3-yl}ethyl)(methyl)amino]but-3-en-2one (**17d**).* Purified by column chromatography (SiO_2, 0.2% methanol/chloroform), yield 50 mg, (19%) as a yellow oil; [found: C, 65.1; H, 5.8; N, 6.6. $C_{23}H_{24}N_2O_4S$ requires C, 65.07; H, 5.70; N, 6.60%]; R_f (sorbfil, ethyl acetate) 0.20; ν_{max} (KBr) 1655, 1603, 1564 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.22 (2H, d, *J* 8.7 Hz, *m*-C_6H_4–NO_2), 7.81 (1H, d, *J* 7.7 Hz, 7-H), 7.67 (1H, d, *J* 7.7 Hz, 4-H), 7.61 (2H, d, *J* 8.7 Hz, *o*-C_6H_4–NO_2), 7.46 (1H, d, *J* 13.2 Hz, α′-H), 7.44–7.39 (1H, m, 6-H), 7.38–7.34 (1H, m, 5-H), 5.68 (1H, s, *CH*–OCH_3), 5.10 (1H, d, *J* 13.2 Hz, β′-H), 3.47 (3H, s, CH–O*CH*$_3$), 3.42 (2H, t, *J* 7.4 Hz, β-CH_2), 3.14–3.10 (2H, m, α-CH_2), 2.78 (3H, br s, N–CH_3), 2.09 (3H, s, $COCH_3$); δ_C (100 MHz, $CDCl_3$) 195.2, 151.3 (2C), 147.7, 147.6, 140.4, 139.3, 139.2, 127.7 (2C), 125.1, 124.6, 123.8 (2C), 122.9, 121.3, 97.4, 78.8, 57.5, 57.0, 36.2, 28.4, 27.1; *m*/*z* (LCMS) 425 $[M+H]^+$.

*4.5.3. 1-[(2Z)-1′-Methyl-2-(4-nitrobenzylidene)-5′,6′-dihydro-1′H-spiro[1-benzothiophene-3,4′-pyridin]-3′-yl]ethanone (**18d**).* Purified by column chromatography (SiO_2, chloroform), yield 39 mg, (16%) as a yellow oil; [found: C, 67.4; H, 5.2; N, 7.1. $C_{22}H_{20}N_2O_3S$ requires C, 67.33; H, 5.14; N, 7.14%]; R_f (sorbfil, ethyl acetate) 0.29; ν_{max} (KBr) 1690, 1584 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.21 (2H, d, *J* 8.6 Hz, *m*-C_6H_4–NO_2), 7.83 (1H, s, 2′-H), 7.53 (d, 2H, *J* 8.6 Hz, *o*-C_6H_4–NO_2), 7.32 (1H, d, *J* 7.7 Hz, 7-H), 7.24–7.21 (1H, m, 6-H), 7.13 (1H, t, *J* 7.5 Hz, 5-H), 7.00 (1H, d, *J* 7.5 Hz, 4-H), 6.41 (1H, s, *CH*–Ar–NO_2), 3.36 (1H, ddd, *J* 13.4, 9.3, 4.0 Hz, 6′-CH_2), 3.20–3.12 (4H, m, 6′-CH_2, N–CH_3), 2.12–2.06 (1H, m, 5′-CH_2), 1.97 (1H, ddd, *J* 13.4, 4.0, 9.3 Hz, 5′-CH_2), 1.83 (3H, s, CO*CH*$_3$); δ_C (100 MHz, $CDCl_3$) 194.4, 154.8, 149.7, 145.6, 145.4, 143.3, 136.2, 128.6 (2C), 127.9, 125.7, 123.8 (2C), 123.1, 122.0, 117.3, 117.2, 56.5, 43.5, 43.4, 38.2, 26.3; *m*/*z* (LCMS) 393 $[M+H]^+$.

4.6. Experimental procedure for the synthesis of benzothienoazocine 16f and spiro compound 18d in acetonitrile

Acetylacetylene (0.329 mL, 4.2 mmol) was added to a solution of benzothienopyridine **15c** (200 mg, 0.6 mmol) in acetonitrile (20 mL). The reaction mixture was heated at the reflux for 92 h (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography to give benzothienoazocine **16f** (136 mg, 56%) as a white solid and spiro compound **18d** (70 mg, 29%) as a yellow oil.

*4.6.1. 1-[3-Methyl-6-(4-nitrophenyl)-1,2,3,6-tetrahydro[1]benzothieno[3,2-d]azocin-5-yl]ethanone (**16f**).* Purified by column chromatography (SiO_2, chloroform), yield 136 mg, (56%) as a white solid, mp 216–218 °C (ethyl acetate/hexane).

*4.6.2. 1-[(2Z)-1′-Methyl-2-(4-nitrobenzylidene)-5′,6′-dihydro-1′H-spiro[1-benzothiophene-3,4′-pyridin]-3′-yl]ethanone (**18d**).* Purified by column chromatography (SiO_2, chloroform), yield 70 mg, (29%) as a yellow oil

4.7. Experimental procedure for the synthesis of benzothienopyridine 17e in methanol

DMAD (0.132 mL, 1.1 mmol) was added to a stirred solution of benzothienopyridine **15a** (250 mg, 0.9 mmol) in methanol (20 mL). The stirring was continued for 25 h (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:40) to give benzothienopyridine **17e** (367 mg, 90%) as a white oil.

*4.7.1. Dimethyl (2E)-2-[2-{2-[methoxy(phenyl) methyl]-1-benzothien-3-yl}ethyl(methyl)amino]but-2-enedioate (**17e**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:40), yield 367 mg (90%) as a white oil; [found: C, 66.3; H, 6.0; N, 3.1. $C_{25}H_{27}NO_5S$ requires C, 66.20; H, 6.00; N, 3.09%]; R_f (sorbfil, ethyl acetate/hexane, 1:2) 0.53; ν_{max} (KBr) 1740, 1693, 1578 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.80 (1H, d, *J* 7.9 Hz, 7-H), 7.69 (1H, d, *J* 7.9 Hz, 4-H), 7.47 (2H, dd, *J* 8.7, 1.1 Hz, 5-H, 6-H), 7.40–7.30 (5H, m, C_6H_5), 5.65 (1H, s, *CH*–OCH_3), 4.63 (1H, s, β′-CH), 3.91 (3H, s, CO_2CH_3), 3.67 (3H, s, CO_2CH_3), 3.44 (3H, s, CH–*OCH*$_3$), 3.27–3.08 (4H, m, α-CH_2 and β-CH_2), 2.66 (3H, s, N–CH_3); δ_C (100 MHz, $CDCl_3$) 168.1, 166.1, 154.4, 142.7, 140.6, 139.7, 139.3, 128.7 (2C), 128.5, 128.3, 127.3 (2C), 124.5, 124.3, 122.7, 121.3, 84.9, 80.0, 57.2, 53.0, 52.8, 50.8, 37.9, 25.9; *m*/*z* (EI, 70 eV) 453 (4, M^+), 188 (9), 186 (100), 82 (14).

4.8. Experimental procedure for the synthesis of benzotheinoazocine 16a, spiro compound 18a and benzothiophene 17a in methanol

Methyl propiolate (0.095 mL, 1.1 mmol) was added to a stirred solution of benzothienopyridine **15a** (250 mg, 0.9 mmol) in methanol (25 mL). The stirring was continued for 20 h (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography to give benzothienoazocine **16a** (263 mg, 81%) as a white solid, spiro compound **18a** (16 mg, 5%) as a white solid and benzothiophene **17a** (39 mg, 11%) as a white solid.

*4.8.1. Methyl 3-methyl-6-phenyl-1,2,3,6-tetrahydro[1]benzothieno [3,2-d]azocine-5-carboxylate (**16a**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:50), yield 263 mg (81%) as

a white solid, mp 208–210 °C (ethyl acetate/hexane); [found: C, 72.6; H, 5.9; N, 3.9. $C_{22}H_{21}NO_2S$ requires C, 72.70; H, 5.82; N, 3.85%]; R_f (sorbfil, ethyl acetate/hexane, 1:3) 0.42; ν_{max} (KBr) 1665, 1616 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.80 (1H, d, *J* 7.6 Hz, 8-H), 7.71 (1H, s, 4-H), 7.61 (1H, d, *J* 7.6 Hz, 11-H), 7.38 (1H, dt, *J* 7.6, 1.2 Hz, 9-H), 7.33 (1H, dt, *J* 7.6, 1.2 Hz, 10-H), 7.28–7.24 (2H, m, 6-Ph), 7.18–7.13 (3H, m, 6-Ph), 6.12 (1H, s, 6-H), 3.75 (3H, s, CO_2CH_3), 3.95–3.88 (1H, m, 2-CH_2), 3.29 (1H, ddd, *J* 17.5, 13.5, 4.4 Hz, 1-CH_2), 3.00 (3H, s, N–CH_3), 2.81 (1H, ddd, *J* 15.0, 4.4, 2.8 Hz, 2-CH_2), 2.72 (1H, td, *J* 17.5, 2.8 Hz, 1-CH_2); δ_C (100 MHz, $CDCl_3$) 170.7, 152.1, 146.9, 142.1, 140.4, 138.3, 128.8 (2C), 126.8, 126.3, (2C), 125.9, 124.0, 123.9, 122.2, 121.3, 96.4, 51.5, 48.8, 44.2, 41.6, 28.4; *m*/*z* (EI, 70 eV) 363 (87, M^+), 306 (31), 304 (50), 273 (13), 261 (16), 234 (14), 216 (10), 202 (15), 184 (10), 160 (76), 152 (9), 140 (16), 128 (9), 115 (18), 91 (9), 77 (10), 59 (65), 42 (100).

*4.8.2. Methyl (2Z)-2-benzylidene-1′-methyl-5′,6′-dihydro-1′H-spiro [1-benzothiophene-3,4′-pyridine]-3′-carboxylate (**18a**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:45), yield 16 mg (5%) as a white solid, mp 174–176 °C (ethyl acetate/hexane); [found: C, 72.7; H, 5.7; N, 3.9. $C_{22}H_{21}NO_2S$ requires C, 72.70; H, 5.82; N, 3.85%]; R_f (sorbfil, ethyl acetate/hexane, 1:3) 0.27; ν_{max} (KBr) 1687, 1613 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.82 (1H, s, 2′-H), 7.42 (2H, d, *J* 7.7 Hz, C_6H_5), 7.36 (2H, t, *J* 7.7 Hz, C_6H_5), 7.27–7.24 (1H, m, 7-H), 7.20 (1H, d, *J* 7.7 Hz, C_6H_5), 7.16 (1H, dt, *J* 7.5, 1.2 Hz, 6-H), 7.07 (1H, dt, *J* 7.5, 1.2 Hz, 5-H), 6.99 (1H, dd, *J* 7.5, 1.2 Hz, 4-H), 6.40 (1H, s, *CH*–Ar), 3.41–3.35 (4H, m, 6′-CH_2, CO_2CH_3), 3.10 (3H, s, N–CH_3), 3.05 (1H, td, *J* 12.8, 4.5 Hz, 6′-CH_2), 2.09 (1H, ddd, *J* 13.6, 4.5, 3.8 Hz, 5′-CH_2), 1.90 (1H, ddd, *J* 13.6, 10.5, 4.5 Hz, 5′-CH_2); δ_C (100 MHz, $CDCl_3$) 167.1, 148.9, 148.2, 146.1, 137.0, 136.9, 128.4 (2C), 128.3 (2C), 127.3, 126.2, 124.9, 122.8, 121.4, 119.5, 97.4, 55.5, 50.4, 43.3, 42.9, 37.7; *m*/*z* (EI, 70 eV) 363 (18, M^+), 306 (12), 304 (10), 272 (15), 247 (9), 91 (11), 77 (12), 59 (100), 42 (72).

*4.8.3. Methyl (2E)-3-[(2-{2-[methoxy(phenyl) methyl]-1-benzothien-3-yl}ethyl)(methyl)amino] acrylate (**17a**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:40), yield 39 mg (11%) as a white solid, mp 82–83 °C (ethyl acetate/hexane); [found: C, 69.8; H, 6.5; N, 3.6. $C_{23}H_{25}NO_3S$ requires C, 69.84; H, 6.37; N, 3.54%]; R_f (sorbfil, ethyl acetate/hexane, 1:3) 0.26; ν_{max} (KBr) 1663, 1613 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.81 (1H, d, *J* 7.9 Hz, 7-H), 7.62 (1H, d, *J* 7.9 Hz, 4-H), 7.47–7.40 (4H, m, Ph, α′-CH), 7.39–7.36 (2H, m, 5-H, 6-H), 7.35–7.30 (2H, m, Ph), 5.59 (1H, s, *CH*–OCH_3), 4.60 (1H, d, *J* 12.8 Hz, β′-CH), 3.70 (3H, s, CO_2CH_3), 3.44 (3H, s, CH–*OCH*$_3$), 3.26–3.19 (1H, m, β-CH_2), 3.12–3.01 (3H, m, α-CH_2 and β-CH_2), 2.70 (3H, s, N–CH_3); δ_C (100 MHz, $CDCl_3$) 169.9, 151.9, 142.6, 140.5, 139.6, 139.2, 132.6, 128.7 (2C), 128.4, 127.3 (2C), 124.4, 124.2, 122.7, 121.0, 84.8, 80.3, 57.4, 55.3, 50.6, 40.9, 26.3; *m*/*z* (LCMS) 396 $[M+H]^+$.

4.9. Experimental procedure for the synthesis of benzothienoazocine 16a and spiro compounds 18a in acetonitrile

Methyl propiolate (0.800 mL, 9.0 mmol) was added to a solution of benzothienopyridine **15a** (250 mg, 0.9 mmol) in acetonitrile (25 mL). The reaction mixture was heated at reflux for 175 h (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography to give benzothienoazocine **16a** (205 mg, 63%) as a white solid and spiro compound **18a** (73 mg, 22%) as a white solid.

*4.9.1. Methyl 3-methyl-6-phenyl-1,2,3,6-tetrahydro[1]benzothieno [3,2-d]azocine-5-carboxylate (**16a**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:50), yield 205 mg (63%) as a white solid, mp 208–210 °C (ethyl acetate/hexane).

*4.9.2. Methyl (2Z)-2-benzylidene-1′-methyl-5′,6′-dihydro-1′H-spiro [1-benzothiophene-3,4′-pyridine]-3′-carboxylate (**18a**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:45), yield 73 mg (22%) as a white solid, mp 174–176 °C (ethyl acetate/hexane).

4.10. Experimental procedure for the synthesis of benzothienoazocine 16a, spiro compound 18a and benzothienopyridine 19a in dichloromethane

Methyl propiolate (0.196 mL, 2.2 mmol) was added to a stirred solution of benzothienopyridine **15a** (250 mg, 0.9 mmol) in CH_2Cl_2 (25 mL). The stirring was continued for 30 days (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography to give benzothienoazocine **16a** (201 mg, 62%) as a white solid, spiro compound **18a** (62 mg, 19%) as a white solid and benzothienopyridine **19a** (23 mg, 7%) as a white oil.

*4.10.1. Methyl 3-methyl-6-phenyl-1,2,3,6-tetrahydro[1]benzothieno [3,2-d]azocine-5-carboxylate (**16a**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:50), yield 201 mg (62%) as a white solid, mp 208–210 °C (ethyl acetate/hexane).

*4.10.2. Methyl (2Z)-2-benzylidene-1′-methyl-5′,6′-dihydro-1′H-spiro [1-benzothiophene-3,4′-pyridine]-3′-carboxylate (**18a**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:45), yield 62 mg (19%) as a white solid, mp 174–176 °C (ethyl acetate/hexane).

*4.10.3. Methyl (2E)-3-(2-methyl-1-phenyl-1,2,3,4-tetrahydro[1]benzothieno[2,3-c]pyridine-1-yl)acrylate (**19a**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:45), yield 23 mg (7%) as a white oil; [found: C, 72.6; H, 5.9; N, 3.9. $C_{22}H_{21}NO_2S$ requires C, 72.70; H, 5.82; N, 3.85%]; R_f (sorbfil, ethyl acetate/hexane, 1:3) 0.85; ν_{max} (KBr) 1721, 1647 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.65–7.63 (2H, m, 5H, 8H), 7.52 (2H, d, *J* 7.2 Hz, 6H, 7H), 7.50 (1H, d, *J* 15.9 Hz, CH=*CH*–CO_2Me), 7.39–7.31 (4H, m, 1-Ph), 7.28–7.25 (1H, m, 1-Ph), 5.82 (1H, d, *J* 15.9 Hz, *CH*=CH–CO_2Me), 3.77 (3H, s, CO_2CH_3), 3.10–3.00 (2H, m, 4-CH_2), 2.96–2.87 (2H, m, 3-CH_2), 2.35 (3H, s, N–CH_3); δ_C (100 MHz, $CDCl_3$) 166.4, 147.9, 143.7, 140.5, 140.1, 138.6, 129.2, 128.4 (2C), 128.0, 127.7 (2C), 126.0, 124.3, 124.0, 122.3, 121.1, 61.1, 51.6, 46.7, 38.9, 24.4; *m*/*z* (EI, 70 eV) 363 (10, M^+), 286 (47), 278 (15), 261 (11), 77 (35), 59 (32), 42 (100).

4.11. Experimental procedure for the synthesis of benzothienoazocine 16d and benzothiophene 17b in methanol

Acetylacetylene (0.084 mL, 1.1 mmol) was added to a stirred solution of benzothienopyridine **15a** (250 mg, 0.9 mmol) in methanol (25 mL). The stirring was continued for 5 min (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography to give benzothienoazocine **16d** (94 mg, 30%) as a white solid and benzothiophene **17b** (203 mg, 60%) as a white oil.

*4.11.1. 1-(3-Methyl-6-phenyl-1,2,3,6-tetrahydro [1]benzothieno[3,2-d]azocin-5-yl)ehtanone (**16d**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:15), 94 mg (30%) as a white solid, mp 203–205 °C (ethyl acetate/hexane); [found: C, 76.1; H, 6.2; N, 4.0. $C_{22}H_{21}NOS$ requires C, 76.04; H, 6.09; N, 4.03%]; R_f (sorbfil, ethyl acetate/hexane, 1:2) 0.48; ν_{max} (KBr) 1630, 1580, 1575 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.80 (1H, d, *J* 7.5 Hz, 8-H), 7.62 (1H, d, *J* 7.5 Hz, 11-H), 7.51 (1H, s, 4-H), 7.38 (1H, dt, *J* 7.5, 1.2 Hz, 9-H), 7.33 (1H, dt, *J* 7.5, 1.2 Hz, 10-H), 7.24 (2H, t, *J* 7.9 Hz, *o*-6-Ph), 7.14 (1H, t, *J* 7.9 Hz, *p*-6-Ph), 7.08 (2H, d, *J* 7.9 Hz, *m*-6-Ph), 6.47 (1H, s, 6-H), 4.04–3.96 (1H, m, 2-CH_2), 3.32 (1H, ddd, *J* 17.1, 13.6, 4.5 Hz, 1-CH_2), 3.06 (3H, s, N–CH_3), 2.85 (1H, ddd, *J* 15.0, 4.5, 2.7 Hz, 2-CH_2), 2.74 (1H, td, *J* 17.1, 2.7 Hz, 1-CH_2), 2.37 (3H, s, COMe); δ_C (100 MHz, $CDCl_3$) 194.2, 154.1, 146.6, 142.0, 140.5, 138.4, 128.8 (2C), 126.8, 126.2 (2C), 125.7, 124.0,

123.9, 122.2, 121.1, 111.4, 48.9, 44.6, 39.5, 28.1, 25.1; *m*/*z* (EI, 70 eV) 347 (8, M^+), 304 (5), 43 (100).

*4.11.2. (3E)-4-[(2-{2-[Methoxy(phenyl)methyl]-1-benzothien-3-yl} ethyl)(methyl)amino]but-3-en-2-one (**17b**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:15), 94 mg (30%) as a white oil; [found: C, 72.9; H, 6.7; N, 3.7. $C_{23}H_{25}NO_2S$ requires C, 72.79; H, 6.64; N, 3.69%]; R_f (sorbfil, ethyl acetate/hexane, 1:2) 0.21; ν_{max} (KBr) 1655, 1602, 1563 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.82 (1H, d, *J* 8.1 Hz, 7-H), 7.62 (1H, d, *J* 8.1 Hz, 4-H), 7.46–7.31 (8H, m, Ph, 5-H, 6-H and β′-*CH*–Ac), 5.58 (1H, s, *CH*–OCH_3), 5.07 (1H, d, *J* 13.2 Hz, α′-CH), 3.44 (3H, s, CH–O*CH*$_3$), 3.32–3.23 (1H, m, β-CH_2), 3.13–3.03 (3H, m, α-CH_2 and β-CH_2), 2.73 (3H, br s, N–CH_3), 2.09 (3H, s, $COCH_3$); δ_C (100 MHz, $CDCl_3$) 195.3, 151.6 (2C), 142.7, 140.5, 139.7, 139.2, 128.8 (2C), 128.5, 127.3 (2C), 124.5, 124.3, 122.8, 121.8, 97.4, 80.3, 57.3, 56.6, 36.2, 28.2, 27.1; *m*/*z* (LCMS) 380 $[M+H]^+$.

4.12. Experimental procedure for the synthesis of benzothienoazocine 16d and spiro compound 18b in acetonitrile

Acetylacetylene (0.129 mL, 1.8 mmol) was added to a stirred solution of benzothienopyridine **15a** (250 mg, 0.9 mmol) in acetonitrile (25 mL). The stirring was continued for 7 days (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography to give benzothienoazocine **16d** (255 mg, 82%) as a white solid and spiro compound **18b** (48 mg, 15%) as a yellow oil.

*4.12.1. 1-(3-Methyl-6-phenyl-1,2,3,6-tetrahydro [1]benzothieno[3,2-d]azocin-5-yl)ehtanone (**16d**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:15), 255 mg (82%) as a white solid, mp 203–205 °C (ethyl acetate/hexane).

*4.12.2. 1[(2Z)-2-Benzylidene-1′-methyl-5′,6′-dihydro-1′H-spiro[1-benzothiophene-3,4′-pyridin]-3′-yl]ethanone (**18b**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:5), yield 48 mg (15%) as a yellow oil; [found: C, 76.1; H, 6.2; N, 4.0. $C_{22}H_{21}NOS$ requires C, 76.08; H, 6.09; N, 4.03%]; R_f (sorbfil, ethyl acetate/hexane, 1:3) 0.28; ν_{max} (KBr) 1594 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.89 (1H, s, 2′-H), 7.40–7.39 (2H, m, 4-H, 7-H), 7.37–7.35 (2H, m, 5-H, 6-H), 7.29–7.28 (1H, m, Ph), 7.23–7.18 (2H, m, Ph), 7.09 (1H, td, *J* 7.5, 1.0 Hz, Ph), 7.01 (1H, d, *J* 7.5 Hz, Ph), 6.40 (1H, s, *CH*–Ar), 3.39–3.34 (1H, m, 6′-CH_2), 3.15 (3H, s, N–CH_3), 3.06 (1H, td, *J* 13.0, 4.3 Hz, 6′-CH_2), 2.10 (1H, ddd, *J* 13.8, 4.3, 3.7 Hz, 5′-CH_2), 1.91 (1H, ddd, *J* 13.8, 10.6, 4.3 Hz, 5′-CH_2), 1.69 (3H, s, CO*CH*$_3$); δ_C (100 MHz, $CDCl_3$) 195.0, 149.3, 147.6, 145.7, 137.2, 136.6, 128.3 (2C), 128.2 (2C), 127.7, 126.5, 125.3, 123.2, 121.9, 120.4, 97.6, 56.0, 43.5, 43.2, 37.9, 27.2; *m*/*z* (LCMS) 348 $[M+H]^+$.

4.13. Experimental procedure for the synthesis of benzotheinoazocine 16b in methanol

Methyl propiolate (0.087 mL, 1.0 mmol) was added to a stirred solution of benzothienopyridine **15b** (250 mg, 0.8 mmol) in acetonitrile (25 mL). The stirring was continued for 24 h (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 1:50) to give benzothienoazocine **16b** (263 mg, 83%) as a white solid.

*4.13.1. Methyl 6-(4-methoxyphenyl)-3-methyl-1,2,3,6-tetrahydro[1]benzothieno[3,2-d]azocine-5-carboxylate (**16b**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:50), 263 mg (83%) as a white solid, mp 177–178 °C (ethyl acetate/hexane); [found: C, 70.1; H, 6.0; N, 3.7. $C_{23}H_{23}NO_3S$ requires C, 70.20; H, 5.89; N, 3.56%]; R_f (sorbfil, ethyl acetate/hexane, 1:3) 0.41; ν_{max} (KBr) 1667, 1612 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.80 (1H, d, *J* 7.3 Hz, 8-H) 7.72 (1H, s, 4-H), 7.62 (1H, d, *J* 7.3 Hz, 11-H), 7.38 (1H, dt, *J* 7.3, 1.2 Hz, 9-H), 7.33 (1H, dt, *J* 7.3, 1.2 Hz, 10-H), 7.09 (2H, dd, *J* 8.8, 1.2 Hz, *o*-Ph–OCH_3), 6.81 (2H, d, *J* 8.8 Hz, *m*-Ph–OCH_3), 6.06 (1H, s, 6-H), 4.03–3.95 (1H, m, 2-CH_2), 3.77 (3H, s, $COCH_3$), 3.76 (3H, s, OCH_3), 3.30 (1H, ddd, *J* 4.4, 13.5, 17.4 Hz, 1-CH_2), 3.01 (3H, s, N–CH_3), 2.83 (1H, ddd, *J* 14.9, 4.4, 2.8 Hz, 2-CH_2), 2.72 (1H, td, *J* 17.4, 2.8 Hz, 1-CH_2); δ_C (100 MHz, $CDCl_3$) 170.7, 157.8, 152.2, 142.1, 140.7, 139.1, 138.2, 127.3 (2C), 126.7, 123.9 (2C), 122.1, 121.2, 114.1 (2C), 96.5, 55.3, 51.5, 48.9, 44.1, 41.0, 28.3; *m*/*z* (EI, 70 eV) 393 (62, M^+), 362 (11), 336 (63), 334 (66), 330 (16), 319 (14), 303 (20), 291 (24), 277 (33), 272 (19), 258 (20), 247 (21), 234 (27), 232 (37), 226 (24), 220 (23), 202 (23), 200 (25), 184 (20), 171 (28), 160 (100), 145 (23), 140 (48), 128 (22), 121 (56), 115 (35), 91 (11), 77 (15), 58 (37), 44 (23), 42 (93).

4.14. Experimental procedure for the synthesis of benzothienoazocine 16b in acetonitrile

Methyl propiolate (0.356 mL, 4.0 mmol) was added to a solution of benzothienopyridine **15b** (250 mg, 0.8 mmol) in acetonitrile (25 mL). The reaction mixture was heated at reflux for 11 h (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 1:50) to give benzothienoazocine **16b** (247 mg, 78%) as a white solid.

*4.14.1. Methyl 6-(4-methoxyphenyl)-3-methyl-1,2,3,6-tetrahydro[1]benzothieno[3,2-d]azocine-5-carboxylate (**16b**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:50), 247 mg (78%) as a white solid, mp 177–178 °C (ethyl acetate/hexane).

4.15. Experimental procedure for the synthesis of benzothienoazocine 16b and benzothienopyridine 19b in dichloromethane

Methyl propiolate (0.356 mL, 4.0 mmol) was added to a stirred solution of benzothienopyridine **15b** (250 mg, 0.8 mmol) in acetonitrile (25 mL). The stirring was continued for 20 days (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 1:50) to give benzothienoazocine **16b** (216 mg, 68%) as a white solid and benzothienopyridine **19b** (45 mg, 15%) as a white oil.

*4.15.1. Methyl 6-(4-methoxyphenyl)-3-methyl-1,2,3,6-tetrahydro[1]benzothieno[3,2-d]azocine-5-carboxylate (**16b**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:50), 216 mg (68%) as a white solid, mp 177–178 °C (ethyl acetate/hexane).

*4.15.2. Methyl (2E)-3-[2-methyl-1-(4-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydro[1]benzothieno[2,3-c]pyridine-1-yl]acrylate (**19b**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:50), 216 mg (68%) as a white oil; [found: C, 70.3; H, 6.0; N, 3.6. $C_{23}H_{23}NO_3S$ requires C, 70.20; H, 5.89; N, 3.56%]; R_f (sorbfil, ethyl acetate/hexane, 1:3) 0.85; ν_{max} (KBr) 1721, 1647 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.65–7.61 (2H, m, CH–Ar), 7.47 (1H, d, *J* 15.8 Hz, CH=*CH*–CO_2Me), 7.41 (2H, d, *J* 8.9 Hz, *o*-C_6H_4–OCH_3), 7.36–7.32 (1H, m, 7-H), 7.28–7.24 (1H, m, 6-H), 6.88 (2H, d, *J* 8.9 Hz, *m*-C_6H_4–OCH_3), 5.81 (1H, d, *J* 15.8 Hz, *CH*=CH–CO_2Me), 3.81 (3H, s, OCH_3), 3.76 (3H, s, CO_2CH_3), 3.07–2.99 (2H, m, 4-CH_2), 2.97–2.84 (2H, m, 3-CH_2), 2.33 (3H, s, N–CH_3); δ_C (100 MHz, $CDCl_3$) 166.5, 159.2, 148.2, 141.0, 140.1, 138.6, 135.7, 129.1, 128.9 (2C), 125.8, 124.3, 123.9, 122.3, 121.1, 113.7 (2C), 66.6, 55.2, 51.6, 46.8, 38.8, 24.4; *m*/*z*

(EI, 70 eV) 393 (10, M^+), 308 (25), 286 (20), 259 (9), 92 (11), 77 (25), 59 (53), 42 (100).

4.16. Experimental procedure for the synthesis benzothiophene 17f in methanol

DMAD (0.095 mL, 0.8 mmol) was added to a stirred solution of benzothienopyridine **15b** (200 mg, 0.6 mmol) in acetonitrile (20 mL). The stirring was continued for 26 h (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 1:13) to give benzothiophene **17f** (294 mg, 94%) as a white oil.

*4.16.1. Dimethyl (2E)-2-[(2-{2-[methoxy(4-methoxyphenyl)methyl]-1-benzothien-3-yl}ethyl)(methyl)amino]but-2-enedioate (**17f**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:13), 294 mg (94%) as a white oil; [found: C, 64.7; H, 6.1; N, 2.9. $C_{26}H_{29}NO_6S$ requires C, 64.58; H, 6.04; N, 2.90%]; R_f (sorbfil, ethyl acetate/hexane, 1:2) 0.45; ν_{max} (KBr) 1737, 1687, 1585 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.80 (1H, d, *J* 7.8 Hz, 7-H), 7.68 (1H, d, *J* 7.8 Hz, 4-H), 7.39 (2H, d, *J* 8.7 Hz, *o*-C_6H_4—OCH_3), 7.31 (2H, t, *J* 7.8 Hz, 5-H, 6-H), 6.89 (2H, d, *J* 8.7 Hz, *m*-C_6H_4—OCH_3), 5.60 (1H, s, *CH*—OCH_3), 4.62 (1H, s, β′-CH), 3.91 (3H, s, CO_2CH_3), 3.80 (3H, s, CO_2CH_3), 3.67 (3H, s, OCH_3), 3.42 (3H, s, CH—*OCH*$_3$), 3.31–3.03 (4H, m, α-CH_2 and β-CH_2), 2.66 (3H, s, N—CH_3); δ_C (100 MHz, $CDCl_3$) 168.0, 166.0, 159.6, 154.3, 143.1, 139.7, 139.1, 132.6, 128.6 (2C), 128.1, 124.3, 124.2, 122.6, 121.1, 114.0 (2C), 84.8, 79.6, 57.0, 55.2, 52.9, 52.7, 50.7, 37.9, 25.8; *m*/*z* (LCMS) 484 $[M+H]^+$.

4.17. Experimental procedure for the synthesis of benzotheinoazocine 16g in acetonitrile

DMAD (0.736 mL, 6.0 mmol) was added to a stirred solution of benzothienopyridine **15b** (200 mg, 0.6 mmol) in acetonitrile (20 mL). The stirring was continued for 35 days (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 1:7) to give benzothienoazocine **16g** (93 mg, 32%) as a white oil.

*4.17.1. Dimethyl 6-(4-methoxyphenyl)-3-methyl-1,2,3,6-tetrahydro[1]benzothieno[3,2-d]azocine-4,5-dicarboxylate (**16g**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:7), 93 mg (32%) as a white oil; [found: C, 66.5; H, 5.7; N, 3.2. $C_{25}H_{25}NO_5S$ requires C, 66.50; H, 5.58; N, 3.10%]; R_f (sorbfil, ethyl acetate/hexane, 1:2) 0.51; ν_{max} (KBr) 1738, 1683, 1561 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.84 (1H, dd, *J* 7.1, 1.3 Hz, 8-H), 7.64 (1H, dd, *J* 7.1, 1.3 Hz, 11-H), 7.41–7.33 (2H, m, 9-H, 10-H), 7.05 (2H, dd, *J* 8.8, 1.1 Hz, *o*-C_6H_4—OCH_3), 6.80 (2H, d, *J* 8.8 Hz, *m*-C_6H_4—OCH_3), 6.11 (1H, s, 6-H), 3.88–3.84 (1H, m, 2-CH_2), 3.81 (3H, s, CO_2CH_3), 3.77 (3H, s, CO_2CH_3), 3.75 (3H, s, OCH_3), 3.32 (1H, ddd, *J* 16.7, 13.5, 6.2 Hz, 1-CH_2), 3.05 (1H, ddd, *J* 14.8, 6.2, 1.3 Hz, 2-CH_2), 2.67 (3H, s, N—CH_3), 2.46 (1H, ddd, *J* 16.7, 4.4, 1.3 Hz, 1-CH_2); δ_C (100 MHz, $CDCl_3$) 169.4, 167.1, 158.0, 155.8, 141.5, 138.9, 138.7, 136.8, 127.7, 127.3 (2C), 124.0, 123.9, 122.3, 120.8, 114.0 (2C), 99.5, 55.2, 52.7, 52.5, 51.9, 43.2, 37.8, 25.9; *m*/*z* (EI, 70 eV) 451 (1, M^+), 393 (15), 362 (11), 334 (15), 308 (33), 306 (16), 291 (11), 286 (24), 276 (9), 258 (12), 247 (11), 221 (11), 202 (13), 185 (18), 150 (10), 92 (13), 77 (29), 59 (65), 44 (33), 42 (100).

4.18. Experimental procedure for the synthesis benzothienoazocine 16e and benzothiophene 17c in methanol

Acetylacetylene (0.061 mL, 0.8 mmol) was added to a stirred solution of benzothienopyridine **15b** (200 mg, 0.6 mmol) in acetonitrile (20 mL). The stirring was continued for 5 min (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography to give benzothienoazocine **16e** (104 mg, 43%) as a white solid and benzothiophene **17c** (123 mg, 48%) as a white oil.

*4.18.1. 1-[6-(4-Methoxyphenyl)-3-methyl-1,2,3,6-tetrahydro[1]benzothieno[3,2-d]azocin-5-yl]ethanone (**16e**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:13), 104 mg (43%) as a white solid, mp 227–229 °C (ethyl acetate/hexane); [found: C, 73.3; H, 6.2; N, 3.7. $C_{23}H_{23}NO_2S$ requires C, 73.18; H, 6.14; N, 3.71%]; R_f (sorbfil, ethyl acetate/hexane, 1:1) 0.40; ν_{max} (KBr) 1614, 1578 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.79 (1H, d, *J* 7.6 Hz, 8-H), 7.62 (1H, d, *J* 7.6 Hz, 11-H), 7.52 (1H, s, 4-H), 7.38 (1H, dt, *J* 7.6, 1.1 Hz, 9-H), 7.33 (1H, dt, *J* 7.6, 1.1 Hz, 10-H), 6.99 (2H, d, *J* 8.3 Hz, *o*-C_6H_4—OCH_3), 6.78 (2H, d, *J* 8.3 Hz, *m*-C_6H_4—OCH_3), 6.36 (1H, s, 6-H), 4.07–4.05 (1H, m, 2-CH_2), 3.76 (3H, s, —Ar—*OCH*$_3$), 3.32 (1H, ddd, *J* 17.3, 13.4, 4.3 Hz, 1-CH_2), 3.07 (3H, s, N—CH_3), 2.86 (1H, ddd, *J* 15.0, 4.5, 2.7 Hz, 2-CH_2), 2.74 (1H, td, *J* 17.3, 2.7 Hz, 1-CH_2), 2.36 (3H, s, COMe); δ_C (100 MHz, $CDCl_3$) 194.1, 157.7, 154.1, 141.9, 140.8, 138.7, 138.2, 127.1 (2C), 126.7, 123.9, 123.8, 122.1, 121.0, 114.1 (2C), 111.5, 55.2, 49.0, 44.4, 38.8, 28.0, 25.1; *m*/*z* (EI, 70 eV) 377 (1, M^+), 235 (10), 202 (23), 155 (14), 92 (14), 77 (24), 58 (15), 42 (100).

*4.18.2. (3E)-4-[(2-{2-[Methoxy(4-methoxyphenyl)methyl]-1-benzothieno-3-yl}ethyl)(methyl)amino]but-3-en-2-one (**17c**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:5), 123 mg (48%) as a white oil; [found: C, 70.3; H, 6.7; N, 3.4. $C_{24}H_{27}NO_3S$ requires C, 70.39; H, 6.65; N, 3.42%]; R_f (sorbfil, ethyl acetate/hexane, 1:1) 0.18; ν_{max} (KBr) 1656, 1609 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.81 (1H, d, *J* 7.6 Hz, 7-H), 7.61 (1H, d, *J* 7.6 Hz, 4-H), 7.41 (1H, d, *J* 12.7 Hz, α′-CH), 7.39–7.29 (4H, m, 5-H, 6-H, *o*-C_6H_4—OCH_3), 6.91 (2H, d, *J* 8.7 Hz, *m*-C_6H_4—OCH_3), 5.53 (1H, s, *CH*—OCH_3), 5.07 (1H, d, *J* 13.4 Hz, β′-CH), 3.80 (3H, s, Ar—O*CH*$_3$), 3.41 (3H, s, CH—*OCH*$_3$), 3.28 (1H, ddd, *J* 5.9, 9.0, 13.0 Hz, β-CH_2), 3.15–3.00 (3H, m, α-CH_2 and β-CH_2), 2.73 (3H, br s, N—CH_3), 2.09 (3H, s, $COCH_3$); δ_C (100 MHz, $CDCl_3$) 195.3, 159.6, 151.7, 151.6, 143.1, 139.6, 139.1, 132.5, 128.6 (2C), 124.3, 124.2, 122.7, 120.8, 114.0 (2C), 97.3, 79.8, 57.0, 56.7, 55.3, 35.8, 38.0, 27.0; *m*/*z* (LCMS) 410 $[M+H]^+$.

4.19. Experimental procedure for the synthesis of benzothienoazocine 16e in acetonitrile

Acetylacetylene (0.094 mL, 1.2 mmol) was added to a stirred solution of benzothienopyridine **15b** (200 mg, 0.6 mmol) in acetonitrile (20 mL). The stirring was continued for 11 days (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 1:13) to give benzothienoazocine **16e** (217 mg, 89%) as a white solid.

*4.19.1. 1-[6-(4-Methoxyphenyl)-3-methyl-1,2,3,6-tetrahydro[1]benzothieno[3,2-d]azocin-5-yl]ethanone (**16e**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:13), 217 mg (89%) as a white solid, mp 227–229 °C (ethyl acetate/hexane).

4.20. Experimental procedure for the synthesis of spiro compound (*E*)-18c

Spiro compound (*Z*)-**18c** (50 mg, 0.1 mmol) was dissolved in ethyl acetate (10 mL) at rt. After 1 h the solvent was evaporated. The residue was triturated with 10 mL of diethyl ether. The yellow precipitate was filtered-off to give (*E*)-**18c** (12 mg, 24%). According to the NMR data the mother liquor contained 2:1 mixture of (*E*)-**18c** and (*Z*)-**18c**.

*4.20.1. Methyl (2E)-1′-methyl-2-(4-nitrobenzylidene)-5′,6′-dihydro-1′H-spiro[1-benzothiophene-3,4′-pyridine]-3′-carboxylate (E-**18c**).* A yellow solid mp 203–202 °C (ethyl acetate/hexane); [found: C, 64.7; H, 4.9; N, 6.9. $C_{22}H_{20}N_2O_4S$ requires C, 64.69; H, 4.94; N, 6.86%]; R_f (sorbfil, 1:3, ethyl acetate/hexane) 0.40; ν_{max} (KBr) 1674, 1614 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.07 (2H, d, *J* 8.9 Hz, *m*-C_6H_4—NO_2), 7.37 (2H, d, *J*

8.9 Hz, *o*-C_6H_4—NO_2), 7.31 (1H, s, 2′-H), 7.21–7.15 (m, 2H, 4-H, 7-H), 7.04 (1H, dt, *J* 7.3, 1.7 Hz, 6-H), 6.83 (1H, d, 7.3 Hz, 5-H), 6.58 (1H, s, *CH*—Ar—NO_2), 3.38 (3H, s, CO_2Me), 3.25–3.17 (1H, m, 6′-CH_2), 3.07 (1H, ddd, *J* 13.0, 4.9, 3.6 Hz, 6′-CH_2), 3.03 (3H, s, N—CH_3), 2.40 (1H, ddd, *J* 13.9, 11.6, 4.9 Hz, 5′-CH_2), 2.01 (1H, td, *J* 13.9, 3.6 Hz, 5′-CH_2); δ_C (100 MHz, $CDCl_3$) 166.0, 154.5, 149.0, 147.7, 143.4, 129.8 (2C), 128.7, 127.9, 124.5, 123.9, 123.8, 122.8 (2C), 121.2, 117.4, 117.2, 51.9, 50.5, 44.0, 43.0, 35.0; *m*/*z* (EI, 70 eV) 408 (10, M^+), 349 (20), 281 (20), 272 (90), 259 (150), 240 (35), 226 (15), 213 (44), 207 (62), 200 (26), 171 (24), 127 (26), 89 (23), 59 (65), 44 (87), 36 (100).

4.21. Experimental procedure for the synthesis of spiro compound (*E*)-18d

Spiro compound (*Z*)-**18d** (50 mg, 0.1 mmol) was dissolved in ethyl acetate (10 mL) at rt. After 1 h the solvent was evaporated. The residue was purified by column chromatography to give spiro compound (*E*)-**18d** (8 mg, 16%) as a yellow solid and spiro compound (*Z*)-**18d** (38 mg, 76%) as a yellow oil.

*4.21.1. 1-[(2E)-1′-Methyl-2-(4-nitrobenzylidene)-5′,6′-dihydro-1′H-spiro[1-benzothiophene-3,4′-pyridin]-3′-yl]ethanone (E-**18d**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:1), yield 8 mg, (16%) as a yellow solid, mp 207–208°C (ethyl acetate/hexane); [found: C, 67.3; H, 5.1; N, 7.1. $C_{22}H_{20}N_2O_3S$ requires C, 67.33; H, 5.14; N, 7.14%]; R_f (sorbfil, ethyl acetate/hexane, 1:1) 0.58; ν_{max} (KBr) 1691, 1582 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.07 (2H, d, *J* 8.7 Hz, *m*-C_6H_4—NO_2), 7.35 (d, 2H, *J* 8.7 Hz, *o*-C_6H_4—NO_2), 7.22 (1H, s, 2′-H), 7.21 (1H, dd, *J* 7.5, 1.2 Hz, 7-H), 7.16 (1H, dt, *J* 7.5, 1.2 Hz, 6-H), 7.01 (1H, dt, *J* 7.5, 1.2 Hz, 5-H), 6.75 (1H, dd, *J* 7.5, 1.2 Hz, 4-H), 6.52 (1H, s, C=*CH*—Ar—NO_2), 3.28–3.21 (1H, m, 6′-CH_2), 3.16–3.11 (4H, m, 6′-CH_2, N—CH_3), 2.42 (1H, ddd, *J* 13.8, 11.7, 5.0 Hz, 5′-CH_2), 2.03 (1H, dt, *J* 13.8, 3.5 Hz, 5′-CH_2), 1.73 (3H, s, CO*CH*$_3$); δ_C (100 MHz, $CDCl_3$) 191.3, 154.8, 148.4, 147.5, 145.6, 143.4, 136.0, 129.8 (2C), 127.8, 124.5, 123.4, 122.6 (2C), 121.2, 116.7 (2C), 51.9, 44.1, 43.4, 40.1, 34.9; *m*/*z* (EI, 70 eV) 392 (30, M^+), 350 (100), 335 (15), 304 (10), 293 (34), 276 (25), 260 (21), 256 (24), 247 (30), 243 (44), 229 (77), 215 (25), 213 (50), 200 (50), 198 (61), 184 (19), 171 (34), 149 (13), 134 (10), 127 (15), 115 (17), 101 (22), 96 (27), 94 (25), 91 (37), 81 (20), 68 (17), 59 (53), 57 (90), 53 (65), 44 (65).

*4.21.2. 1-[(2Z)-1′-Methyl-2-(4-nitrobenzylidene)-5′,6′-dihydro-1′H-spiro[1-benzothiophene-3,4′-pyridin]-3′-yl]ethanone (Z-**18d**).* Purified by column chromatography (Al_2O_3, ethyl acetate/hexane, 1:1), yield 38 mg, (76%) as a yellow oil.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.09.098. These data include MOL files and InChiKeys of the most important compounds described in this article.

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