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The first example of tetrahydrothieno[3,2-*d*]azocines synthesis

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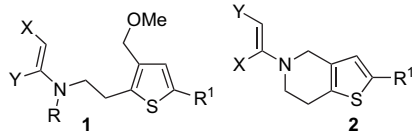
ABSTRACT

A novel and efficient one-pot synthesis of thieno[3,2-*d*]azocines based on tamden transformation of tetrahydropyridine ring was elaborated.

1. Introduction

Annulated azocines are of great interest to chemists as bioactive compounds and models for stereochemistry and intermolecular interactions in so called 'medium rings'. Thienoazocines (as almost all other members of this family) are not exhaustively studied most likely due to the difficulties associated with their synthesis. The majority of synthetic procedures described in the literature relate to the synthesis of thieno- and bisthienoazocines where the heterocyclic fragment is fused with bicyclic[3.3.1]azanonane ring.[1–3] However, some publications on the synthesis of other thienoazocines are available. Thus hexahydrothieno[3,2-*b*]azocines can be obtained by the cyclization of esters of 5-(3-aminothienyl-2) valeric acid[4] or by reactions of arylketones with the trimethylsilyl ethers of enols.[5] Hexahydrothieno[3,2-*c*]- and [2,3-*c*]azocines can be synthesized via the Sommelet–Hauser rearrangement of quaternary salts of thienyl-2 and thienyl-3-pyrrolidinium.[6] To the best of our knowledge, methods for the preparation of tetrahydrothieno[3,2-*d*]azocines have not been described in the literature yet.

Recently, we have reported a new method for the preparation of tetrahydropyrrolo[2,3-*d*]azocines[7] and tetrahydroazocino[4,5-*b*] and [5,4-*b*]indoles using tandem transformation of tetrahydropyrrolo[3,2-*c*]pyridines, tetrahydro-β- and γ-carbolines[8] under the action of activated alkynes. Our attempts to apply this method to tetrahydrothieno[3,2-*c*]pyridine and tetrahydrobenzo[*b*]thieno[2,3-*c*]pyridine systems were unsuccessful. Tetrahydrothieno[3,2-*c*]pyridines reacted with dimethyl acetylene dicarboxylate (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(hydroxyl) substituted thiophenes (**1**), or the elimination of the benzyl fragment, producing *N*-dimethoxycarbonyl(ethoxycarbonyl)vinyl tetrahydrothieno[3,2-*c*]pyridines (**2**)[9] (Scheme 1).



R = Et, *o*-Cl-$C_6H_4CH_2$; R^1 = H, CHO
X = Y = CO_2Me; X = H, Y = CO_2Et

Scheme 1.

Unlike tetrahydrothieno[3,2-*c*]pyridines 1,2,3-trimethylbenzo[*b*]-thieno[2,3-*c*]pyridines **3** reacted with activated alkynes (methyl or ethyl propiolates, acetylacetylene, DMAD) in methanol at room temperature giving multi-component mixtures. The target tetrahydrobenzo[*b*]thieno[3,2-*d*]azocines **4** were isolated in 2–9% yields whereas the main products of the reactions were 2-methoxyethyl substituted benzo[*b*]thiophenes **5** resulting from the tandem cleavage of the tetrahydropyridine ring under the action of methanol (Scheme 2).[9]

The formation of the multi-component mixtures and the considerable quantity of substituted benzo[*b*]thiophenes **5** led us to presume that in the intermediate zwetterion **A**—the product of Michael addition—the C(1)–N bond cleavage takes place forming the secondary carbonium cation **B**. Presumably methoxy group facilitates such bond cleavage. The further transformations of the cation **B** lead to the multi-component mixtures.

To check our presumptions we studied the transformations of ethyl 2-acetylamino-3-ethoxycarbonyl-6-*R*-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridines under the action of activated alkynes.

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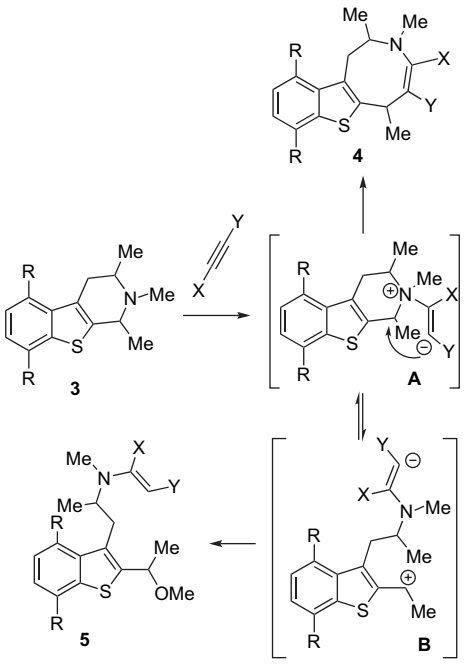
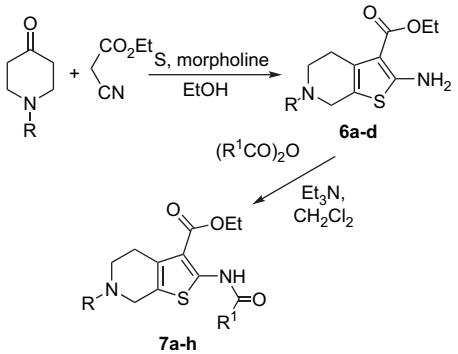


Scheme 2.

2. Results and discussion

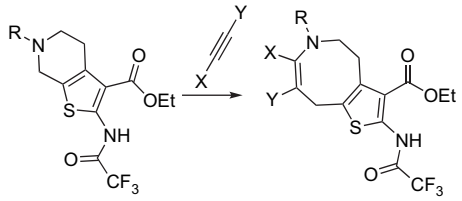
Thienopyridines **7** were obtained by the well-known Gewald reaction[10] starting from the appropriate 1-(alkyl)-piperidine-4-ones and ethyl cyanoacetate followed by N-acetylation of the intermediate *NH*-thienopyridines with acetic anhydride or trifluoroacetic anhydride (Scheme 3).



6a, **7a**, **7e** R = Me; **6b**, **7b**, **7f** R = Et;
6c, **7c**, **7g** R = *i*-Pr; **6d**, **7d**, **7h** R = Bn;
7a-d $R^1 = CF_3$; **7e-h** R^1 = Me

Scheme 3.

N-Triflouroacetyl substituted tetrahydrothienopyridines **7a–d** reacted with methyl propiolate, acetylacetylene, *p*-tosylacetylene or DMAD smoothly at room temperature in methanol or in acetonitrile to form tetrahydrothieno[3,2-*d*]azocines **8a–r**. Usually, reactions carried out in methanol took less time to finish than in acetonitrile. However, the use of acetonitrile as the solvent increased the yields of the target azocine derivatives. Generally, *N*-benzyl substituted thienopyridine **7d** reacted with activated alkynes slower than its *N*-alkyl analogues. The reactivity of thienopyridines decreased in the row Me>Et>*i*-Pr>Bn (the only exception was the reaction of thienopyridine **7d** with acetylacetylene). As expected, DMAD proved to be less active alkyne than methyl propiolate, acetyl- and tosylacetylenes. In acetonitrile reactions of thienopyridine **7d** with methyl propiolate, acetylacetylene and DMAD required the excess of the reagent. Moreover in the case of DMAD reflux was applied (Scheme 4, Table 1).



Scheme 4.

Table 1
Yields of thieno[3,2-*d*]azocines **8a–p**

Product	R	X	Y	Yield, %
8a	Me	H	COMe	45 (MeOH)
				79 (MeCN)
8b	Me	H	CO_2Me	44 (MeOH)
				73 (MeCN)
8c	Me	H	*p*-Ts	73 (MeCN)
8d	Me	CO_2Me	CO_2Me	73 (MeCN)
8e	Et	H	COMe	53 (MeOH)
				58 (MeCN)
8f	Et	H	CO_2Me	70 (MeOH)
				62 (MeCN)
8g	Et	H	*p*-Ts	87 (MeCN)
8h	Et	CO_2Me	CO_2Me	30 (MeOH)
				35 (MeCN)
8i	*i*-Pr	H	COMe	86 (MeOH)
				88 (MeCN)
8j	*i*-Pr	H	CO_2Me	80 (MeOH)
				83 (MeCN)
8k	*i*-Pr	H	*p*-Ts	71 (MeCN)
8l	*i*-Pr	CO_2Me	CO_2Me	14 (MeOH)
				62 (MeCN)
8m	Bn	H	COMe	40 (MeOH)
				92 (MeCN)
8n	Bn	H	CO_2Me	74 (MeOH)
				75 (MeCN)
8o	Bn	H	*p*-Ts	92 (MeCN)
8p	Bn	CO_2Me	CO_2Me	45 (MeOH)
				68 (MeCN)

X-ray crystallographic analysis was carried out on a suitable monocrystal of tetrahydrothieno[3,2-*d*]azocine **8n** obtained by recrystallization from ethyl acetate by slow evaporation at room temperature. The refined X-ray crystal structure of **8n** is shown in Figure 1.

The conformation of the eight-membered ring is a twisted boat in which the C(4), C(3), C(9) and C(8) atoms are almost coplanar. The N(1)–C(6) bond is shorter than the N(1)–C(5) (1.337 and 1.457 Å, respectively), denoting the presence of conjugation in the enamine fragment. CCDC 696201 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; tel.: +44 1223 336 408; e-mail: deposit@ccdc.cam.ac.uk].

Analogously 2-acetyl substituted tetrahydrothienopyridines **7e–h** under the action of acetylacetylene, methyl propiolate or DMAD in acetonitrile produced thienoazocines **9a–h**, **j–l**. The reaction of thienopyridine **7g** and DMAD yielded a multi-component reaction mixture, which we failed to separate. The yields of thienoazocines varied from 30 to 59% (Scheme 5).

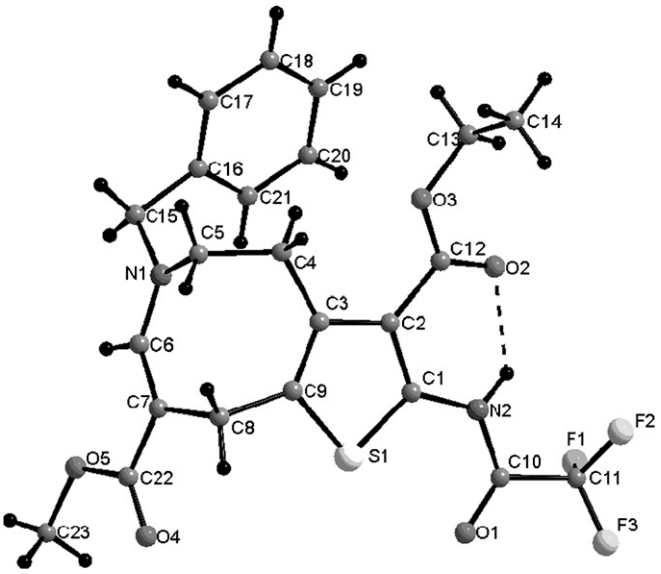
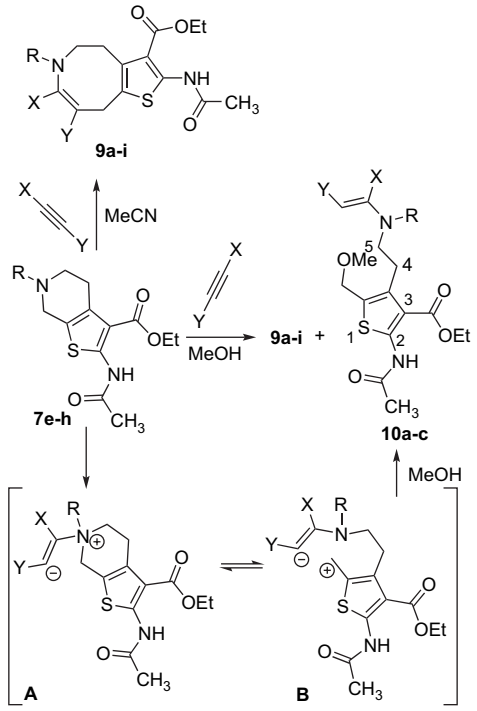


Figure 1.



Scheme 5.

The reactions of thienopyridines **7e**–**h** with activated alkynes in methanol led to the formation of the reaction mixtures containing thienoazocines **9a**–**i** and substituted thiophenes—products of the cleavage of the tetrahydropyridine ring. Only thiophenes **10a**–**c** were isolated individually, the rest of them were registered by NMR analysis of the reaction mixtures. In the case of reactions of thienopyridines **7h** with DMAD we failed to separate the reaction mixture (Tables 2 and 3).

N-Trifluoroacetyl group in thienoazocines **8a**–**d** was easily removed by simply percolating their ethyl acetate solutions through a pad of basic alumina oxide (pH=10±0.5). The resulting 2-amino substituted thienoazocines **11a**–**d** are of interest both as synthons for the construction of more complex molecules containing thienoazocine fragment and in view of their potential bioactivity.

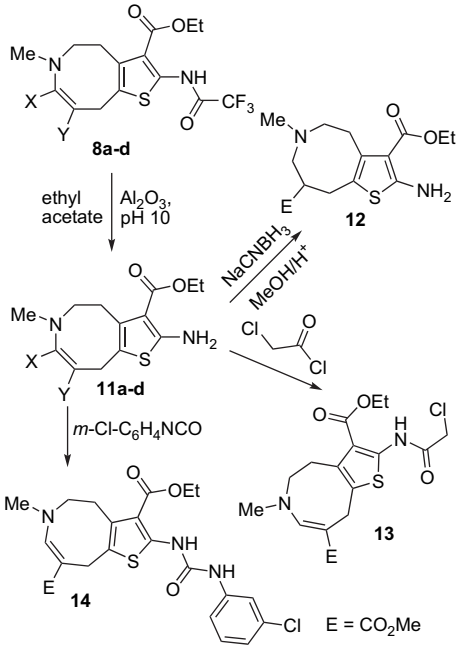
Table 2
Yields of thieno[3,2-*d*]azocines **9a**–**l**

Product	R	X	Y	Yield, %
9a	Me	H	COMe	31 (MeOH) 16 (MeCN)
9b	Me	H	CO_2Me	12 (MeOH) 15 (MeCN)
9c	Me	CO_2Me	CO_2Me	3 (MeOH) 7 (MeCN)
9d	Et	H	COMe	56 (MeOH) 59 (MeCN)
9e	Et	H	CO_2Me	60 (MeOH) 56 (MeCN)
9f	Et	CO_2Me	CO_2Me	58 (MeOH) 37 (MeCN)
9g	*i*-Pr	H	COMe	52 (MeOH) 59 (MeCN)
9h	*i*-Pr	H	CO_2Me	81 (MeOH) 57 (MeCN)
9i	*i*-Pr	CO_2Me	CO_2Me	Trace (MeOH) — (MeCN)
9j	Bn	H	COMe	64 (MeOH) 65 (MeCN)
9k	Bn	H	CO_2Me	37 (MeOH) 45 (MeCN)
9l	Bn	CO_2Me	CO_2Me	30 (MeCN)

Table 3
Yields of thiophenes **10a**–**c**

Product	R	X	Y	Yield, %
10a	Me	CO_2Me	CO_2Me	22
10b	*i*-Pr	H	COMe	19
10c	*i*-Pr	CO_2Me	CO_2Me	49

To explore the reactivity of the synthesized compounds, thienoazocine **11b** was reduced by the action of $NaCNBH_3$ in methanol to the corresponding hexahydrothieno[3,2-*d*]azocine **12**. The reactions of thienoazocine **11b** with chloroacetyl chloride and 3-chlorophenylisocyanate gave *N*-substituted derivatives **13** and **14** (Scheme 6, Table 4).



Scheme 6.

Table 4
Yields of thieno[3,2-*d*]azocines **11a–d**

Product	X	Y	Yield, %
11a	H	COMe	70
11b	H	CO_2Me	77
11c	H	*p*-Ts	65
11d	CO_2Me	CO_2Me	68

3. Conclusion

We have elaborated a novel and original approach towards thienoazocines starting from available tetrahydrothienopyridines. Our method based on the tandem transformation of tetrahydropyridine ring enables to obtain thienoazocines by the one-pot procedure.

4. Experimental

4.1. General

All solvents were distilled and dried before use, DMAD, acetylacetylene and methyl propiolate were purchased from ACROS ORGANICS and were used without any additional purification. *p*-Tosylacetylene was synthesized by a literature procedure.[11] Column chromatography was performed with aluminium oxide, activated, neutral, Brockmann I purchased from ACROS ORGANICS. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions or in DMSO-d_6, at 25 °C, using a 400 MHz NMR spectrometer operating at 400 and 100 MHz correspondingly, 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. Vario Micro cube element analyzer was used to perform C, H, N, O analyses.

4.2. General experimental procedure for the synthesis of thienopyridines 7a–d

Trifluoroacetic anhydride (15 mmol) was added to a stirred solution of thienopyridines **6a–d** (10 mmol) and triethylamine (15 mmol) in dry CH_2Cl_2 (50 mL). The reaction was stirred at room temperature (TLC monitoring). The crude reaction mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (3×70 mL). The solvent was evaporated under reduced pressure to give thienopyridines **7a–d**.

4.3. General experimental procedure for the synthesis of thienopyridines 7e–h

Acetic anhydride (20 mmol) was added to a stirred solution of thienopyridines **6a–d** (10 mmol) and triethylamine (20 mmol) in dry CH_2Cl_2 (50 mL). The reaction was stirred at room temperature (TLC monitoring). The crude reaction mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (3×70 mL). The solvent was evaporated under reduced pressure to give thienopyridines **7e–h**.

4.4. General experimental procedure for the synthesis of thienoazocines 8a–l

DMAD, methyl propiolate, acetyl- or *p*-tosylacetylene (1.2 mmol) was added to a solution of one of the thienopyridines **7a–c** (1 mmol) in methanol or acetonitrile (15 mL). The reaction was stirred at 25 °C (TLC monitoring). The solvent was evaporated under reduced pressure. In the cases of reactions with methyl propiolate, acetyl- or *p*-tosylacetylene the residue was recrystallized (ethyl acetate/hexane) to give thienoazocines **8a–c**, **e–g**, **i–k**. In the case of reactions with DMAD the resulting residue was purified by column chromatography with ethyl acetate/hexane (1:5) as eluent to yield thienoazocines **8d**, **h**, **l**.

*4.4.1. Ethyl 8-acetyl-6-methyl-2-[(trifluoroacetyl)amino]-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3-carboxylate (**8a**)*

White powder mp 223–224 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ=9.56 (s, 1H, $NHCOCF_3$), 7.25 (s, 1H, 7-H), 4.40 (q, 2H, *J*=7.1 Hz, O–CH_2–CH_3), 4.07 (s, 2H, 9-CH_2), 3.99–3.88 (m, 2H, 5-CH_2), 3.38 (t, 2H, *J*=5.4 Hz, 4-CH_2), 3.10 (s, 3H, N–CH_3), 2.18 (s, 3H, $COCH_3$), 1.42 (t, 3H, *J*=7.1 Hz, O–CH_2–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=191.6, 164.0, 153.1 (q, $^2J_{C,F}$=38 Hz), 153.0, 138.9, 131.7, 130.3, 119.5, 115.3 (q, $^1J_{C,F}$=287 Hz), 107.0, 61.0, 47.0, 43.8, 39.5, 30.3, 24.4, 21.0, 13.7 ppm. IR (KBr): ν=1732, 1656, 1642, 1585 cm^{-1}. EIMS *m*/*z* (%): 404 (M^+, 11), 361 (17), 315 (13), 287 (12), 272 (12), 260 (5), 202 (10), 178 (17), 160 (5), 136 (6), 112 (9), 94 (9), 82 (13), 69 (44), 57 (18), 44 (58), 43 (100), 42 (68). $C_{17}H_{19}F_3N_2O_4S$ (404.10): calcd C 50.49, H 4.74, N 6.93, O 15.83%; found: C 50.58, H 5.01, N 6.72, O 15.80%.

*4.4.2. 3-Ethyl 8-methyl 6-methyl-2-[(trifluoroacetyl)amino]-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3,8-dicarboxylate (**8b**)*

White powder mp 167–168 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ=12.17 (s, 1H, $NHCOCF_3$), 7.43 (s, 1H, 7-H), 4.43 (q, 2H, *J*=7.0 Hz, O–CH_2–CH_3), 4.02 (s, 2H, 9-CH_2), 3.94–3.88 (m, 2H, 5-CH_2), 3.71 (s, 3H, OCH_3), 3.38 (t, 2H, *J*=5.9 Hz, 4-CH_2), 3.05 (s, 3H, N–CH_3), 1.45 (t, 3H, *J*=7.0 Hz, O–CH_2–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.5, 164.0, 153.2 (q, $^2J_{C,F}$=38 Hz), 150.3, 139.0, 131.3, 130.3, 119.5, 115.2 (q, $^1J_{C,F}$=287 Hz), 92.5, 61.5, 50.6, 46.8, 43.7, 30.4, 23.4, 13.7 ppm. IR (KBr): ν=1715, 1700, 1616, 1567 cm^{-1}. EIMS *m*/*z* (%): 420 (M^+, 100), 405 (15), 389 (11), 361 (53), 330 (15), 315 (54), 293 (25), 284 (20), 272 (18), 260 (15), 247 (17), 221 (38), 202 (18), 190 (17), 178 (31), 162 (9), 152 (12), 128 (13), 121 (12), 96 (10), 82 (11), 69 (42), 59 (13), 44 (23), 42 (45). $C_{17}H_{19}F_3N_2O_5S$ (420.10): calcd C 48.57, H 4.56, N 6.66, O 19.03%; found: C 48.71, H 4.52, N 6.84, O 18.94%.

*4.4.3. Ethyl 6-methyl-8-[(4-methylphenyl)sulphonyl]-2-[(trifluoroacetyl)amino]-4,5,6,9-tetrahydrothieno[3,2-d]-azocine-3-carboxylate (**8c**)*

White powder mp 149–151 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ=9.72 (s, 1H, $NHCOCF_3$), 7.67 (d, 2H, *J*=8.1 Hz, CH–Ar), 7.38 (s, 1H, 7-H), 7.27 (d, 2H, *J*=8.1 Hz, CH–Ar), 4.37 (q, 2H, *J*=7.3 Hz, O–CH_2–CH_3), 3.82–3.77 (m, 2H, 5-CH_2), 3.74 (s, 2H, 9-CH_2), 3.32 (t, 2H, *J*=5.4 Hz, 4-CH_2), 3.07 (s, 3H, N–CH_3), 2.41 (s, 3H, Ar–CH_3), 1.39 (t, 3H, *J*=7.3 Hz, O–CH_2–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=164.3, 153.1 (q, $^2J_{C,F}$=38 Hz), 149.0, 140.5, 142.8, 140.0, 131.3, 130.0 (2C), 129.6, 127.3 (2C), 119.4, 115.8 (q, $^1J_{C,F}$=286 Hz), 99.9, 61.5, 47.4, 43.7, 31.0, 24.1, 21.3, 14.1 ppm. IR (KBr): ν=1721, 1665, 1622, 1563 cm^{-1}. EIMS *m*/*z* (%): 516 (M^+, 8), 361 (83), 327 (7), 315 (33), 293 (10), 284 (12), 271 (6), 248 (7), 235 (5), 221 (13), 202 (27), 189 (7), 178 (12), 146 (9), 121 (7), 107 (16), 91 (52), 80 (13), 69 (25), 65 (27), 58 (23), 51 (5), 44 (77), 42 (100), 34 (17). $C_{22}H_{23}F_3N_2O_5S_2$ (516.10): calcd C 51.15, H 4.49, N 5.42, O 15.49%; found: C 51.50, H 4.57, N 5.30, O 15.81%.

*4.4.4. 3-Ethyl 7,8-dimethyl 6-methyl-2-[(trifluoroacetyl)amino]-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3,7,8-tricarboxylate (**8d**)*

White powder mp 135–137 °C (ethyl acetate/hexane). R_f (20% Et_2O/hexane) 0.78. ^1H NMR (400 MHz, $CDCl_3$): δ=9.60 (s, 1H, $NHCOCF_3$), 4.41 (q, 2H, *J*=7.1 Hz, O–CH_2–CH_3), 4.00 (s, 2H, 9-CH_2), 3.84–3.81 (m, 2H, 5-CH_2), 3.80 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.41 (t, 2H, *J*=6.4 Hz, 4-CH_2), 2.75 (s, 3H, N–CH_3), 1.42 (t, 3H, *J*=7.1 Hz, O–CH_2–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.6, 166.1, 163.9, 153.7, 153.1 (q, $^2J_{C,F}$=38 Hz), 139.8, 131.3, 129.6, 119.0, 115.3 (q, $^1J_{C,F}$=287 Hz), 95.9, 61.5, 52.2, 51.3, 50.1, 37.7, 27.4, 25.3, 13.7 ppm. IR

(KBr): ν=1743, 1721, 1687, 1670, 1572 cm^{-1}. EIMS *m*/*z* (%): 478 (M^+, 57), 419 (83), 389 (10), 373 (35), 359 (17), 345 (11), 341 (19), 323 (25), 313 (51), 293 (32), 272 (33), 260 (57), 247 (28), 234 (21), 221 (55), 202 (34), 190 (32), 185 (38), 178 (51), 162 (25), 152 (30), 136 (27), 126 (75), 116 (23), 103 (72), 102 (48), 100 (33), 82 (37), 72 (36), 69 (100), 59 (70), 57 (61), 45 (53), 43 (48). $C_{19}H_{21}F_3N_2O_7S$ (478.10): calcd C 47.70, H 4.42, N 5.86, O 23.41%; found: C 47.74, H 4.49, N 5.75, O 23.50%.

4.4.5. Ethyl 8-acetyl-6-ethyl-2-[(trifluoroacetyl)amino]-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3-carboxylate (**8e**)

White powder mp 195–196 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.68 (s, 1H, $NHCOCF_3$), 7.27 (s, 1H, 7-H), 4.39 (q, 2H, *J*=7.4 Hz, O–*CH*$_2$–CH$_3$), 4.07 (s, 2H, 9-CH_2), 3.97–3.91 (m, 2H, 5-CH_2), 3.36 (t, 2H, *J*=5.6 Hz, 4-CH_2), 3.27 (q, 2H, *J*=7.4 Hz, N–*CH*$_2$–CH$_3$), 2.18 (s, 3H, $COCH_3$), 1.41 (t, 3H, *J*=7.4 Hz, O–CH$_2$–*CH*$_3$), 1.23 (t, 3H, *J*=7.4 Hz, N–CH$_2$–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.1, 164.5, 153.4 (q, $^2J_{C,F}$=38 Hz), 152.6, 139.5, 132.3, 130.9, 119.8, 115.5 (q, $^1J_{C,F}$=287 Hz), 107.7, 61.7, 51.7, 45.3, 32.1, 24.9, 21.6, 15.5, 14.1 ppm. IR (KBr): ν=1720, 1690, 1583 cm^{-1}. EIMS *m*/*z* (%): 418 (M^+, 100), 389 (17), 375 (95), 347 (12), 329 (37), 301 (11), 272 (17), 247 (5), 221 (12), 202 (5), 178 (11), 160 (5), 96 (5), 69 (19), 58 (27), 43 (63). $C_{18}H_{21}F_3N_2O_4S$ (418.12): calcd C 51.67, H 5.06, N 6.69, O 15.29%; found: C 51.74, H 5.19, N 6.72, O 15.35%.

4.4.6. 3-Ethyl 8-methyl 6-ethyl-[(trifluoroacetyl)amino]-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3,8-dicarboxylate (**8f**)

Yellowish powder mp 134–135 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.59 (s, 1H, $NHCOCF_3$), 7.45 (s, 1H, 7-H), 4.40 (q, 2H, *J*=7.2 Hz, O–*CH*$_2$–CH$_3$), 3.99 (s, 2H, 9-CH_2), 3.92–3.87 (m, 2H, 5-CH_2), 3.68 (s, 3H, OCH_3), 3.35 (t, 2H, *J*=5.6 Hz, 4-CH_2), 3.22 (q, 2H, *J*=7.4 Hz, N–*CH*$_2$–CH$_3$), 1.41 (t, 3H, *J*=7.2 Hz, O–CH$_2$–*CH*$_3$), 1.20 (t, 3H, *J*=7.4 Hz, N–CH$_2$–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.9, 164.5, 153.8 (q, $^2J_{C,F}$=38 Hz), 149.9, 139.5, 131.9, 130.9, 119.8, 115.6 (q, $^1J_{C,F}$=287 Hz), 93.2, 61.7, 51.5, 51.2, 45.7, 32.3, 24.1, 15.3, 14.2 ppm. IR (KBr): ν=1719, 1690, 1654, 1602 cm^{-1}. EIMS *m*/*z* (%): 434 (M^+, 34), 405 (10), 375 (25), 329 (45), 317 (5), 301 (11), 293 (28), 272 (13), 247 (7), 221 (25), 194 (6), 178 (12), 162 (5), 142 (17), 121 (7), 97 (11), 82 (16), 69 (100), 58 (77), 56 (96), 42 (45). $C_{18}H_{21}F_3N_2O_5S$ (434.11): calcd C 49.76, H 4.87, N 6.45, O 18.41%; found: C 49.64, H 4.69, N 6.42, O 18.50%.

4.4.7. Ethyl 6-ethyl-8-[(4-methylphenyl)sulphonyl]-2-[(trifluoroacetyl)amino]-4,5,6,9-tetrahydrothieno[3,2-d]-azocine-3-carboxylate (**8g**)

White crystals mp 145–147 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.71 (s, 1H, $NHCOCF_3$), 7.68 (d, 2H, *J*=8.7 Hz, CH–Ar), 7.44 (s, 1H, 7-H), 7.28 (d, 2H, *J*=8.7 Hz, CH–Ar), 4.37 (q, 2H, *J*=7.3 Hz, O–*CH*$_2$–CH$_3$), 3.95–3.81 (m, 2H, 5-CH_2), 3.75 (s, 2H, 9-CH_2), 3.32 (t, 2H, *J*=5.6 Hz, 4-CH_2), 3.25 (q, 2H, *J*=7.2 Hz, N–*CH*$_2$–CH$_3$), 2.42 (s, 3H, Ar–CH$_3$), 1.39 (t, 3H, *J*=7.3 Hz, O–CH$_2$–*CH*$_3$), 1.23 (t, 3H, *J*=7.2 Hz, N–CH$_2$–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=164.4, 153.8 (q, $^2J_{C,F}$=38 Hz), 148.2, 142.9, 140.5, 140.0, 131.6, 130.1 (2C), 129.8, 127.4 (2C), 119.3, 115.8 (q, $^1J_{C,F}$=287 Hz), 100.3, 61.6, 51.2, 45.3, 32.3, 24.2, 21.3, 15.2, 14.2 ppm. IR (KBr): ν=1724, 1659, 1623, 1562 cm^{-1}. EIMS *m*/*z* (%): 530 (M^+, 10), 375 (100), 341 (8), 329 (32), 301 (7), 284 (13), 274 (6), 216 (9), 202 (70), 178 (5), 146 (5), 107 (7), 91 (25), 80 (5), 65 (10), 58 (27), 42 (7). $C_{23}H_{25}F_3N_2O_5S_2$ (530.12): calcd C 52.06, H 4.75, N 5.28, O 15.08%; found: C 52.19, H 4.60, N 5.25, O 15.20%.

4.4.8. 3-Ethyl 7,8-dimethyl 6-ethyl-2-[(trifluoroacetyl)amino]-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3,7,8-tricarboxylate (**8h**)

Yellowish viscous oil. R_f (15% Et_2O/hexane) 0.61. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.60 (s, 1H, $NHCOCF_3$), 4.40 (q, 2H, *J*=7.1 Hz, O–*CH*$_2$–CH$_3$), 3.97 (s, 2H, 9-CH_2), 3.85 (t, 2H, *J*=6.3 Hz, 5-CH_2), 3.79 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.41 (t, 2H, *J*=6.3 Hz, 4-CH_2), 3.03 (q, 2H, *J*=7.1 Hz, N–*CH*$_2$–CH$_3$), 1.41 (t, 3H, *J*=7.1 Hz, O–CH$_2$–*CH*$_3$), 1.03 (t, 3H, *J*=7.1 Hz, N–CH$_2$–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.7, 164.7, 163.8, 153.4 (q, $^2J_{C,F}$=38 Hz), 141.0, 139.8, 131.3, 129.6, 119.0, 115.3 (q, $^1J_{C,F}$=287 Hz), 95.9, 61.7, 53.7, 51.7, 50.9, 45.8, 32.4, 24.6, 15.3, 14.2 ppm. IR (KBr): ν=1735, 1721, 1690, 1567 cm^{-1}. EIMS *m*/*z* (%): 492 (M^+, 60), 473 (5), 433 (100), 421 (10), 387 (19), 357 (11), 327 (12), 293 (15), 260 (20), 247 (8), 212 (6), 200 (11), 190 (9), 164 (6), 140 (19), 116 (31), 97 (8), 80 (16), 71 (57), 59 (40), 42 (36). $C_{20}H_{23}F_3N_2O_7S$ (492.12): calcd C 48.78, H 4.71, N 5.69, O 22.74%; found: C 48.70, H 5.02, N 5.45, O 23.02%.

4.4.9. Ethyl 8-acetyl-6-isopropyl-2-[(trifluoroacetyl)amino]-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3-carboxylate (**8i**)

White powder mp 180–181 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ=12.10 (s, 1H, $NHCOCF_3$), 7.36 (s, 1H, 7-H), 4.40 (q, 2H, *J*=7.3 Hz, O–*CH*$_2$–CH$_3$), 4.08 (s, 2H, 9-CH_2), 3. 89–3. 96 (m, 2H, 5-CH_2), 3.53–3.43 (m, 1H, –*CH*(CH$_3$)$_2$), 3.37 (t, 2H, *J*=6.3 Hz, 4-CH_2), 2.20 (s, 3H, $COCH_3$), 1.40 (t, 3H, *J*=7.3 Hz, O–CH$_2$–*CH*$_3$), 1.25 (d, 6H, *J*=6.5 Hz, –CH(*CH*$_3$)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=191.8, 164.0, 153.1 (q, $^2J_{C,F}$=38 Hz), 150.9, 138.9, 131.8, 130.7, 119.3, 115.3 (q, $^1J_{C,F}$=287 Hz), 107.3, 61.0, 57.1, 42.5, 32.1, 24.5, 21.3, 21.2 (2C), 13.7 ppm. IR (KBr): ν=1725, 1659, 1576 cm^{-1}. EIMS *m*/*z* (%): 432 (M^+, 51), 389 (80), 343 (19), 293 (7), 272 (10), 247 (5), 221 (6), 202 (5), 85 (12), 69 (15), 56 (8), 43 (100), 41 (12). $C_{19}H_{23}F_3N_2O_4S$ (432.13): calcd C 52.77, H 5.36, N 6.48, O 14.80%; found: C 52.92, H 5.23, N 6.36, O 14.91%.

4.4.10. 3-Ethyl 8-methyl 6-isopropyl-2-[(trifluoroacetyl)amino]-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3,8-dicarboxylate (**8j**)

White powder mp 148–150 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ=12.15 (s, 1H, $NHCOCF_3$), 7.53 (s, 1H, 7-H), 4.39 (q, 2H, *J*=7.3 Hz, O–*CH*$_2$–CH$_3$), 3.99 (s, 2H, 9-CH_2), 3.89–3.84 (m, 2H, 5-CH_2), 3.68 (s, 3H, OCH_3), 3.49–3.39 (m, 1H, –*CH*(CH$_3$)$_2$), 3.35 (t, 2H, *J*=5.3 Hz, 4-CH_2), 1.40 (t, 3H, *J*=7.3 Hz, O–CH$_2$–*CH*$_3$), 1.21 (d, 6H, *J*=6.5 Hz, –CH(*CH*$_3$)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.5, 164.1, 153.2 (q, $^2J_{C,F}$=38 Hz), 147.9, 139.2, 131.5, 130.7, 119.3, 115.4 (q, $^1J_{C,F}$=287 Hz), 93.1, 61.0, 56.7, 50.6, 43.1, 32.1, 23.7, 21.4 (2C), 13.7 ppm. IR (KBr): ν=1723, 1663, 1605, 1565 cm^{-1}. EIMS *m*/*z* (%): 448 (M^+, 43), 433 (8), 417 (12), 405 (31), 389 (78), 379 (5), 359 (11), 343 (26), 330 (13), 317 (5), 301 (21), 284 (32), 260 (23), 221 (11), 202 (7), 178 (11), 149 (13), 121 (8), 96 (11), 85 (27), 70 (31), 69 (29), 59 (28), 43 (100), 42 (27), 41 (47). $C_{19}H_{23}F_3N_2O_5S$ (448.13): calcd C 50.89, H 5.17, N 6.23, O 17.84%; found: C 50.74, H 5.29, N 6.35, O 17.90%.

4.4.11. Ethyl 6-isopropyl-[(4-methylphenyl)sulphonyl]-2-[(trifluoroacetyl)amino]-4,5,6,9-tetrahydrothieno[3,2-d]-azocine-3-carboxylate (**8k**)

White powder mp 99–101 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.71 (s, 1H, $NHCOCF_3$), 7.67 (d, 2H, *J*=8.0 Hz, CH–Ar), 7.50 (s, 1H, 7-H), 7.28 (d, 2H, *J*=8.0 Hz, CH–Ar), 4.36 (q, 2H, *J*=7.2 Hz, O–*CH*$_2$–CH$_3$), 3.83–3.77 (m, 2H, 5-CH_2), 3.75 (s, 2H, 9-CH_2), 3.52–3.45 (m, 1H, –*CH*(CH$_3$)$_2$), 3.31 (t, 2H, *J*=5.6 Hz, 4-CH_2), 2.42 (s, 3H, Ar–CH$_3$), 1.38 (t, 3H, *J*=7.2 Hz, O–CH$_2$–*CH*$_3$), 1.24 (d, 6H, *J*=6.7 Hz, –CH(*CH*$_3$)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=164.4, 153.5 (q, $^2J_{C,F}$=38 Hz), 146.8, 142.9, 140.4, 140.1, 131.7, 130.2 (2C), 129.7, 127.4 (2C), 119.3, 115.8 (q, $^1J_{C,F}$=287 Hz), 110.5, 61.6, 57.0, 43.4, 32.7, 24.3, 21.8 (2C), 21.3, 14.2 ppm. IR (KBr): ν=1720, 1670, 1609, 1565 cm^{-1}. EIMS *m*/*z* (%): 544 (M^+, 10), 389 (100), 355 (6), 343 (20), 330 (5), 301 (17), 284 (17), 272 (12), 247 (5), 221 (8), 202 (11), 188 (5), 175 (7), 160 (5), 139 (7), 121 (5), 107 (8), 91 (27), 72 (15), 69 (14), 56 (12), 43 (38). $C_{24}H_{27}F_3N_2O_5S_2$ (544.13): calcd C 52.93, H 5.00, N 5.14, O 14.69%; found: C 53.07, H 4.89, N 5.35, O 14.58%.

*4.4.12. 3-Ethyl 7,8-dimethyl 6-isopropyl-2-[(trifluoroacetyl)-amino]-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3,7,8-tricarboxylate (**8l**)*

White powder mp 145–147 °C (ethyl acetate/hexane). R_f (15% Et_2O/hexane) 0.82. ^1H NMR (400 MHz, $CDCl_3$): δ=9.56 (s, 1H, $NHCOCF_3$), 4.40 (q, 2H, J=7.1 Hz, O–CH_2–CH_3), 3.82–3.79 (m, 5H, OCH_3 and 5-CH_2), 3.66 (s, 3H, OCH_3), 3.52–3.44 (m, 1H, –$CH(CH_3)_2$), 3.41 (t, 2H, J=5.6 Hz, 4-CH_2), 1.41 (t, 3H, J=7.1 Hz, O–CH_2–CH_3), 1.15 (d, 6H, J=6.7 Hz, –$CH(CH_3)_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.6, 166.5, 164.0, 153.6, 153.2 (q, $^2J_{C,F}$=38 Hz), 139.8, 132.8, 130.0, 118.5, 115.4 (q, $^1J_{C,F}$=287 Hz), 97.0, 61.0, 52.5, 52.1, 51.2, 43.8, 29.1, 25.3, 20.6 (2C), 13.7 ppm. IR (KBr): ν=1731, 1680, 1660, 1580 cm^{-1}. EIMS m/z (%): 506 (M^+, 3), 410 (50), 367 (100), 351 (62), 321 (12), 289 (11), 261 (19), 43 (32). $C_{21}H_{25}F_3N_2O_7S$ (506.13): calcd C 49.80, H 4.98, N 5.53, O 22.11%; found: C 49.74, H 5.26, N 5.75, O 22.47%.

4.5. General experimental procedure for the synthesis of thienoazocines 8m, n, p in methanol

DMAD, methyl propiolate or acetylacetylene (1.2 mmol) was added to a solution of thienopyridine **7d** (1 mmol) in methanol (15 mL). The reaction was stirred at 25 °C (TLC monitoring). The solvent was evaporated under reduced pressure, and the residue was recrystallized (ethyl acetate/hexane) to give thienoazocines **8m–p**.

*4.5.1. Ethyl 8-acetyl-6-benzyl-2-[(trifluoroacetyl)amino]-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3-carboxylate (**8m**)*

White powder mp 175–177 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ=12.18 (s, 1H, $NHCOCF_3$), 7.47 (s, 1H, 7-H), 7.32–7.30 (m, 3H, CH–Ar), 7.13–7.12 (m, 2H, CH–Ar), 4.44 (s, 2H, CH_2–Ar), 4.26 (q, 2H, J=7.1 Hz, O–CH_2–CH_3), 4.13 (s, 2H, 9-CH_2), 4.00–3.96 (m, 2H, 5-CH_2), 3.13 (t, 2H, J=6.1 Hz, 4-CH_2), 2.25 (s, 3H, $COCH_3$), 1.31 (t, 3H, J=7.1 Hz, O–CH_2–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.1, 164.0, 153.2 (q, $^2J_{C,F}$=38 Hz), 153.1, 139.5, 138.0, 131.6, 130.6, 128.3 (2C), 128.2, 127.4 (2C), 118.9, 115.4 (q, $^1J_{C,F}$=287 Hz), 107.8, 60.8, 60.6, 46.5, 31.1, 24.5, 21.3, 13.6 ppm. IR (KBr): ν=1721, 1652, 1588 cm^{-1}. EIMS m/z (%): 480 (M^+, 15), 437 (9), 389 (5), 91 (100), 65 (14), 43 (42). $C_{23}H_{23}F_3N_2O_4S$ (480.13): calcd C 57.49, H 4.82, N 5.83, O 13.32%; found: C 57.74, H 4.79, N 5.75, O 13.50%.

*4.5.2. 3-Ethyl 8-methyl 6-benzyl-2-[(trifluoroacetyl)amino]-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3,8-dicarboxylate (**8n**)*

White powder mp 157–159 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ=12.20 (s, 1H, $NHCOCF_3$), 7.63 (s, 1H, 7-H), 7.27–7.25 (m, 3H, CH–Ar), 7.10–7.08 (m, 2H, CH–Ar), 4.36 (s, 2H, CH_2–Ar), 4.23 (q, 2H, J=7.1 Hz, O–CH_2–CH_3), 4.02 (s, 2H, 9-CH_2), 3.91–3.86 (m, 5-CH_2), 3.72 (s, 3H, OCH_3), 3.06 (t, 2H, J=5.8 Hz, 4-CH_2), 1.27 (t, 3H, J=7.1 Hz, O–CH_2–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.6, 164.0, 153.1 (q, $^2J_{C,F}$=38 Hz), 150.5, 139.5, 138.1, 131.3, 130.7, 128.3 (2C), 127.3, 127.2 (2C), 119.0, 115.4 (q, $^1J_{C,F}$=287 Hz), 93.7, 60.9, 60.4, 50.7, 46.5, 31.2, 23.6, 13.6 ppm. IR (KBr): ν=1721, 1676, 1660, 1589 cm^{-1}. EIMS m/z (%): 496 (M^+, 3), 132 (5), 91 (100), 65 (13), 42 (5). $C_{23}H_{23}F_3N_2O_5S$ (496.13): calcd C 55.64, H 4.67, N 5.64, O 16.11%; found: C 55.79, H 4.69, N 5.78, O 16.37%.

*4.5.3. 3-Ethyl 7,8-dimethyl 6-benzyl-2-[(trifluoroacetyl)amino]-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3,7,8-tricarboxylate (**8p**)*

White powder mp 136–138 °C (ethyl acetate/hexane). R_f (20% Et_2O/hexane) 0.65. ^1H NMR (400 MHz, $CDCl_3$): δ=12.17 (s, 1H, $NHCOCF_3$), 7.20–7.11 (m, 3H, CH–Ar), 7.06–7.04 (m, 2H, CH–Ar), 4.23 (q, 2H, J=7.1 Hz, O–CH_2–CH_3), 4.13 (s, 2H, Ar–CH_2), 3.99 (s, 2H, 9-CH_2), 3.84 (t, 2H, J=6.5 Hz, 5-CH_2), 3.79 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.14 (t, 2H, J=6.5 Hz, 4-CH_2), 1.34 (t, 3H, J=7.1 Hz, O–CH_2–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.7, 166.5, 163.9, 153.6, 115.8 (q, $^2J_{C,F}$=38 Hz), 140.8, 137.5, 132.0, 129.2, 128.8, 128.3, 127.8 (2C), 127.1, 126.9, 117.5, 115.3 (q, $^1J_{C,F}$=287 Hz), 98.0, 60.9, 55.3, 52.4, 51.5, 50.4, 28.2, 25.6, 13.6 ppm. IR (KBr): ν=1736, 1721, 1684, 1569 cm^{-1}. EIMS m/z (%): 554 (M^+, 5), 463 (25), 357 (5), 190 (7), 91 (100), 65 (13), 45 (12). $C_{25}H_{25}F_3N_2O_7S$ (554.13): calcd C 54.15, H 4.54, N 5.05, O 20.20%; found: C 54.29, H 4.72, N 5.01, O 20.12%.

4.6. General experimental procedure for the synthesis of thienoazocines 8m, n in acetonitrile

Methyl propiolate or acetylacetylene (3 mmol) was added to a solution of thienopyridine **7d** (1 mmol) in acetonitrile (15 mL). The reaction was stirred at 25 °C (TLC monitoring). The solvent was evaporated under reduced pressure. The residue was recrystallized (ethyl acetate/hexane) to give thienoazocines **8m**, **n**.

4.7. Experimental procedure for the synthesis of thienoazocine 8o in acetonitrile

p-Tosylacetylene (1.2 mmol) was added to a solution of thienopyridine **7d** (1 mmol) in acetonitrile (15 mL). The reaction was stirred at 25 °C (TLC monitoring). The solvent was evaporated under reduced pressure, and the residue was recrystallized (ethyl acetate/hexane) to give thienoazocine **8o**.

4.8. Ethyl 6-benzyl-8-[(4-methylphenyl)sulphonyl]-2-[(trifluoroacetyl)amino]-4,5,6,9-tetrahydrothieno[3,2-*d*]azocine-3-carboxylate (8o)

White powder mp 213–214 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ=9.68 (s, 1H, $NHCOCF_3$), 7.72 (d, 2H, J=8.0 Hz, CH–Ts), 7.33–7.29 (m, 5H, CH–Ar and CH–Ts), 7.10 (m, 2H, CH–Ar), 4.40 (s, 2H, Ar–CH_2), 4.22 (q, 2H, J=7.2 Hz, O–CH_2–CH_3), 3.81–3.77 (m, 4H, 5-CH_2 and 9-CH_2), 3.05 (t, 2H, J=6.0 Hz, 4-CH_2), 2.45 (s, 3H, Ar–CH_3), 1.26 (t, 3H, J=7.2 Hz, O–CH_2–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=164.3, 153.3 (q, $^2J_{C,F}$=38 Hz), 149.3, 143.0, 140.4, 140.4, 138.4, 131.6, 130.1 (2C), 129.4, 128.8 (2C), 127.9, 127.8 (2C), 127.3 (2C), 119.0, 115.7 (q, $^1J_{C,F}$=287 Hz), 101.2, 61.4, 60.3, 46.8, 31.7, 24.2, 21.3, 14.0 ppm. IR (KBr): ν=1722, 1662, 1621, 1562 cm^{-1}. EIMS m/z (%): 592 (M^+, 2), 272, 221 (6), 202 (10), 175 (7), 139 (11), 120 (10), 104 (7), 92 (100), 91 (17), 77 (7), 65 (47), 51 (6), 39 (15). $C_{28}H_{27}F_3N_2O_5S_2$ (592.13): calcd C 56.74, H 4.59, N 4.73, O 13.50%; found: C 56.56, H 4.50, N 4.75, O 13.33%.

4.9. Experimental procedure for the synthesis of thienoazocine 8p in acetonitrile

DMAD (3 mmol) was added to a solution of thienopyridine **7d** (1 mmol) in acetonitrile (15 mL). The reaction mixture was heated to reflux (TLC monitoring). The solvent was evaporated under reduced pressure. The resulting residue was purified by column chromatography with ethyl acetate/hexane (1:1) as eluent to give thienoazocine **8p**.

4.10. General experimental procedure for the synthesis of thienoazocines 9a–c in acetonitrile

To a stirred solution of thienopyridine **7e** (1 mmol) in acetonitrile (15 mL) at 25 °C methyl propiolate, acetylacetylene or DMAD (1.2 mmol) was added and the stirring was continued (TLC monitoring). The solvent was removed evaporated under reduced pressure, the resulting residue was purified by column chromatography.

*4.10.1. Ethyl 8-acetyl-(acetylamino)-6-methyl-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3-carboxylate (**9a**)*

Eluent ethyl acetate/hexane (3:1). White powder mp 148–150 °C (ethyl acetate/hexane). R_f (10% Et_2O/hexane) 0.43. ^1H NMR (400 MHz, $CDCl_3$): δ=11.18 (s, 1H, *NH*COCH$_3$), 7.25 (s, 1H, 7-H), 4.36 (q, 2H, J=7.1 Hz, O–*CH*$_2$–CH$_3$), 4.03 (s, 2H, 9-CH$_2$), 3.94–3.88 (m, 2H, 5-CH$_2$), 3.35 (t, 2H, J=5.8 Hz, 4-CH$_2$), 3.09 (s, 3H, N–CH$_3$), 2.23 (s, 3H, COCH$_3$), 2.19 (s, 3H, COCH$_3$), 1.41 (t, 3H, J=7.1 Hz, O–CH$_2$–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=191.5, 167.0, 164.4, 152.37, 144.4, 128.6, 128.1, 113.7, 107.8, 60.3, 47.3, 43.8, 30.6, 24.4, 23.0, 21.0, 14.0 ppm. IR (KBr): ν=1732, 1686, 1655, 1570 cm^{-1}. EIMS m/z (%): 350 (M$^+$, 36), 307 (47), 293 (12), 279 (10), 265 (21), 251 (16), 239 (17), 233 (10), 219 (27), 206 (8), 197 (15), 191 (17), 176 (240), 164 (18), 149 (15), 136 (13), 125 (33), 112 (98), 94 (12), 82 (17), 77 (10), 70 (32), 60 (18), 43 (100). $C_{17}H_{22}N_2O_4S$ (350.13): calcd C 58.27, H 6.33, N 7.99, O 18.26%; found: C 58.34, H 6.49, N 7.75, O 18.00%.

*4.10.2. 3-Ethyl 8-methyl 2-(acetylamino)-6-methyl-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3,8-dicarboxylate (**9b**)*

Eluent ethyl acetate/hexane (1:7). White powder mp 172–174 °C (ethyl acetate/hexane). R_f (10% Et_2O/hexane) 0.54. ^1H NMR (400 MHz, $CDCl_3$): δ=11.20 (s, 1H, *NH*COCH$_3$), 7.41 (s, 1H, 7-H), 4.37 (q, 2H, J=7.1 Hz, O–*CH*$_2$–CH$_3$), 3.95 (s, 2H, 9-CH$_2$), 3.89–3.84 (m, 2H, 5-CH$_2$), 3.68 (s, 3H, OCH$_3$), 3.33 (t, 2H, J=5.8 Hz, 4-CH$_2$), 3.03 (s, 3H, N–CH$_3$), 2.24 (s, 3H, COCH$_3$), 1.41 (t, 3H, J=7.1 Hz, O–CH$_2$–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.8, 166.9, 166.3, 150.5, 147.3, 128.5, 128.3, 113.0, 94.6, 60.7, 51.2, 47.9, 44.1, 31.5, 23.9, 23.7, 14.4 ppm. IR (KBr): ν=1685, 1660, 1587, 1526 cm^{-1}. EIMS m/z (%): 366 (M$^+$, 100), 351 (20), 335 (19), 323 (22), 307 (73), 281 (22), 276 (17), 267 (20), 261 (49), 239 (38), 234 (19), 220 (17), 219 (42), 197 (29), 195 (18), 176 (21), 164 (18), 125 (26), 43 (22). $C_{17}H_{22}N_2O_5S$ (366.12): calcd C 55.72, H 6.05, N 7.64, O 21.83%; found: C 55.49, H 6.09, N 7.42, O 21.89%.

*4.10.3. 3-Ethyl 7,8-dimethyl 2-(acetylamino)-6-methyl-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3,7,8-tricarboxylate (**9c**)*

Eluent ethyl acetate/hexane (1:5). White powder mp 147–149 °C (ethyl acetate/hexane). R_f (10% Et_2O/hexane) 0.49. ^1H NMR (400 MHz, $CDCl_3$): δ=11.19 (s, 1H, *NH*COCH$_3$), 4.37 (q, 2H, J=7.2 Hz, O–*CH*$_2$–CH$_3$), 3.95 (s, 2H, 9-CH$_2$), 3.84–3.79 (m, 5H, OCH$_3$ and 5-CH$_2$), 3.70 (s, 3H, OCH$_3$), 3.38 (t, 2H, J=6.5 Hz, 4-CH$_2$), 2.74 (s, 3H, N–CH$_3$), 2.25 (s, 3H, COCH$_3$), 1.41 (t, 3H, J=7.2 Hz, O–CH$_2$–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.8, 166.9, 166.3, 165.8, 150.2, 146.9, 128.2, 127.3, 112.4, 97.2, 60.7, 56.3, 51.2, 48.2, 44.4, 31.8, 23.8, 23.5, 14.2 ppm. IR (KBr): ν=1735, 1680, 1667, 1569 cm^{-1}. EIMS m/z (%): 424 (M$^+$, 35), 367 (45), 366 (20), 365 (100), 364 (31), 333 (15), 325 (23), 321 (16), 319 (33), 305 (16), 277 (28), 276 (19), 259 (16), 234 (16), 217 (17), 186 (73), 164 (16), 125 (18), 82 (18), 43 (28). $C_{19}H_{24}N_2O_7S$ (424.13): calcd C 53.76, H 5.70, N 6.60, O 26.38%; found: C 53.44, H 5.49, N 6.75, O 26.17%.

4.11. General experimental procedure for the synthesis of thienoazocines 9d–h in acetonitrile

To a stirred solution of thienopyridines **7f**, **g** (1 mmol) in acetonitrile (15 mL) at 25 °C methyl propiolate, acetylacetylene or DMAD (1.2 mmol) was added and stirring was continued (TLC monitoring). The solvent was evaporated under reduced pressure. In the cases of reactions with methyl propiolate or acetylacetylene the resulting residue was recrystallized with ethyl acetate/hexane to give thienoazocines **9d**, **e**, **g**, **h**. In the case of reactions with DMAD the residue was purified by column chromatography with ethyl acetate/hexane (1:7) as eluent to give thienoazocines **9f**, **i**.

*4.11.1. Ethyl 8-acetyl-2-(acetylamino)-6-ethyl-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3-carboxylate (**9d**)*

Yellowish powder mp 167–169 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ=10.6 (s, 1H, *NH*COCH$_3$), 7.29 (s, 1H, 7-H), 4.35 (q, 2H, J=7.2 Hz, O–*CH*$_2$–CH$_3$), 4.03 (s, 2H, 9-CH$_2$), 3.96–3.89 (m, 2H, 5-CH$_2$), 3.34 (t, 2H, J=6.0 Hz, 4-CH$_2$), 3.26 (q, 2H, J=7.1 Hz, N–*CH*$_2$–CH$_3$), 2.22 (s, 3H, COCH$_3$), 2.19 (s, 3H, COCH$_3$), 1.40 (t, 3H, J=7.2 Hz, O–CH$_2$–*CH*$_3$), 1.23 (t, 3H, J=7.1 Hz, N–CH$_2$–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=193.3, 166.9, 166.3, 151.5, 147.4, 128.6, 128.4, 112.8, 109.0, 60.7, 51.9, 46.0, 32.4, 24.9, 23.7, 22.1, 15.0, 14.5 ppm. IR (KBr): ν=1683, 1654, 1630, 1585 cm^{-1}. EIMS m/z (%): 364 (M$^+$, 12), 321 (13), 293 (5), 125 (5), 58 (20), 43 (100). $C_{18}H_{24}N_2O_4S$ (364.15): calcd C 59.32, H 6.64, N 7.69, O 17.56%; found: C 59.54, H 6.69, N 7.55, O 17.32%.

*4.11.2. 3-Ethyl 8-methyl 2-(acetylamino)-6-ethyl-4,5,6,9-tetrahdyrothieno[3,2-d]azocine-3,8-dicarboxylate (**9e**)*

White powder mp 175–177 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ=11.19 (s, 1H, NHCOCH$_3$), 7.46 (s, 1H, 7-H), 4.36 (q, 2H, J=7.0 Hz, O–C*H*$_2$–CH$_3$), 3.95 (s, 2H, 9-CH$_2$), 3.91–3.85 (m, 2H, 5-CH$_2$), 3.68 (s, 3H, OCH$_3$), 3.32 (t, 2H, J=6.0 Hz, 4-CH$_2$), 3.22 (q, 2H, J=7.2 Hz, N–*CH*$_2$–CH$_3$), 2.24 (s, 3H, COCH$_3$), 1.40 (t, 3H, J=7.0 Hz, O–CH$_2$–*CH*$_3$), 1.19 (t, 3H, J=7.2 Hz, N–CH$_2$–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.6, 167.0, 164.6, 149.2, 144.4, 128.9, 128.0, 113.7, 93.7, 60.3, 51.2, 50.4, 45.5, 32.0, 23.3, 23.0, 14.7, 14.0 ppm. IR (KBr): ν=1717, 1676, 1594 cm^{-1}. EIMS m/z (%): 380 (M$^+$, 87), 351 (53), 321 (100), 293 (12), 281 (23), 275 (37), 267 (14), 247 (9), 239 (43), 233 (27), 220 (12), 197 (24), 176 (17), 164 (16), 136 (7), 125 (24), 121 (6), 59 (5), 58 (11). $C_{18}H_{24}N_2O_5S$ (380.14): calcd C 56.82, H 6.36, N 7.36, O 21.03%; found: C 56.74, H 6.49, N 7.38, O 21.20%.

*4.11.3. 3-Ethyl 7,8-dimethyl 2-(acetylamino)-6-ethyl-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3,7,8-tricarboxylate (**9f**)*

White powder mp 145–146 °C (ethyl acetate/hexane). R_f (15% Et_2O/hexane) 0.77. ^1H NMR (400 MHz, $CDCl_3$): δ=11.18 (s, 1H, *NH*COCH$_3$), 4.36 (q, 2H, J=7.1 Hz, O–*CH*$_2$–CH$_3$), 3.93 (s, 2H, 9-CH$_2$), 3.86 (t, 2H, J=5.9 Hz, 5-CH$_2$), 3.79 (s, 3H, OCH$_3$), 3.68 (s, 3H, OCH$_3$), 3.37 (t, 2H, J=5.9 Hz, 4-CH$_2$), 3.03 (q, 2H, J=7.2 Hz, N–*CH*$_2$–CH$_3$), 2.22 (s, 3H, N–CH$_3$), 1.40 (t, 3H, J=7.1 Hz, O–CH$_2$–*CH*$_3$), 1.02 (t, 3H, J=7.2 Hz, N–CH$_2$–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.5, 167.4, 167.0, 166.2, 153.7, 147.7, 129.9, 126.7, 112.2, 98.6, 60.8, 52.5, 51.7, 49.2, 46.2, 29.3, 25.9, 23.7, 14.5, 14.4 ppm. IR (KBr): ν=1736, 1682, 1671, 1560 cm^{-1}. EIMS m/z (%): 438 (M$^+$, 27), 407 (7), 380 (17), 379 (100), 367 (27), 349 (11), 333 (16), 319 (11), 276 (12), 261 (8), 239 (10), 234 (8), 198 (6), 197 (8), 164 (11), 128 (5), 125 (12), 117 (5), 59 (6), 43 (24). $C_{20}H_{26}N_2O_7S$ (438.15): calcd C 54.78, H 5.98, N 6.39, O 25.54%; found: C 54.64, H 6.19, N 6.25, O 25.61%.

*4.11.4. Ethyl 8-acetyl-2-(acetylamino)-6-isopropyl-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3-carboxylate (**9g**)*

White powder mp 146–147 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ=10.60 (s, 1H, *NH*COCH$_3$), 7.37 (s, 1H, 7-H), 4.35 (q, 2H, J=7.2 Hz, O–*CH*$_2$–CH$_3$), 4.02 (s, 2H, 9-CH$_2$), 3.92–3.85 (m, 2H, 5-CH$_2$), 3.51–3.44 (m, 1H, *CH*(CH$_3$)$_2$), 3.33 (t, 2H, J=5.6 Hz, 4-CH$_2$), 2.22 (s, 3H, COCH$_3$), 2.19 (s, 3H, COCH$_3$), 1.39 (t, 3H, J=7.2 Hz, O–CH$_2$–*CH*$_3$), 1.24 (d, 6H, J=6.7 Hz, CH(*CH*$_3$)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.2, 167.6, 165.0, 151.2, 144.7, 129.3, 128.5, 113.7, 108.2, 60.8, 57.5, 43.1, 32.8, 25.0, 23.5, 21.7 (2C), 21.5, 14.4 ppm. IR (KBr): ν=1686, 1655, 1617, 1587 cm^{-1}. EIMS m/z (%): 378 (M$^+$, 32), 363 (5), 289 (6), 265 (5), 176 (6), 125 (7), 72 (8), 56 (11), 43 (100). $C_{19}H_{26}N_2O_4S$ (378.16): calcd C 60.29, H 6.92, N 7.40, O 16.91%; found: C 60.34, H 6.89, N 7.25, O 17.02%.

*4.11.5. 3-Ethyl 8-methyl 2-(acetylamino)-6-isopropyl-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3,8-dicarboxylate (**9h**)*

White powder mp 140–141 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ=10.59 (s, 1H, *NH*COCH$_3$), 7.53 (s, 1H, 7-H), 4.34 (q, 2H, J=7.2 Hz, O–*CH*$_2$–CH$_3$), 3.94 (s, 2H, 9-CH$_2$), 3.88–3.80 (m, 2H, 5-CH$_2$), 3.67 (s, 3H, OCH$_3$), 3.48–3.40 (m, 1H, *CH*(CH$_3$)$_2$), 3.32 (t, 2H, J=5.6 Hz, 4-CH$_2$), 2.23 (s, 3H, COCH$_3$), 1.20 (d, 6H, J=6.7 Hz,

$CH(CH_3)_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.1, 167.7, 165.1, 148.3, 144.7, 128.4, 128.2, 113.9, 93.7, 60.9, 57.1, 51.1, 43.5, 32.9, 23.8, 23.5, 21.9 (2C), 14.4 ppm. IR (KBr): ν=1693, 1670, 1653, 1605 cm^{-1}. EIMS *m*/*z* (%): 394 (M^+, 6), 335 (5), 125 (7), 43 (100). $C_{19}H_{26}N_2O_5S$ (394.16): calcd C 57.85, H 6.64, N 7.10, O 20.28%; found: C 57.78, H 6.59, N 7.16, O 20.17%.

4.12. General experimental procedure for the synthesis of thienoazocines 9j–l in acetonitrile

To a stirred solution of thienopyridine **7h** (1 mmol) in acetonitrile (15 mL) at 25 °C methyl propiolate, acetylacetylene or DMAD (2 mmol) was added and stirring was continued (TLC monitoring). The solvent was evaporated under reduced pressure and the resulting residue was recrystallized with ethyl acetate/hexane to give thienoazocines **9j**, **k**. In the case of DMAD the residue was purified by column chromatography with ethyl acetate/hexane (1:5) as eluent to give thienoazocine **9l**.

*4.12.1. Ethyl 8-acetyl-2-(acetylamino)-6-benzyl-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3-carboxylate (**9j**)*

White powder mp 182–184 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ=10.57 (s, 1H, *NH*–$COCH_3$), 7.44 (s, 1H, 7-H), 7.29–7.27 (m, 3H, CH–Ar), 7.11–7.09 (m, 2H, CH–Ar), 4.41 (s, 2H, Ar–CH_2), 4.18 (q, 2H, *J*=7.1 Hz, O–*CH*$_2$–CH_3), 4.06 (s, 2H, 9-CH_2), 3.96–3.89 (m, 2H, 5-CH_2), 3.07 (t, 2H, *J*=5.6 Hz, 4-CH_2), 2.24 (s, 3H, $COCH_3$), 2.22 (s, 3H, $COCH_3$), 1.25 (t, 3H, *J*=7.1 Hz, O–CH_2–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.1, 167.0, 164.5, 152.9, 144.6, 138.0, 128.7 (2C), 128.3, 128.0 (2C), 127.4, 127.3, 113.5, 108.4, 60.6, 60.1, 46.6, 31.3, 24.5, 23.0, 21.1, 13.9 ppm. IR (KBr): ν=1684, 1651, 1588 cm^{-1}. EIMS *m*/*z* (%): 426 (M^+, 12), 383 (9), 335 (14), 293 (8), 265 (10), 247 (7), 239 (11), 218 (5), 188 (6), 176 (5), 120 (9), 106 (5), 91 (100), 65 (13), 43 (59). $C_{23}H_{26}N_2O_4S$ (426.16): calcd C 64.77, H 6.14, N 6.57, O 15.00%; found: C 64.64, H 6.09, N 6.75, O 15.07%.

*4.12.2. 3-Ethyl 8-methyl 2-(acetylamino)-6-benzyl-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3,8-dicarboxylate (**9k**)*

White powder mp 160–162 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ=10.55 (s, 1H, *NH*–$COCH_3$), 7.62 (s, 1H, 7-H), 7.26–7.25 (m, 3H, CH–Ar), 7.10–7.09 (m, 2H, CH–Ar), 4.35 (s, 2H, Ar–CH_2), 4.17 (q, 2H, *J*=7.1 Hz, O–*CH*$_2$–CH_3), 3.97 (s, 2H, 9-CH_2), 3.88–3.81 (m, 2H, 5-CH_2), 3.70 (s, 3H, OCH_3), 3.05–3.02 (m, 2H, 4-CH_2), 2.24 (s, 3H, $COCH_3$), 1.24 (t, 3H, *J*=7.1 Hz, O–CH_2–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.6, 166.9, 164.5, 150.3, 129.0, 128.5, 128.3 (2C), 127.7, 127.3, 127.2 (2C), 127.1, 113.7, 94.4, 60.4, 60.2, 50.5, 46.7, 31.4, 23.4, 23.0, 13.8 ppm. IR (KBr): ν=1730, 1687, 1667, 1614 cm^{-1}. EIMS *m*/*z* (%): 442 (M^+, 17), 383 (9), 351 (35), 309 (6), 265 (7), 239 (15), 204 (13), 197 (10), 190 (6), 176 (5), 132 (12), 125 (10), 106 (7), 91 (100), 65 (10), 43 (37). $C_{23}H_{26}N_2O_5S$ (442.16): calcd C 62.42, H 5.92, N 6.33, O 18.08%; found: C 62.34, H 5.84, N 6.25, O 18.24%.

*4.12.3. 3-Ethyl 7,8-dimethyl 2-(acetylamino)-6-benzyl-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3,7,8-tricarboxylate (**9l**)*

Viscous yellow oil. R_f (20% Et_2O/hexane) 0.59. ^1H NMR (400 MHz, $CDCl_3$): δ=10.58 (s, 1H, *NH*–$COCH_3$), 7.19–7.12 (m, 3H, CH–Ar), 7.09–7.05 (m, 2H, CH–Ar), 4.18 (q, 2H, *J*=7.2 Hz, O–*CH*$_2$–CH_3), 4.13 (s, 2H, Ar–CH_2), 3.94 (s, 2H, 9-CH_2), 3.81 (t, 2H, *J*=6.4 Hz, 5-CH_2), 3.76 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.09 (t, 2H, *J*=6.4 Hz, 4-CH_2), 2.27 (s, 3H, $COCH_3$), 1.31 (t, 3H, *J*=7.2 Hz, O–CH_2–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.8, 167.0, 166.5, 164.3, 153.3, 145.4, 133.3, 130.4, 127.8 (2C), 127.2 (2C), 127.0, 125.5, 112.8, 99.0, 60.1, 55.2, 52.1, 51.3, 50.2, 28.3, 25.6, 23.1, 13.9 ppm. IR (KBr): ν=1736, 1687, 1654, 1564 cm^{-1}. EIMS *m*/*z* (%): 500 (M^+, 5), 409 (25), 349 (7), 303 (5), 261 (6), 190 (7), 125 (8), 91 (100), 65 (14), 59 (7), 43 (55). $C_{25}H_{28}N_2O_7S$ (500.16): calcd C 59.99, H 5.64, N 5.60, O 22.37%; found: C 59.87, H 5.72, N 5.39, O 22.06%.

4.13. General experimental procedure for the synthesis of thienoazocines 9a, b, d–h, j, k and substituted thiophenes 10a–c

To a stirred solution of thienopyridines **7e**–**h** (1 mmol) in methanol (15 mL) at 25 °C DMAD, methyl propiolate or acetylacetylene (1.2 mmol) was added and stirring was continued (TLC monitoring). Methanol was evaporated under reduced pressure and the resulting residue was purified using column chromatography providing compounds **9a**–**c**, **10a** (for **7e**), **9d**–**f** (for **7f**), **9g**, **h**, **10b**, **c** (for **7g**). In the case of thienopyridine **7h** after the evaporation of the solvent thienoazocines **9j**, **k** were recrystallized from the reaction mixtures with ethyl acetate/hexane.

*4.13.1. Dimethyl (2E)-2-[{2-[5-(acetylamino)-4-(ethoxycarbonyl)-2-(methoxymethyl)-3-thienyl]ethyl}(methyl)amino]but-2-enedioate (**10a**)*

White powder mp 130–132 °C (ethyl acetate/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ=11.29 (s, 1H, *NH*$COCH_3$), 4.67 (s, 1H, =CH), 4.49–4.42 (m, 4H, O–*CH*$_2$–CH_3 and *CH*$_2$–OCH_3), 3.94 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.39 (s, 3H, CH_2–*OCH*$_3$), 3.34–3.19 (m, 2H, 5-CH_2), 3.13–3.08 (m, 2H, 4-CH_2), 2.77 (s, 3H, N–CH_3), 2.28 (s, 3H, $COCH_3$), 1.42 (t, 3H, *J*=7.0 Hz, O–CH_2–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.3, 166.5, 164.3, 149.6, 143.8, 139.6, 133.7, 127.4, 113.3, 86.7, 68.1, 61.4, 57.8, 54.7, 52.3, 51.4, 38.5, 29.7, 23.5, 14.1 ppm. IR (KBr): ν=1736, 1694, 1663, 1565 cm^{-1}. EIMS *m*/*z* (%): 456 (M^+, 3), 397 (9), 252 (8), 187 (9), 186 (100), 158 (5), 82 (16), 45 (6). $C_{20}H_{28}N_2O_8S$ (456.16): calcd C 52.62, H 6.18, N 6.14, O 28.04%; found: C 52.44, H 6.29, N 6.05, O 28.29%.

*4.13.2. Ethyl 2-(acetylamino)-4-(2-{isopropyl[(1E)-3-oxobut-1-en-1-yl]amino}ethyl)-5-(methoxymethyl)thiophene-3-carboxylate (**10b**)*

Yellow viscous oil. ^1H NMR (400 MHz, $CDCl_3$): δ=7.62 (d, 1H, *J*=12.4 Hz, N–CH=), 5.30 (d, 1H, *J*=12.4 Hz, =*CH*–$COCH_3$), 4.43–4.42 (m, 4H, O–*CH*$_2$–CH_3 and *CH*$_2$–OCH_3), 3.37 (s, 3H, OCH_3), 3.34–3.28 (m, 3H, 5-CH_2 and –*CH*$(CH_3)_2$), 3.11–3.03 (m, 2H, 4-CH_2), 2.28 (s, 3H, $COCH_3$), 2.12 (s, 3H, $COCH_3$), 1.45 (t, 3H, *J*=7.0 Hz, O–CH_2–*CH*$_3$), 1.15 (d, 6H, *J*=6.0 Hz, –CH(*CH*$_3$)$_2$) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=192.7, 167.3, 164.3, 148.6, 147.4, 132.6, 126.8, 112.3, 96.9, 66.0, 60.7, 57.4, 54.0, 47.9, 27.3, 25.9, 23.1, 20.8 (2C), 14.0 ppm. IR (KBr): ν=1738, 1707, 1620 cm^{-1}. EIMS *m*/*z* (%): 410 (M^+, 18), 396 (7), 395 (38), 335 (5), 283 (5), 268 (5), 241 (50), 141 (9), 140 (100), 98 (49), 80 (15), 70 (5), 56 (10), 55 (6), 43 (42), 41 (5). $C_{20}H_{30}N_2O_5S$ (410.19): calcd C 58.51, H 7.37, N 6.82, O 19.49%; found: C 58.44, H 7.49, N 6.75, O 19.30%.

*4.13.3. Dimethyl (2E)-2-[{2-[5-(acetylamino)-4-(ethoxycarbonyl)-2-(methoxymethyl)-3-thienyl]ethyl}(isopropyl)amino]but-2-enedioate (**10c**)*

Yellow viscous oil. ^1H NMR (400 MHz, $CDCl_3$): δ=10.44 (s, 1H, NH), 4.84 (s, 1H, =*CH*), 4.50 (q, 2H, *J*=7.2 Hz, O–*CH*$_2$–CH_3), 4.46 (s, 2H, *CH*$_2$–OCH_3), 3.93 (s, 3H, OCH_3), 3.65 (s, 3H, CH_2–*OCH*$_3$), 3.57–3.51 (m, 1H, –*CH*$(CH_3)_2$), 3.38 (s, 3H, OCH_3), 3.25–3.21 (m, 2H, 5-CH_2), 3.13–3.10 (m, 2H, 4-CH_2), 2.28 (s, 3H, N–CH_3), 1.41 (t, 3H, *J*=7.2 Hz, O–CH_2–*CH*$_3$), 1.06 (d, 6H, *J*=6.7 Hz, –CH(*CH*$_3$)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=190.9, 189.6, 188.6, 187.9, 173.5, 168.0, 146.8, 139.9, 120.2, 86.3, 63.6, 56.9, 53.1, 46.7 (2C), 43.7, 35.7, 20.3, 11.9, 10.1, 6.3 (2C) ppm. IR (KBr): ν=1737, 1867, 1655, 1578 cm^{-1}. EIMS *m*/*z* (%): 484 (M^+, 5), 425 (6), 215 (10), 214 (100), 172 (12), 164 (5), 140 (28), 112 (8), 43 (6). $C_{22}H_{32}N_2O_8S$ (484.19): calcd C 54.53, H 6.66, N 5.78, O 26.41%; found: C 54.35, H 6.48, N 5.65, O 26.17%.

4.14. General procedure for the synthesis of thienoazocines 11a–d

To the stirred solution of thienoazocines **8a–d** (1 g) alkaline alumina oxide (pH=10±0.5) (30 g) was added, the stirring was continued at 25 °C (TLC monitoring). The reaction mixture was filtrated and washed with ethyl acetate. The filtrate was gathered and the solvent was evaporated under reduced pressure to give thienoazocines **11a–d**.

*4.14.1. Ethyl 8-acetyl-2-amino-6-methyl-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3-carboxylate (**11a**)*

White powder mp 239–241 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.27 (s, 1H, 7-H), 5.90 (s, 2H, NH_2), 4.28 (q, 2H, J=7.1 Hz, O–*CH*$_2$–CH$_3$), 3.91–3.84 (m, 4H, 5-CH_2 and 9-CH_2), 3.29 (t, 2H, J=5.6 Hz, 4-CH_2), 3.10 (s, 3H, N–CH_3), 2.19 (s, 3H, $COCH_3$), 1.35 (t, 3H, J=7.1 Hz, O–CH_2–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=191.6, 164.7, 161.3, 152.6, 129.5, 117.8, 108.2, 105.4, 58.7, 47.5, 43.7, 31.1, 24.3, 21.2, 14.3 ppm. IR (KBr): ν=3387, 3281, 1732, 1666, 1573 cm^{-1}. EIMS *m*/*z* (%): 308 (M$^+$, 63), 293 (5), 279 (5), 265 (36), 251 (17), 237 (10), 229 (7), 219 (39), 208 (13), 197 (10), 191 (23), 176 (29), 164 (15), 151 (7), 136 (9), 125 (31), 110 (6), 94 (6), 82 (12), 77 (7), 66 (11), 53 (7), 44 (68), 43 (100), 42 (62). $C_{15}H_{20}N_2O_3S$ (308.12): calcd C 58.42, H 6.54, N 9.08, O 15.56%; found: C 58.34, H 6.49, N 8.79, O 15.40%.

*4.14.2. 3-Ethyl 8-methyl 2-amino-6-methyl-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3,8-dicarboxylate (**11b**)*

White crystals mp 156–158 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.40 (s, 1H, 7-H), 5.83 (s, 2H, NH_2), 4.28 (q, 2H, J=7.2 Hz, O–*CH*$_2$–CH$_3$), 3.83–3.79 (m, 4H, 5-CH_2 and 9-CH_2), 3.66 (s, 3H, OCH_3), 3.27 (t, 2H, J=6.0 Hz, 4-CH_2), 3.02 (s, 3H, N–CH_3), 1.35 (t, 3H, J=7.2 Hz, O–CH_2–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.0, 165.7, 161.0, 150.6, 130.0, 119.2, 107.4, 94.5, 59.6, 51.2, 47.9, 44.2, 31.8, 23.9, 14.6 ppm. IR (KBr): ν=3400, 3297, 1666, 1619, 1589 cm^{-1}. EIMS *m*/*z* (%): 324 (M$^+$, 57), 309 (11), 293 (13), 281 (7), 265 (32), 248 (5), 234 (15), 219 (35), 210 (10), 204 (6), 197 (23), 191 (14), 176 (22), 164 (32), 151 (15), 139 (12), 125 (64), 110 (16), 105 (7), 96 (16), 91 (12), 82 (13), 66 (17), 53 (14), 43 (53), 42 (100), 39 (22). $C_{15}H_{20}N_2O_4S$ (324.11): calcd C 55.54, H 6.21, N 8.64, O 19.73%; found: C 55.38, H 6.39, N 8.78, O 19.59%.

*4.14.3. Ethyl 2-amino-6-methyl-8-[(4-methylphenyl)sulphonyl]-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3-carboxylate (**11c**)*

White powder mp 231–233 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.67 (d, 2H, J=8.1 Hz, CH–Ar), 7.38 (s, 1H, 7-H), 7.25 (d, 2H, J=8.1 Hz, CH–Ar), 5.73 (s, 2H, NH_2), 4.26 (q, 2H, J=7.3 Hz, O–*CH*$_2$–CH$_3$), 3.76–3.73 (m, 2H, 5-CH_2), 3.58 (s, 2H, 9-CH_2), 3.25 (t, 2H, J=5.6 Hz, 4-CH_2), 3.06 (s, 3H, N–CH_3), 2.42 (s, 3H, Ar–CH_3), 1.34 (t, 3H, J=7.3 Hz, O–CH_2–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=164.6, 161.6, 148.5, 141.8, 140.9, 130.5, 129.3 (2C), 126.5 (2C), 115.2, 105.3, 100.9, 58.7, 47.4, 43.2, 31.4, 23.8, 20.8, 14.2 ppm. IR (KBr): ν=3416, 3319, 1657, 1631, 1584 cm^{-1}. EIMS *m*/*z* (%): 420 (M$^+$, 11), 265 (36), 247 (8), 237 (9), 219 (34), 191 (14), 175 (18), 164 (5), 149 (6), 125 (17), 104 (6), 91 (31), 82 (7), 77 (8), 65 (18), 51 (7), 44 (43), 43 (100), 42 (71), 39 (19). $C_{20}H_{24}N_2O_4S_2$ (420.12): calcd C 57.12, H 5.75, N 6.66, O 15.22%; found: C 57.24, H 5.67, N 6.77, O 15.44%.

*4.14.4. 3-Ethyl 7,8-dimethyl 2-amino-6-methyl-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3,7,8-tricarboxylate (**11d**)*

White powder mp 146–148 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.88 (s, 2H, NH_2), 4.28 (q, 2H, J=7.1 Hz, O–*CH*$_2$–CH$_3$), 3.81 (s, 3H, OCH_3), 3.80 (s, 2H, 9-CH_2), 3.75 (t, 2H, J=6.2 Hz, 5-CH_2), 3.67 (s, 3H, OCH_3), 3.31 (t, 2H, J=6.2 Hz, 4-CH_2), 2.74 (s, 3H, N–CH_3), 1.35 (t, 3H, J=7.1 Hz, O–CH_2–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=167.8, 166.3, 164.6, 162.0, 153.3, 130.7, 115.5, 105.0, 97.2, 58.8, 51.9, 50.9, 50.7, 37.7, 28.3, 25.5, 14.3 ppm. IR (KBr): ν=3475, 3351, 1739, 1689, 1659, 1600 cm^{-1}. EIMS *m*/*z* (%): 382 (M$^+$, 75), 351 (8), 335 (6), 325 (67), 323 (100), 307 (8), 293 (21), 277 (53), 263 (14), 245 (16), 234 (27), 217 (21), 210 (13), 197 (14), 189 (6), 175 (9), 164 (21), 152 (7), 136 (10), 125 (27), 116 (9), 103 (6), 82 (7), 72 (6), 65 (5), 59 (12), 42 (27), 39 (10). $C_{17}H_{22}N_2O_6S$ (382.12): calcd C 53.39, H 5.80, N 7.33, O 25.10%; found: C 53.24, H 5.74, N 7.25, O 25.26%.

4.15. Experimental procedure for the synthesis of thienoazocine 12

$NaCNBH_3$ (98 mg, 1.55 mmol) and a few drops of acetic acid, as a catalyst, were added to a solution of thienoazocine **11a** (250 mg, 0.77 mmol) in methanol (20 mL). The reaction mixture was heated at reflux (TLC monitoring). The solvent was evaporated under reduced pressure. Water (15 mL) was added to the residue and the pH was adjusted to 8–9 (Na_2CO_3). The resulting solution was extracted with ether (3×25 mL). The solvent was evaporated under reduced pressure to give hexahydrothienoazocine **12** (216 mg, 86%).

*4.15.1. 3-Ethyl 8-methyl 2-amino-6-methyl-4,5,6,7,8,9-hexahydrothieno[3,2-d]azocine-3,8-dicarboxylate (**12**)*

Yellowish viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.92 (s, 2H, NH_2), 4.27 (q, 2H, J=7.1 Hz, O–*CH*$_2$–CH$_3$), 3.71 (s, 3H, OCH_3), 3.15–3.03 (m, 2H, 7-CH_2), 2.90–2.85 (m, 2H, 9-CH_2), 2.80–2.75 (m, 1H, 4-CH_2), 2.72–2.66 (m, 1H, 5-CH_2), 2.61–2.54 (m, 3H, 4-CH_2 and 8-CH), 2.38 (s, 3H, N–CH_3), 1.33 (t, 3H, J=7.1 Hz, O–CH_2–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.3, 165.9, 161.9, 135.0, 117.1, 106.3, 59.6, 59.3, 56.4, 51.7, 48.1, 47.1, 29.3, 26.8, 14.5 ppm. IR (KBr): ν=3434, 3330, 1730, 1665 cm^{-1}. EIMS *m*/*z* (%): 326 (M$^+$, 85), 293 (27), 247 (29), 240 (54), 239 (100), 224 (21), 211 (39), 210 (44), 198 (36), 197 (67), 194 (21), 193 (22), 180 (20), 178 (23), 164 (30), 152 (18), 125 (26), 109 (44), 58 (25), 43 (23). $C_{15}H_{22}N_2O_4S$ (326.13): calcd C 55.19, H 6.79, N 8.58, O 19.61%; found: C 55.34, H 6.87, N 8.25, O 19.52%.

4.16. Experimental procedure for the synthesis of thienoazocine 13

To a stirred solution of thienoazocine **11a** (250 mg, 0.77 mmol) dry CH_2Cl_2 (20 mL) triethylamine (0.13 mL, 0.93 mmol) and chloroacetyl chloride (0.07 mL, 0.93 mmol) were added, the stirring was continued (TCL monitoring). The reaction mixture was poured into water (20 mL) and was extracted with CH_2Cl_2 (3×20 mL). The solvent was evaporated under reduced pressure to give thienoazocine **13** (261 mg, 84%).

*4.16.1. 3-Ethyl 8-methyl 2-[(chloroacetyl)amino]-6-methyl-4,5,6,9-tetrahydrothieno[3,2-d]azocine-3,8-dicarboxylate (**13**)*

White powder mp 201–203 °C (ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.81 (s, 1H, NH), 7.40 (s, 1H, 7-H), 4.41 (q, 2H, J=7.1 Hz, O–*CH*$_2$–CH$_3$), 4.24 (s, 2H, CH_2–CO), 3.97 (s, 2H, 9-CH_2), 3.90–3.85 (m, 2H, 5-CH_2), 3.68 (s, 3H, OCH_3), 3.38–3.34 (m, 2H, 4-CH_2), 3.03 (s, 3H, N–CH_3), 1.41 (t, 3H, J=7.1 Hz, O–CH_2–*CH*$_3$) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=168.5, 164.4, 163.7, 150.1, 143.3, 129.4, 128.9, 115.3, 93.7, 60.6, 50.4, 47.4, 43.5, 42.4, 30.7, 23.4, 13.9 ppm. IR (KBr): ν=1663, 1615, 1598 cm^{-1}. EIMS *m*/*z* (%): 400 (M$^+$, 16), 341 (17), 310 (6), 295 (9), 273 (15), 219 (6), 194 (12), 176 (7), 166 (11), 151 (6), 136 (5), 125 (7), 108 (5), 94 (6), 77 (47), 65 (6), 59 (13), 49 (43), 43 (46), 42 (100). $C_{17}H_{21}ClN_2O_5S$ (400.09): calcd C 50.93, H 5.28, N 6.99, O 19.96%; found: C 50.88, H 5.24, N 7.13, O 19.88%.

4.17. Experimental procedure for the synthesis of thienoazocine 14

To a stirred solution of thienoazocine **11a** (300 mg, 0.93 mmol) in dry CH_2Cl_2 (20 mL) triethylamine (0.38 mL, 2.78 mmol) and 3-chlorophenylisocyanate (0.34 mL, 2.78 mmol) were added and the stirring was continued (TLC monitoring). The reaction mixture was poured into water (25 mL) and extracted CH_2Cl_2 (3×25 mL). The solvent was evaporated under reduced pressure to give thienoazocine **14** (326 mg, 74%).

*4.17.1. 3-Ethyl 8-methyl 2-({[(3-chlorophenyl)amino]-carbonyl}amino)-6-methyl-4,5,6,9-tetrahydrothieno-[3,2-d]azocine-3,8-dicarboxylate (**14**)*

White powder mp 211–213 °C (ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.81 (s, 1H, NH), 7.58 (s, 1H, NH), 7.40 (s, 1H, 7-H), 7.28–7.15 (m, 2H, CH–Ar), 7.06 (d, 1H, J=7.6 Hz, CH–Ar), 7.04 (s, 1H, CH–Ar), 4.32 (q, 2H, J=7.1 Hz, O–CH_2–CH_3), 3.97 (s, 2H, 9-CH_2), 3.86–3.85 (m, 2H, 5-CH_2), 3.68 (s, 3H, OCH_3), 3.30 (t, 2H, J=5.5 Hz, 4-CH_2), 3.01 (s, 3H, N–CH_3), 1.36 (t, 3H, J=7.1 Hz, O–CH_2–CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=168.6, 165.2, 151.1, 150.1, 147.5, 140.7, 133.3, 130.2, 128.4, 126.9, 122.2, 118.3, 117.1, 112.0, 93.9, 60.1, 50.3, 47.5, 43.6, 30.9, 23.3, 14.0 ppm. IR (KBr): ν=1701, 1658, 1611, 1595, 1525 cm^{-1}. EIMS m/z (%): 477 (M^+, 15), 350 (19), 324 (30), 293 (11), 291 (27), 281 (12), 267 (15), 265 (21), 263 (13), 245 (17), 235 (16), 234 (15), 220 (10), 219 (35), 218 (12), 217 (12), 202 (10), 197 (15), 191 (13), 190 (11), 178 (12), 176 (18), 164 (18), 162 (11), 155 (29), 154 (11), 153 (100), 151 (12), 127 (26), 126 (12), 125 (63), 100 (18), 90 (27), 72 (13), 63 (14), 44 (12), 42 (16). $C_{22}H_{24}ClN_3O_5S$ (477.11): calcd C 55.28, H 5.06, N 8.79, O 16.74%; found: C 55.34, H 4.89, N 8.85, O 16.81%.

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