Investigation of ring transformations of diaryl-β-lactams condensed with 1,3-benzothiazines

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Dedicated to Professor Ferenc Fülöp on the occasion of his 60th birthday

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Abstract

Reactions of derivatives of the isoquinoline analog *trans*-2,2a-diaryl-2,2a-dihydro-5,6-dimethoxy-1*H*,8*H*-azeto[2,1-*b*][1,3]benzothiazin-1-one were studied under basic conditions. Their treatment with sodium methoxide in methanol resulted first in alcoholysis of the β-lactam ring, followed by opening of the thiazine ring and oxidation of the thiol moiety to disulfide. Thus, the corresponding β-amino acid derivatives, disulfides of *N*-(*ortho*-mercaptobenzyl)-substituted diaryl-3-aminoacrylic acid methyl esters, were obtained in good yields. The structures of the new molecules were proved by means of NMR and IR spectroscopy. Geometric isomerism investigations indicated the presence of the *Z* forms of the acrylic acid moiety.

Keywords: 1,3-Benzothiazine, β-lactam, β-amino acid, 3-aminoacrylic acid, ring opening, disulfide

Introduction

There has recently been a rapid increase in research interest in β-lactams from both medical and chemical aspects.[1–8] A considerable proportion of drugs contain an azetidinone ring (e.g. β-lactam antibiotics and taxol derivatives).[2] Besides their inestimable pharmacological effects, β-lactams play a crucial role as intermediates in the preparation of many molecules.[1–8]

Starting from β-lactams, a wide variety of β-amino acids can be obtained,[3] including

enantiopure β-amino acids prepared by the direct or indirect enzymatic treatment of β-lactams.[4] They are good starting materials for functionalized β-amino acids,[5] various chiral catalysts[6] and β-peptides.[7] Many heterocycles have been prepared from compounds containing an azetidinone ring.[8]

In the course of our recent studies on *S*- and *N*-containing condensed-skeleton heterocycles, we investigated reactions of 1,3- and 3,1-benzothiazines condensed with a β-lactam ring (Figure 1).[9–15] The ring expansion of monochloroazeto[2,1-*b*][1,3]benzothiazin-1-ones **1** with sodium methoxide afforded 1,4-benzothiazepines **4** as single products in good yields (path **A**).[9] When the aryl substituent of **1** contained an *ortho*-nitro group, an excess of sodium methoxide in methanol yielded indolo-1,4-benzothiazepines **5** via a novel rearrangement (path **B**).[10] Basic treatment of dichloro-β-lactam condensed-1,3-benzothiazines **1** provided three interesting heterocyclic products: 1,4-benzothiazepines **4**, isoquinolines **6** and thiazoles **7** (path **C**).[11] The reactions of 1,3-benzothiazines angularly condensed with a β-lactam ring **2** were also studied in the presence of sodium methoxide. The dichloro-β-lactam ring of **2** proved to be useful protection strategy for the synthesis of 4-aryl-2*H*-1,3-benzothiazine 1,1-dioxides (path **D**).[12] After the oxidation of 1,1-dichloroazeto[2,1-*c*][1,3]-benzothiazin-2-ones **2**, the thiazine ring could be recovered selectively and in good yield by treatment with sodium methoxide (path **D**). A series of aryl-substituted β-lactams condensed with 1,3-benzothiazines and isoquinolines **2** were isomerized in the presence of sodium methoxide to the thermodynamically more stable form **9** (path **E**).[13]

The ring transformations of (2*R**,2a*S**)-2-chloro-2a-aryl-2,2a-dihydro-2*H*,4*H*-azeto[1,2-*a*][3,1]benzothiazin-1-ones **3** with sodium ethoxide in ethanol provided variously substituted (*R**)-3-ethoxycarbonyl-2-aryl-3,5-dihydro-4,1-benzothiazepines **10** and 3-ethoxycarbonyl-2-aryl-1,5-dihydro-4,1-benzothiazepines **11** (path **F**).[14] Surprisingly, the tautomers obtained could be separated by column chromatography and proved unexpectedly stable in solution; **10** and **11** exhibit the rare phenomenon of desmotropy.[14] As a continuation of such studies, we were interested in the reactivity of azeto[2,1-*b*][1,3]benzothiazin-1-ones **2**, and set out to investigate their reactions with sodium methoxide in methanol (path **G**).

Results and Discussion

For the preparation of 2,2a-diaryl-2,2a-dihydro-5,6-dimethoxy-1*H*,8*H*-azeto[2,1-*b*][1,3]benzothiazin-1-ones **13a–f** (Scheme 1), we subjected 2-aryl-2*H*-1,3-benzothiazines **12a–f** to the Staudinger reaction with substituted phenylacetyl chlorides in refluxing toluene. In these reactions, only one isomer was obtained selectively, as described earlier for **13a**.[15] Thus, isomers of **13a–f** were formed in which 2-Ar is *cis* to 2a-Ar. Treatment of **13a–f** with two equivalents of sodium methoxide in refluxing methanol in each case provided only one product, **17a–f**, as revealed by NMR spectroscopy.

As concerns the mechanism (Scheme 1), the first step in this reaction is most probably alcoholysis of the β-lactam ring[14] of **13**, resulting in diphenyl ester **14**. The thiazine ring of **14**

can be further transformed to the corresponding chain intermediate **15**. This latter imine **15** converts to an enamine, providing an acrylic acid derivative **16**, which is followed by oxidation to disulfide **17** by air.

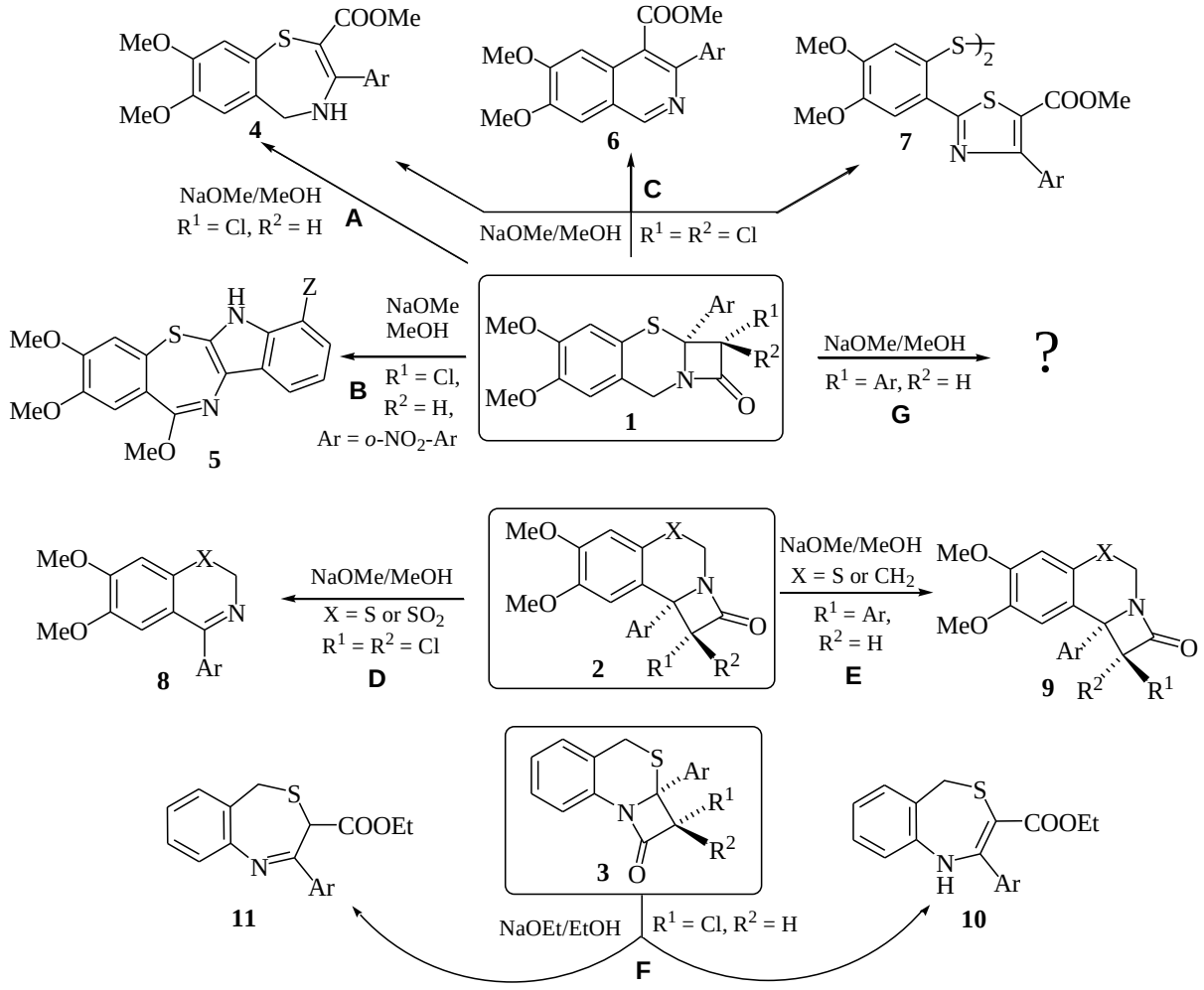


Figure 1. Transformations of various β-lactam-condensed 1,3-benzothiazines.

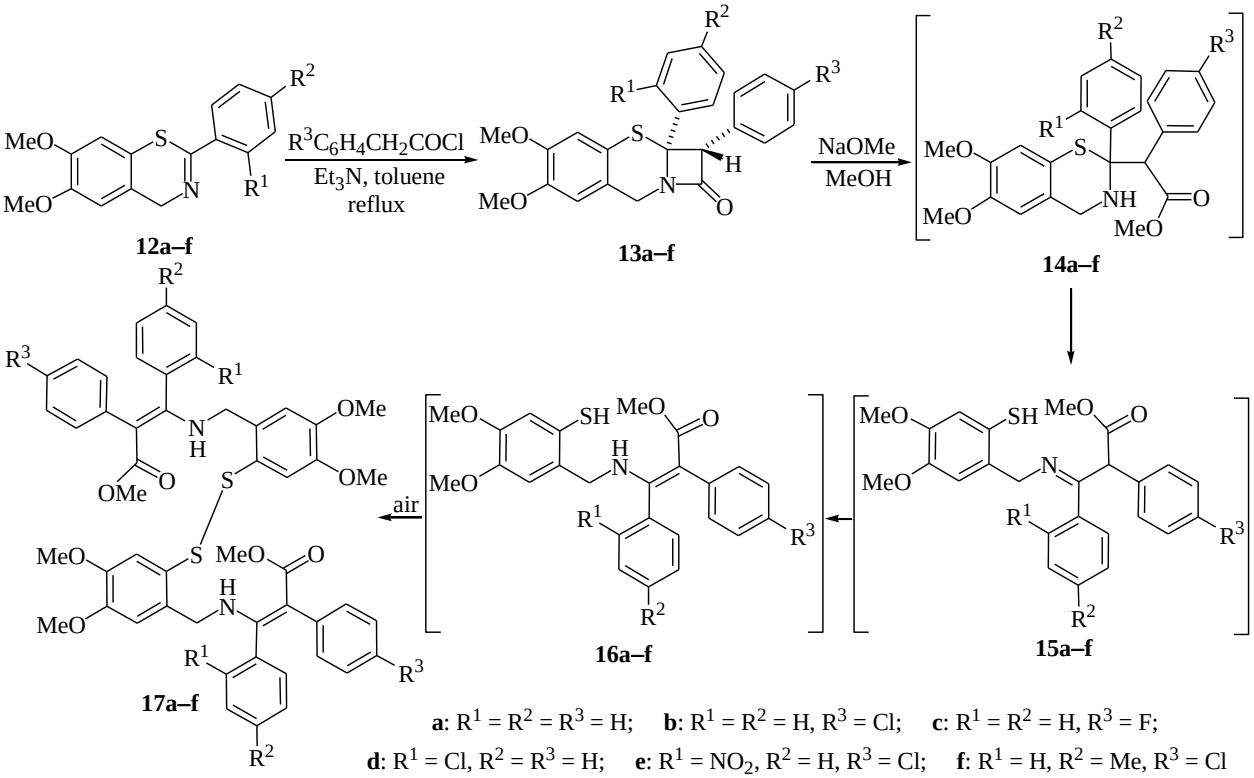
The IR, ^{1}H- and ^{13}C-NMR spectral data (Tables 1 and 2) furnish unambiguous proof of the presumed structures of the new compounds **13b–f** and **17a–f**. Merely the following comments are necessary.

The presence of the azetidinone ring in compounds of type **13** is obvious from the νC=O IR band in the expected interval,[16a] 1762–1777 cm^{-1}, and the carbon line with chemical shifts 169.0–170.1 ppm, also in accordance with the literature data.[17a]

The assignment of the carbon line and the position of the oxo group are confirmed by the cross peaks with the methylene hydrogens H's in the 2D-HMBC spectra.

The H-2 chemical shifts of **13d** and **13e** are higher (4.90 and 5.08 ppm) than those of **13b,c,f** (4.81–4.84 ppm) due to the *ortho* substituent on the benzene ring attached to C-2′. As a

consequence of the steric hindrance between the two aromatic rings (on C-2 and C-2′) the C-2 substituent is forced into an orientation in which H-2 is coplanar with the benzene ring on C-2. The parallel orientation of the benzene rings on C-2 and C-2′ and their position *cis* to the azetidinone ring are confirmed by the mutual anisotropic effects on the aromatic H's, as described earlier for **13a**.[15] As a consequence, the chemical shifts of the H's mentioned above are ~7 ppm for the *cis* isomers, while for the *trans* counterparts they are downfield-shifted by 0.55–0.70 ppm.



Scheme 1. Synthesis of 3-aminoacrylic acid derivatives.

Since the signals of the aromatic H's appear in the interval 6.78–7.16 in the spectra of **13b–f** (except for that on the C-2 nitro-substituted ring on C-2′ in **13e**, where the *–I* effect of the nitro group results in a significant downfield shift), the *cis* position of the two benzene rings is obvious.

The postulated open-chain structure of **17a–f** is proved by the characteristic spectral data on the carbomethoxy group: νC=O (ß-enaminoesters[18], ν_{as}C–O and ν_{s}C–O IR bands[16b] (1634–1638, 1249–1257 and 1039–1161 cm^{-1}), the OCH_3 singlet in the ^{1}H-NMR spectrum (3.61–3.64 ppm,[17b] for **17d** 3.48 ppm) and the carbon lines of the OMe and C=O groups (51.3–51.4 ppm[17c] and 170.2–171.1 ppm[17a]).

Further proof is given by the lines of the unsaturated carbons between the NH and the ester groups (C-2: 159.8–163.8 ppm and C-2′: 97.2–99.6 ppm) and the NH signal in the IR (3285–

3290 cm^{-1}) and in the ^{1}H-NMR spectrum (9.56–9.65 ppm), and also the couplings of the H's in the CH_2NH moiety, resulting in doublet and triplet splits, respectively, of the CH_2 and NH signals.

Table 1. Characteristic IR frequencies[a] and ^{1}H NMR data[b] of compounds **13b–f** and **17a–f**.[c,*]

Com-pound	νC=O band	$\gamma C_{Ar}H$ band[d]	$\gamma C_{Ar}H$ band[e]	$\gamma C_{Ar}H$ & $\gamma C_{Ar}C_{Ar}$[f]	OCH_3 Pos. 5	OCH_3 Pos. 6	NCH_2 2 x *d*[g]	CH[h] *s*	H-4 *s*	H-7 *s*	H-2′,6′ Aryl group[i]	H-3′,5′ Aryl group[i]	H-2′,6′ Aryl group[k]	H-3′,5′ Aryl group[k]	H-4′
13b	1774		804	749, 694	3.83	3.87	4.40, 5.04	4.83	6.69	6.72	6.92	7.07	7.16	7.11	7.08
13c	1773	867	828	726, 696	3.82	3.87	4.40, 5.04	4.84	6.69	6.72	6.95[l]	6.78[m]	7.15	7.09	7.06
13d	1777	874	741	741, 695	3.79	3.89	4.53, 5.11	4.90	6.66	6.78	7.00 – 7.15 *m* (9H)				
13e	1762	850	830	784	3.75	3.86	4.58, 5.14	5.08	6.52	6.70	7.00	7.04	7.37[n]	7.47[o]	7.30
13f	1773	870	794	766, 729	3.81	3.85	4.38, 5.02	4.81	6.68	6.70	6.93	7.08	7.04	6.89	–
17a	1637	866	–	766, 701	3.71	3.86	4.08	3.64	6.73	6.62	~7.12[p]	7.00	6.91	6.95[r]	~7.12[p]
17b	1635	861	792	773, 701	3.83	3.69	4.04	3.62	6.72	6.56	6.80	6.69	6.91	~7.13 *m* (3)	
17c	1634	862	806	773, 701	3.83	3.69	4.04	3.62	6.72	6.57	6.83[l]	6.67[m]	6.90	~7.12 *m* (3)	
17d	1637	865	752	764, 705	3.61	3.65	see[g]	3.48	6.76	6.45	6.92[p]	6.95[p]	7.01	7.30	7.18
17e	1648	868	821	791	3.70	3.89	3.93, 4.08	3.61	6.68	6.80	6.77	6.95	7.18[n]	7.85[o]	7.38
17f	1638	859	817	789, ~705	3.82	3.69	4.05	3.61	6.72	6.56	6.81	6.95	6.80	6.93	–

[*] The numbering of the **13**-type compounds was used also for **16a–f**.

[a] In KBr discs (cm^{-1}); [b] In $CDCl_3$ solution (DMSO-d_6 for **17d**) at 500 MHz. Chemical shifts in ppm (δ_{TMS} = 0 ppm), coupling constants in Hz. Further signals:

νNH IR band: 3285–3290 (**17a–e**) and 3275 cm^{-1} (**17f**); ν_{as}C–O and ν_sC–O IR bands (**17a–f**): 1249-1257 and 1039–1161 cm^{-1}; (Ar)CH_3: 2.18 (**13f**), 2.23 (**17f**); OCH_3: 3.64 (**17a**), 3.62 (**17b,c**), 3.48 (**17d**), 3.61 (**17e,f**); NH, *t* (1H): 9.65 (**17a–d,f**): 9.56 (**17e**); [c] Assignments were supported by HMQC (except for **13b**) and HMBC measurements (except for **17d**); [d] Condensed benzene ring; [e] *p*-, for **13d** and **17d** *o*-disubstituted ring; [f] Phenyl ring, for **13e** and **17e** $\gamma C_{Ar}H$ band of *o*-disubstituted ring. Two further bands at 783 and 738 cm^{-1} (**17a**); [g] 2 x *d* (2 x 1H), *J*: 16.1 (**13b,c,f**), 16.4 (**13d,e**), *d* (2H), *J*: 6.2 (**17a–c,f**, enamine), ~*s* (2H): ~3.72 (**17d**, imine), 2 x *dd* (2 x 1H), enamine: 3.66, 3.98 (**17d**), *J*: 14.7, 5.8 and 5.8 (**17e**); [h] 1H (**13b–f**), CH_3 (3H, ester group) for **17a–f**; [i]Attached to CH or COO; [k] Attached to $C_{quat.}$ or CNH; [l, m] *dd*, *t* (2 x 2H) due to ^3J(H,H) and ^4J(F,H), ^3J(F,H) couplings; [n] H-6′; [o] H–5′, H–3′: 7.88; [p] Overlapping signals; [r] In overlap with the H-4′ of Ar [i].

Table 2. ^{13}C NMR chemical shifts[a] of compounds **13b–f** and **17a–f**[b]

Com-pound	OCH_3 Pos.5,6	CH_2 Pos.8	C=O Pos.1	C-2	C-2'	C-3a	C-4	C-5	C-6	C-7	C-7a	C_{subst}(1′)	C_{ortho}	C_{meta}	C_{para}
						benzothiazine moiety[c]						aryl groups attached to the C-2', C-2			
13b	56.4, 56.5	43.4	169.0	70.8	71.2	122.5	113.0	149.0[d]	148.4[d]	111.6	121.2	138.4, 134.1	126.9, 130.85[e]	128.42, 128.9	128.37, 130.87[e]
13c	56.4, 56.5	43.4	169.2	70.8	71.3	122.5	113.0	149.0	148.4	111.6	122.5	138.5, 128.23[e]	127.0, 131.2[f]	128.3, 115.6 [f]	128.25[e], 162.5[f]
13d	56.4, 56.5	43.9	170.1	71.9	71.0	121.8[e]	112.9	149.1	148.3	111.3	121.8[e]	137.3, 132.3	129.5[d], 130.4	126.6, 128.09	128.3[d], 130.8[d]
13e	56.4, 56.5	43.6	169.3	71.7	70.5	121.1	112.7	149.1	149.5	111.1	119.9	136.0, 130.4	129.0, 131.8	133.6, 128.7	129.7, 134.5
13f	56.4, 56.5	43.3	169.0	70.8	71.2	122.4	113.0	149.0	148.4	111.6	121.3	138.5, 134.0	126.9, 130.9	129.2, 128.9	138.1, 131.0
17a	56.3, 56.4	47.0	171.1	163.7	99.6	126.3	118.2	148.3	150.6	112.0	135.5	135.0, 138.1	133.1, 128.1	129.6, 127.4	128.5, 125.6
17b	56.30, 56.35	47.0	170.7	163.7	98.2	126.4	118.2	148.4	150.6	112.0	135.2	134.7, 136.7	129.4, 134.3	128.8, 127.6	125.3, 131.4
17c	56.3, 56.4	47.0	170.9	163.8	98.3	126.4	118.2	148.4	150.6	112.0	135.3	134.8, 134.0[f]	129.4, 134.4[f]	128.2, 114.2[f]	128.6, 161.0[f]
17d	56.3, 56.8	47.6	170.2	159.9	97.4	126.3[e]	118.6	148.7[g]	148.7[g]	113.6	134.2[h]	134.2,[h] 138.3	132.0, 132.6	127.4, 127.8	131.0, 126.3[e]
17e	56.4, 56.5	47.3	170.4	159.8	97.2	126.2	118.4	148.6	151.0	112.2	134.4	131.9, 135.7	133.6[e]	130.3, 128.1	124.9, 132.3
17f	56.25, 56.34	47.0	170.7	164.0	98.1	126.4	118.2	148.4	150.5	112.1	135.3	131.7, 136.9	129.3, 134.3	129.0, 127.6	138.6, 131.3

[a] In ppm (δ_{TMS} = 0 ppm) at 125.7 MHz. Solvent: $CDCl_3$ (DMSO-d_6 for **17d**). Further signals, CH_3: 21.4 (**13f**), 21.6 (1**7f**); (COO)CH_3: 51.3 (**17a–d, f**), 51.4 (**17e**); 2′-Ar, C–2: 131.9 (**13d**), 132.5 (**17d**), C-3: 128.05 (**13d**), 129.8 (**17d**); [b] Assignments were supported by DEPT, 2D-HMQC (except for **13b**) and 2D-HMBC (except for **17d**) measurements; [c] This numbering was used also for compounds **17a–f**; [d] Reversed assignments is also possible; [e, g, h] Two overlapping lines; [f] Due to C,F-coupling *d* [Hz], ^1J: 247.0 **13c**), 244.4 (**17c**), ^2J: 21.7 (**13c**), 21.1 (**17c**), ^3J: 8.3 (**13c**), 7.9 (**17c**), ^4J: < 1 (**13c**), 3.5 (**17c**).

Due to free rotation around the S–S and C–N bonds the methylene H's are chemically equivalent in the compounds of type **17** in contrast with **13b–f**. The only exception is **17e**, in which the *ortho*-nitro substituent hinders this motion and the methylene H's become non-equivalent in this crowded molecule.

It should be noted that **17b** is poorly soluble in $CDCl_3$ and we measured the NMR spectra in DMSO-d_6. In this solution, a better-soluble contamination gives well-identifiable signals in the ^{1}H-NMR spectrum.

Conclusions

The reactions of diarylazeto[2,1-*b*][1,3]benzothiazin-1-one derivatives with sodium methoxide in methanol provided *N*-substituted 3-aminoacrylic acid derivatives in *Z* forms. The reactivity of β-lactams **13a–f** in the presence of base differs from that of other isomeric lactams investigated earlier.[9–15]

Experimental Section

General. Melting points were determined on a Kofler micro melting apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyzer. The mass spectra were recorded in the interval 200-2200 m/z on an Agilent 1100 LCMSD trap instrument equipped with an electrospray source.

Merck Kieselgel 60F_{254} plates were used for TLC, and Merck Silica gel 60 (0.063-0.100) for column chromatography. Substituted phenylacetyl chloride derivatives were purchased from Aldrich. 1,3-Benzothiazines **12a**–**f**[19] and β-lactam **13a**[15] were prepared earlier.

The ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution in 5-mm tubes at room temperature, on a Bruker DRX 500 spectrometer at 500 (^{1}H) and 126 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The standard Bruker micro program NOEMULT.AU to generate NOE was used with a selective preirradiation time. DEPT spectra were run in a standard manner, using only the $\Theta = 135^{o}$ pulse to separate CH/CH_3 and CH_2 lines phased "up" and "down", respectively. The 2D-HSC and HMBC spectra were obtained by using the standard Bruker pulse programs.

General procedure for diaryl β-lactam derivatives (13b–f)

1,3-Benzothiazines **12b**–**f** (5 mmol) were dissolved in toluene (30 ml), followed by addition of the appropriate substituted phenylacetyl chloride (5 mmol). The mixture was refluxed, and a solution of triethylamine (0.50 g, 5 mmol) in toluene (30 ml) was added dropwise, with stirring, during 1 h. The crystalline triethylamine hydrochloride was removed by filtration, the toluene solution was evaporated and the residue was crystallized and recrystallized from ethanol to obtain white crystals.

2-(4-Chlorophenyl)-2a-phenyl-2,2a-dihydro-5,6-dimethoxy-1*H*,8*H*-azeto[2,1-*b*][1,3]benzothiazin-1-one (13b). White crystalline powder, m.p.: 170–173 °C (from EtOH); yield 92%. Anal. Calcd. for $C_{24}H_{20}ClNO_3S$ (437.94): C, 65.82; H, 4.60; N, 3.20; S, 7.32. Found: C, 65.66; H, 4.72; N, 3.45; S, 7.50. MS(ESI+) $[M+1]^+ = 438.0$

2-(4-Fluorophenyl)-2a-phenyl-2,2a-dihydro-5,6-dimethoxy-1*H*,8*H*-azeto[2,1-*b*][1,3]benzothiazin-1-one (13c). White crystalline powder, m.p.: 163–165 °C (from EtOH); yield 95%. Anal. Calcd. for $C_{24}H_{20}FNO_3S$ (421.48): C, 68.39; H, 4.78; N, 3.32; S, 7.61. Found: C, 68.58; H, 4.85; N, 3.52; S, 7.38. MS(ESI+) $[M+1]^+ = 422.0$

2a-(2-Chlorophenyl)-2-phenyl-2,2a-dihydro-5,6-dimethoxy-1*H*,8*H*-azeto[2,1-*b*][1,3]benzothiazin-1-one (13d). White crystalline powder, m.p.: 222–225 °C (from EtOH); yield 90%. Anal. Calcd. for $C_{24}H_{20}ClNO_3S$ (437.94): C, 65.82; H, 4.60; N, 3.20; S, 7.32. Found: C, 65.58; H, 4.80; N, 3.48; S, 7.55. MS(ESI+) $[M+1]^+$ = 438.0

2-(4-Chlorophenyl)-2a-(2-nitrophenyl)-2,2a-dihydro-5,6-dimethoxy-1*H*,8*H*-azeto[2,1-*b*][1,3]benzothiazin-1-one (13e). White crystalline powder, m.p.: 226–230 °C (from EtOH); yield 92%. Anal. Calcd. for $C_{24}H_{19}ClN_2O_5S$ (482.94): C, 59.69; H, 3.97; N, 5.80; S, 6.64. Found: C, 59.42; H, 4.11; N, 6.02; S, 6.87. MS(ESI+) $[M+1]^+$ = 483.0

2-(4-Chlorophenyl)-2a-(4-methylphenyl)-2,2a-dihydro-5,6-dimethoxy-1*H*,8*H*-azeto[2,1-*b*][1,3]benzothiazin-1-one (13f). White crystalline powder, m.p.: 139–142 °C (from EtOH); yield 94%. Anal. Calcd. for $C_{25}H_{22}ClNO_3S$ (451.97): C, 66.44; H, 4.91; N, 3.10; S, 7.10. Found: C, 66.73; H, 5.18; N, 2.86; S, 7.36. MS(ESI+) $[M+1]^+$ = 452.0

General procedure for 3-aminoacrylic acid derivatives (17a–f)

Azeto-1,3-thiazines **13a–f** (2.8 mmol) were dissolved in dry methanol (100 ml). To this stirred solution, sodium methoxide (300 mg, 5.6 mmol) was added and the reaction mixture was stirred under reflux for 2 h. After evaporation to 30 ml, the solution was left to stand overnight at room temperature. The crystals that separated out were filtered off and recrystallized from methanol to give 3-aminoacrylic acid derivatives **17a**–**f** as white crystalline products.

2,2′-Di-[(*Z*-1″,2″-diphenyl-2″-methoxycarbonylvinyl)aminomethyl]-4,4′,5,5′-tetramethoxydiphenyl disulfide (**17a**). White crystalline powder, m.p.: 159–161 °C (from MeOH); yield 75%. Anal. Calcd. for $C_{50}H_{48}N_2O_8S_2$ (869.06): C, 69.10; H, 5.57; N, 3.22; S, 7.38. Found: C, 68.82; H, 5.75; N, 3.48; S, 7.62. MS(ESI+) $[M+1]^+$ = 869.2; $[M+K]^+$ = 907.2

2,2′-Di-[(*Z*-1″-phenyl-2″-(4-chlorophenyl)-2″-methoxycarbonylvinyl)aminomethyl]-4,4′,5,5′-tetramethoxydiphenyl disulfide (**17b**). White crystalline powder, m.p.: 181–184 °C (from MeOH); yield 82%. Anal. Calcd. for $C_{50}H_{46}Cl_2N_2O_8S_2$ (937.95): C, 64.02; H, 4.94; N, 3.00; S, 6.84. Found: C, 64.41; H, 5.17; N, 3.09; S, 7.11. MS(ESI+) $[M+1]^+$ = 937.1; $[M+K]^+$ = 975.2

2,2′-Di-[(*Z*-1″-phenyl-2″-(4-fluorophenyl)-2″-methoxycarbonylvinyl)aminomethyl]-4,4′,5,5′-tetramethoxydiphenyl disulfide (**17c**): White crystalline powder, m.p.: 178–181 °C (from MeOH); yield 79%. Anal. Calcd. for $C_{50}H_{46}F_2N_2O_8S_2$ (905.04): C, 66.35; H, 5.12; N, 3.10; S, 7.09. Found: C, 66.12; H, 5.44; N, 3.28; S, 7.31. MS(ESI+) $[M+1]^+$ = 905.2; $[M+K]^+$ =943.2

2,2′-Di-[(*Z*-1″-(2-chlorophenyl)-2″-phenyl-2″-methoxycarbonylvinyl)aminomethyl]-4,4′,5,5′-tetramethoxydiphenyl disulfide (**17d**). White crystalline powder, m.p.: 217–220 °C (decomp.) (from MeOH); yield 74%. Anal. Calcd. for $C_{50}H_{46}Cl_2N_2O_8S_2$ (937.95): C, 64.02; H, 4.94; N, 3.00; S, 6.84. Found: C, 64.15; H, 5.24; N, 3.18; S, 7.02. MS(ESI+) $[M+1]^+$ = 937.1; $[M+K]^+$ =975.2

2,2′-Di-[(*Z*-1″-(2-nitrophenyl)-2″-(4-chlorophenyl)-2″-methoxycarbonylvinyl)aminomethyl]-4,4′,5,5′-tetramethoxydiphenyl disulfide (**17e**). White crystalline powder, m.p.: 216–220 °C (decomp.) (from MeOH); yield 71%. Anal. Calcd. for

$C_{50}H_{44}Cl_2N_4O_{12}S_2$ (1027.94): C, 58.42; H, 4.31; N, 5.45; S, 6.24. Found: C, 58.28; H, 4.60; N, 5,71; S, 6.33. MS(ESI+) $[M+1]^+$ = 1027.2; $[M+Na]^+$ = 1049.2

2,2′-Di-[(*Z*-1″-(4-methylphenyl)-2″-(4-chlorophenyl)-2″-methoxycarbonylvinyl)amino-methyl]-4,4′,5,5′-tetramethoxydiphenyl disulfide (**17f**). White crystalline powder, m.p.: 212–215 °C (decomp.) (from MeOH); yield 69%. Anal. Calcd. for $C_{52}H_{50}Cl_2N_2O_8S_2$ (966.00): C, 64.65; H, 5.22; N, 3.00; S, 6.64. Found: C, 64.49; H, 5.41; N, 3.20; S, 6.86. MS(ESI+) $[M+1]^+$ = 965.2; $[M+K]^+$ = 1004.2.

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