A Convenient Synthesis of 1,4-Benzothiazepines from 1,3-Benzothiazines via the Ring Transformation of β-Lactam-Condensed 1,3-Benzothiazine Derivatives

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Abstract: A convenient synthesis was devised for rare 2,3-disubstituted 4,5-dihydro-1,4-benzothiazepines from 2-aryl-4*H*-1,3-benzothiazines. The Staudinger reaction of 1,3-benzothiazines obtained with chloroacetyl chloride selectively furnished *trans*-monochloro-β-lactam-condensed thiazines. The ring expansion of azeto[2,1-*b*][1,3]benzothiazin-1-one derivatives with sodium methoxide afforded 1,4-benzothiazepines as the sole product in good yields. The structures of the new molecules were proved by means NMR and IR spectroscopy.

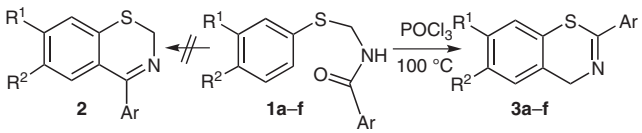
Key words: 1,4-benzothiazepine, 1,3-benzothiazine, β-lactams, ring expansion, S,N-heterocycles

During recent years, increased attention has been focused on the synthesis of condensed S,N-heterocycles.[1] Several representatives of this group are bioisosteres of various alkaloids or drugs, e.g. 1,3-benzothiazine derivatives are analogues of isoquinoline alkaloids and 1,4-benzothiazepines related to the well-known 1,4-benzodiazepine family of drugs, and a broad range of pharmacological effects have been observed for these heterocycles. Besides 1,3-benzothiazines, which exhibit a wide variety of pharmacological effects,[2–5] 1,4-benzothiazepines exert bile acid absorption inhibitory activity,[6] antidepressant activity,[7] anti-arrhythmic activity,[8] and reversal of P-glycoprotein-mediated multidrug resistance.[9]

2,3,4,5-Tetrahydro-1,4-benzothiazepine derivatives can be prepared relatively easily from the corresponding bifunctional thioamide or aminothiol derivatives.[10] On the other hand, there are only rare examples of the synthesis of 4,5-dihydro-1,4-benzothiazepines.[11–13]

In the course of our recent studies on S- and N-containing condensed-skeleton heterocycles,[14–16] we prepared and isolated 2,3-disubstituted 4,1-benzothiazepines: ethyl 2-phenyl-3,5-dihydro-4,1-benzothiazepine-3-carboxylate and ethyl 2-phenyl-1,5-dihydro-4,1-benzothiazepine-3-carboxylate, which are in a tautomeric relationship with each other.[17] Surprisingly, these 4,1-benzothiazepines could be separated by column chromatography and they manifested the rare phenomenon of desmotropy. As a continuation, our present aim was to devise a convenient and general procedure for differently substituted 4,5-dihydro-1,4-benzothiazepines and to investigate their structures in order to reveal possible desmotropy.

In the synthesis of the starting thiazines, {[(benzoylamino)methyl]sulfanyl}benzene derivatives **1a–f** were treated with phosphorus oxychloride (Scheme 1). Interestingly, instead of the expected Bischler–Napieralski products, the 4-aryl-2*H*-1,3-benzothiazines **2**, which could be isolated in trace amounts only, the isomeric 2-aryl-2*H*-1,3-benzothiazine derivatives **3a–f** were formed in moderate yields. The mechanism can be explained via an intermediate formed by proton-catalyzed intermolecular rearrangement of acid amide-thioether-type compounds to the *N*-aroyl-2-sulfanylbenzylamine, followed by ring closure to the benzothiazine.[18]



a Ar = 4-BrC_6H_4
b Ar = 3-BrC_6H_4
c Ar = 3,4,5-$(MeO)_3C_6H_2$
d Ar = 4-ClC_6H_4
e Ar = 4-FC_6H_4
f Ar = 4-MeC_6H_4

a–c $R^1 = R^2$ = MeO
d–f R^1 = H, R^2 = Me

Scheme 1

The reaction most widely used for the construction of azetidinone rings is [2+2] ketene–imine cycloaddition, the Staudinger reaction.[19] For our target β-lactams **4a–f**, we set out to use this process. The reaction of **3a** with chloroacetyl chloride in refluxing toluene furnished azeto[2,1-*b*][1,3]benzothiazin-1-one derivative **4a** in good yield (Table 1). Compounds **4b–f** were obtained under similar conditions.

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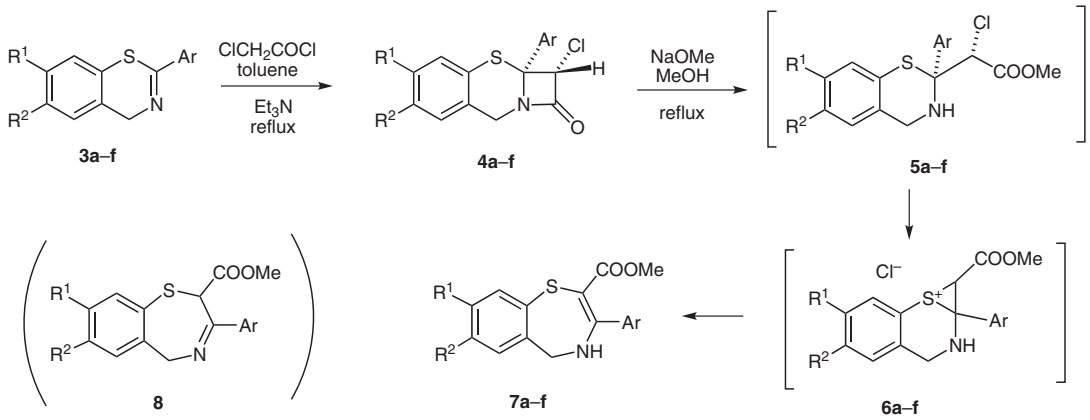
Table 1 Synthesis of 1,4-Benzothiazines from 1,3-Benzothiazines via the Ring Transformation of β-Lactam-Condensed 1,3-Thiazine Derivatives



Entry	Ar	R^1	R^2	Thiazine	Yield (%)	β-Lactam	Yield (%)	Thiazepine	Yield (%)
1	4-BrC_6H_4	OMe	OMe	**3a**	41	**4a**	92	**7a**	83
2	3-BrC_6H_4	OMe	OMe	**3b**	37	**4b**	90	**7b**	85
3	3,4,5-$(MeO)_3C_6H_2$	OMe	OMe	**3c**	ref. 23	**4c**	95	**7c**	82
4	4-ClC_6H_4	H	Me	**3d**	ref. 14	**4d**	ref. 14	**7d**	85
5	4-FC_6H_4	H	Me	**3e**	16	**4e**	90	**7e**	89
6	4-MeC_6H_4	H	Me	**3f**	12	**4f**	87	**7f**	79

The reactions of monochloro-β-lactam derivatives **4a–f** with sodium methoxide in dry methanol at reflux temperature in each case afforded only one product **7a–f** (Table 1). NMR investigations demonstrated only the presence of the enamine tautomer of 4,5-dihydro-1,4-benzothiazepines. In contrast with the 4,1-benzothiazepine derivatives, desmotropy was not observed for 1,4-benzothiazepines.[17b]

In this reaction, the first step is most probably alcoholysis of the β-lactam ring of **4a–f**, resulting in α-chloro esters **5a–f**, which lead to the products **7a–f** through episulfonium salt **6a–f** after elimination of HCl (Table 1).

The IR and ^1H and ^{13}C NMR spectral data given in Tables 2 and 3 offer unambiguous proof of the presumed structures.

The presence of the azetidinone ring in **4a–c**,**e**,**f** is obvious from the C=O IR frequency in the expected region[20] between 1774 and 1791 cm^{-1} and from the presence of the carbonyl line in the ^{13}C NMR spectra (δ = 164.6–165.2) in the region of chemical shifts characteristic of β-lactams.[21a] The molecular asymmetry caused by the condensed ring leads to chemical non-equivalence (2 d) of CH_2 protons in the **4**-type compounds, in contrast with the symmetric starting compounds of type **3**, where the CH_2 signal is a singlet (at δ = 4.75 ± 0.02). One of the methylene protons in **4a–c**,**e**,**f** is more shielded (δ = 4.22–4.30) than the other (δ = 4.94 ± 0.02), and also than those in **3a**,**b**,**e**,**f**, due to anisotropy of the aromatic ring[21b] at C2a.

Concerning the *cis*- or *trans*-position of the substituents on the azetidinone ring (2-Cl and 2a-Ar), the identical ^{13}C NMR chemical shifts of the three carbons in the four-membered ring of **4a** to those for the Ar = Ph analogue[22] confirm the *trans*-position of the substituents (*cis*-orientation of the 2-Cl and 2a-Ar groups). In accord with our earlier results,[22] the proof of this arrangement of the substituents was provided by comparison of the ^1H NMR chemical shifts of the protons of the aryl group in the 2-chloro and 2-phenyl analogues. The mutual anisotropic shielding of the two benzene rings in the 2,2a-diphenyl compounds revealed in dramatic upfield shifts (0.55 and 0.70 ppm) of the protons in both rings.

Since the ^{13}C NMR shifts of the azetidinone carbons did not change more than expected as a consequence of the difference in the substitution, the analogous stereostructure was obvious. The same holds for compounds **4a–c**,**e**,**f**.

It should be noted that, as H2 lies on the opposite side of the four-membered ring from the aryl group, NOE could not be expected between them. Thus, NOE measurements could only provide negative results on the structural problem in question.

The analogous stereostructure of the **4**-type molecules follows straightforwardly from the very similar ^1H and ^{13}C NMR chemical shifts of the CHCl group (δ = 5.12 ± 0.03 and 68.8 ± 0.5, respectively).

As concerns the tautomerism/desmotropy of **7a–f**, they are all in the enamine tautomeric form, as confirmed by

Table 2 Characteristic IR and ^{1}H NMR Data of Compounds **3a**,**b**,**e**,**f**, **4a–c**,**e**,**f**, and **7a–f**

3, **4**, **7**	IR[a] (KBr, cm^{-1})				^{1}H NMR[b–d] δ									
	N–H	C=O	C_{Ar}–H[e]	C_{Ar}–H[f]	CH_2 (s or 2 d, 2 H)[g]	6,7-OMe (2 s, 6 H)[h]	CHCl (s, 1 H)	H5 (1 H)	H8 (1 H)	H7 (1 H)	H2′, H6′ (d, 2 H)[i]	H3′, H5′ (d/t, 2 H)	H4′ (dd, 1 H)	NH (t, 1 H)
3a	–	–	855	810[j]	4.73	3.90, 3.91	–	6.86 (s)	6.88 (s)	–	7.87	7.57	–	–
3b	–	–	856	765	4.75	3.91, 3.92	–	6.86 (s)	6.88 (s)	–	8.17	7.31[k]	7.60	–
3e	–	–	837	814	4.75	2.38	–	7.17 (~s)	7.27[l]	7.13[m]	8.01	7.11[m]	–	–
3f	–	–	759	815	4.76	2.41	–	7.17 (~s)	7.28[l]	7.12 (~d)	7.90	7.24	–	–
4a	–	1791	849	810	4.28, 4.94	3.83, 3.85	5.11	6.68 (s)	6.67 (s)	–	7.33	7.51	–	–
4b	–	1782	857	806	4.30, 4.95	3.86, 3.85	5.11	6.69 (9 s)	6.69(6 s)	–	7.61	7.27[k]	7.49	–
4c	–	1774	848	815	4.22, 4.92	3.84, 3.85	5.09	6.69 (s)	6.76 (s)	–	6.66	3.87[n]	3.85[n]	–
4e	–	1776	846	829	4.30, 4.96	2.30	5.12	7.02 (~s)	7.12[l]	7.01 (~d)	7.45	7.08[o]	–	–
4f	–	1782	757	819	4.30, 4.96	2.30	5.14	7.01[m]	7.12[l]	7.00[m]	7.35	7.21	–	–
7a	3253	1656	877	831	4.78	3.77, 3.78	–	6.96 (s)	7.05 (s)	–	7.04	7.48	–	7.13
7b	3277	1685	860	756	4.88	3.86, 3.88	–	6.78 (s)	7.16 (s)	–	7.32	7.15[k]	7.42	4.52
7c	3278	1653	863	863	4.90	3.86, 3.88	–	6.74 (s)	7.14 (s)	–	6.40	3.76[n]	3.80[n]	4.63
7d	3292	1645	759	815	4.80	2.30	–	~7.12[m]	~7.35[p]	~7.15[m]	~7.34[p]	~7.11[m]	–	~7.11[m]
7e	3290	1659	758	837	4.80	2.30	–	~7.12[m]	7.35[l]	~7.12[m]	7.09–7.15	–[m]	–	7.12[m]
7f	3381	1660	752	817	4.78	2.30	–	7.11 (~s)	7.34[l]	7.13 (~d)	6.98	7.10	–	7.02

[a] Further bands, C=N: 1 or 2 two strong–medium bands between 1499–1602; C–O: 2–4 strong bands between 1282–1046.
[b] The numbering of **3a–f** was used such that protons have retained the same number in **4a–f** and **7a–f**.
[c] In $CDCl_3$ or DMSO-d_6 (**7a**,**d–f**) soln at 500 MHz. Further signals: Ar-CH_3 (s, 3 H): 2.38 (**3f**), 2.36 (**4f**), 2.29 (**7f**); OCH_3 (ester group) (s, 3 H): 3.25 (**7a**,**d**), 3.40 (**7c**), 3.22 (**7e**), 3.20 (**7f**).
[d] Assignments were supported by HMQC and HMBC (except for **3b**) measurements.
[e] Benzothiazine or benzothiazepine ring.
[f] Ar substituent.
[g] 2 × 1 H for **4**-type compounds, 2 × d and d for **4**- and **7**-type compounds, respectively, J = 16.2 Hz (**4a**,**b**), 16.5 Hz (**4c**,**e**,**f**), 5.2 ± 0.1 Hz (**7a**,**d–f**), 5.6 Hz (**7c**).
[h] 6-CH_3 for **d**,**e**,**f**-type compounds.
[i] A part of an AA′BB′ spectrum (for **a**,**d–e**-type compounds), H2′ signal for **b**-type compounds (t, J = 1.8 Hz) (**3b**, **4b**, **7b**), (dd, $^3J_{H,H}$ and $^4J_{F,H}$ = 8.8 and 5.4 Hz) (**3e**), (dd, $^3J_{H,H}$ and $^4J_{F,H}$ = 8.5 and 5.2 Hz) (**4e**), (s, 2 H) (**4c** and **7c**); H6′: (~d, J = 8.0 Hz) (~d, J = 7.92 Hz) (**3b**), (~d, J = 7.39 Hz) (**4b**), (~d, J = 7.10 Hz (**7b**).
[j] Split band with the second maximum at 826 (**3a**), 1633 (**7e**).
[k] H5′ (t, 1 H).
[l] (d, J = 7.8 ± 0.1).
[m] Overlapping signals.
[n] OCH_3: 3′-OCH_3, 5′-OCH_3 (s, 6 H), 4′-OCH_3 (s, 3 H).
[o] For **4e** t, $^3J_{H,H}$ and $^3J_{F,H}$ couplings of similar values.
[p] Overlapping signals.

the presence of (a) NH signals in the IR and ^{1}H NMR spectra, (b) the doublet and triplet split of the CH_2 and NH ^{1}H NMR signals, respectively, (c) the ^{13}C NMR shifts of the olefinic carbons (S–C= and NH–C=) in the azepine ring in the expected regions (δ = 86.5–91.5 and 155.8–159.2, respectively), and (d) the absence of a methine ^{13}C NMR line (SCH group), as proved by DEPT measurement. It is worthy of note that the methylene protons in the azepine ring of **7a–f** are chemically equivalent, demonstrating a fast inversion of the seven-membered ring in these compounds.

In summary, we report a convenient and general synthesis for a rare ring system, 2,3-disubstituted 4,5-dihydro-1,4-benzothiazepines, from 2-aryl-4*H*-1,3-benzothiazines. The Staudinger reactions of 1,3-benzothiazines with chloroacetyl chloride provided condensed thiazines selectively, in which the 2a-aryl is *cis* to the 2-chloro substituent. The ring expansion reactions of azeto[2,1-*b*][1,3]benzothiazin-1-one derivatives with sodium methoxide yielded 1,4-benzothiazepines, in each case as a single product with an enamine structure in good yield.

Table 3 ^{13}C NMR Chemical Shifts[a,b] (δ) of Compounds **3a**,**b**,**e**,**f**, **4a**–**c**,**e**,**f**, and **7a**–**f**[c]

3,**4**,**7**	6-Me	6,7-OMe[d]	4-CH_2	CH or C_q[e]	C=O[f]	Benzothiazine/benzothiazepine[a]							Aryl group[j]			
						C=N[g]	C4a	C5	C6	C7	C8	C8a	C1′	C_o[h]	C_m[i]	C_p
3a	–	56.6[k]	57.0	–	–	161.4	123.6	110.6	149.5	149.2	110.0	121.7	136.3	129.6	132.1	126.1
3b	–	56.60, 56.61	57.0	–	–	161.0	123.5	110.6	149.5	149.2	110.0	121.7	139.3	131.1	123.1	134.3
3e	21.5	–	57.1	–	–	161.2	131.6	128.0	138.0	128.8	126.8	127.7	133.7	130.2	115.9	165.1
3f	21.8	21.5	57.1	–	–	162.2	131.8	127.9	137.8	128.7[k]	126.8	128.7[k]	134.9	128.1	129.6	141.8
4a	–	56.46, 56.48	43.4	68.3	164.6	71.2	121.9	111.6	148.7	149.2	112.9	120.1	136.2	121.1	132.0	123.7
4b	–	56.5[k]	43.5	68.5	164.6	71.0	122.1	111.6	148.7	149.3	112.9	120.1	139.4	130.42	123.1	132.6
4c	–	56.5	43.5	69.1	165.2	72.0	122.7	111.6	148.6	149.3	112.8	120.7	132.3	104.8	153.6	139.0
4e	21.3	–	43.6	68.9	164.8	71.3	129.9	129.6	137.5	129.3[l]	130.0	126.3	132.9	129.2[l]	115.9	163.3
4f	21.3	21.6	43.6	69.2	165.0	71.8	130.1	129.2	137.2	129.5	129.9	126.7	134.1	127.2	129.6	139.3
7a	–	51.5,[m] 56.6[k]	48.4	87.2	167.7	158.0	136.3	113.3	149.6	149.2	116.0	129.5	140.7	130.6	131.6	122.4
7b	–	51.9,[m] 56.6[k]	49.3	91.5	167.9	155.8	135.5	111.8	149.5	149.3	116.1	129.4	143.3	130.7	122.4	132.1
7c	–	51.9,[m] 56.6[k]	49.3	90.6	168.5	157.1	135.6	111.9	149.4	149.2	116.0	129.7	137.0	105.1	153.3	138.8
7d	21.6	51.5[m]	48.8	87.1	167.6	158.0	143.3	129.9	139.3	130.1	132.2	135.4	133.8	128.7	130.4	140.2
7e	21.6	51.5[m]	48.8	87.0	167.8	158.1	143.3	129.9	139.2	130.1	132.2	135.5	137.7	130.7	115.5	163.0
7f	21.63[l]	21.67,[l] 51.4[m]	48.8	86.5	168.0	159.2	143.3	130.0[l]	139.1[n]	129.9[l]	132.1	135.8	138.6[n]	128.4	129.2	138.4[n]

[a] The numbering of **3a**–**f** was used such that carbons have retained the same number in **4a**–**f** and **7a**–**f**.
[b] 125.7 MHz. Solvent: $CDCl_3$/TMS or DMSO-d_6/TMS (**7a**,**d**–**f**).
[c] Assignments were supported by DEPT (except for **3e**), HMQC and HMBC (except for **3b**) measurements.
[d] ArCH_3 for **f**-type compounds OCH_3 (Ar): 56.8 (**4c**) and 56.54 (**7c**)[k] (3′-OCH_3, 5′-OCH_3), 61.2 (**4c**, **7c**, 4′-OCH_3).
[e] SC= for **4**-type compound.
[f] Azetidinone or ester group for **4**- and **7**-type compounds, respectively.
[g] SC_qN (**4a**–**c**,**e**,**f**), NHC= (**7a**–**f**).
[h] C2′, C6′: 126.7 (**3b**), 126.1, (**4b**), 126.7 (**7b**).
[i] C3′, C5′: 130.4 (**3b**), 130.37, (**4b**), 130.1 (**7b**).
[j] Doublets for **3e**, **4e**, and **7e** due to C,F-couplings, ^1J = 251.1 Hz (**3e**), 248.4 Hz (**4e**), 244.9 Hz (**7e**), ^2J = 22.0 Hz (**3e**, **4e**), 21.8 Hz (**7e**), ^3J = 9.2 Hz (**3e**), 8.3 Hz (**7e**), ^4J = <1 Hz (**3e**), 2.8 Hz (**4e**, **7e**).
[k] Two overlapping lines.
[l] Reversed assignments are also possible.
[m] Ester group.
[n] Reversed assignments are also possible.

Melting points were determined on a Kofler micromelting apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyzer in the Institute of Pharmaceutical Chemistry. Merck Kieselgel $60F_{254}$ plates were used for TLC, and Merck silica gel 60 (0.063–0.100) for column chromatography. Chloroacetyl chloride was purchased from Fluka. Substituted (hydroxymethyl)benzamides, {[(benzoylamino)methyl]sulfanyl}benzene derivatives **1a**–**f**, 1,3-benzothiazines **3c**,**d**, and azetobenzothiazin-1-one **4d** were prepared by literature methods.[14,23]

IR spectra were recorded in KBr pellets with a Bruker IFS 55 FT-spectrophotometer. ^1H and ^{13}C NMR spectra were recorded (DMSO-d_6 soln, 5-mm tubes, r.t., TMS internal reference, $CDCl_3$ lock) on a Bruker DRX 500 spectrometer at 500 (^1H) or 125 (^{13}C) MHz. Assignments are supported by DEPT, HMQC and HMBC measurements. DEPT spectra were run in a standard manner, using only the Θ = 135° pulse to separate CH/CH_3 and CH_2 lines phased 'up' and 'down', respectively. 2D-HMQC and 2D-HMBC spectra were obtained by using the standard Bruker pulse programs.

4*H*-1,3-Benzothiazine Derivatives 3a,b,e,f; General Procedure

Substituted *N*-{[(3,4-dimethoxyphenyl)sulfanyl]methyl}benzamides (33 mmol) were heated with $POCl_3$ (10 mL) on a boiling water bath for 1 h. The mixture was cooled and then the reaction was treated with ice, neutralized with Na_2CO_3, and extracted with toluene. The combined toluene extracts were dried (Na_2SO_4) and the

solvent was evaporated off. The residue was dissolved in hot EtOH (6 mL) and crystallized.

2-(4-Bromophenyl)-6,7-dimethoxy-4*H*-1,3-benzothiazine (3a)
White crystalline powder; mp 119–120 °C.

Anal. Calcd for $C_{16}H_{14}BrNO_2S$ (364.26): C, 52.76; H, 3.87; N, 3.85; S, 8.80. Found: C, 52.58; H, 3.79; N, 3.94; S, 8.90.

2-(3-Bromophenyl)-6,7-dimethoxy-4*H*-1,3-benzothiazine (3b)
White crystalline powder; mp 101–102 °C.

Anal. Calcd for $C_{16}H_{14}BrNO_2S$ (364.26): C, 52.76; H, 3.87; N, 3.85; S, 8.81. Found: C, 52.82; H, 3.98; N, 3.92; S, 8.93.

2-(4-Fluorophenyl)-6-methyl-4*H*-1,3-benzothiazine (3e)
White crystalline powder; mp 107–108 °C.

Anal. Calcd for $C_{15}H_{12}FNS$ (257.33): C, 70.01; H, 4.70; N, 5.44; S, 12.46. Found: C, 69.82; H, 4.56; N, 5.68; S, 12.70.

2-(4-Methylphenyl)-6-methyl-4*H*-1,3-benzothiazine (3f)
White crystalline powder; mp 101–102 °C.

Anal. Calcd for $C_{16}H_{15}NS$ (253.36): C, 75.85; H, 5.97; N, 5.53; S, 12.66. Found: C, 75.72; H, 6.11; N, 5.67; S, 12.80.

Azetobenzothiazines 4a–c,e,f; General Procedure
To a stirred soln of the 4*H*-1,3-benzothiazine derivative **3a–c**,**e**,**f** (2.0 mmol) in anhyd toluene (10 mL) was added $ClCH_2COCl$ (3.0 mmol). The soln was refluxed and Et_3N (0.4 mL, 3.0 mmol) in anhyd toluene (20 mL) was added dropwise over 1 h under reflux. The mixture was then cooled and filtered, and the remaining Et_3NHCl was washed with toluene. The organic layer was extracted with brine (20 mL) and dried (Na_2SO_4). After evaporation, the oily residue crystallized on trituration with EtOH.

***trans*-2a-(4-Bromophenyl)-2-chloro-2,2a-dihydro-5,6-dimethoxy-1*H*,8*H*-azeto[2,1-*b*][1,3]benzothiazin-1-one (4a)**
White crystalline powder; mp 189–190 °C.

Anal. Calcd for $C_{18}H_{15}BrClNO_3S$ (440.74): C, 49.05; H, 3.43; N, 3.18; S, 7.28. Found: C, 49.20; H, 3.52; N, 3.09; S, 7.35.

***trans*-2a-(3-Bromophenyl)-2-chloro-2,2a-dihydro-5,6-dimethoxy-1*H*,8*H*-azeto[2,1-*b*][1,3]benzothiazin-1-one (4b)**
White crystalline powder; mp 147–149 °C.

Anal. Calcd for $C_{18}H_{15}BrClNO_3S$ (440.74): C 49.05; H 3.43; N 3.18; S, 7.28. Found: C, 49.22; H, 3.62; N, 3.34; S, 7.46.

***trans*-2-Chloro-5,6-dimethoxy-2,2a-dihydro-2a-(3,4,5-trimethoxyphenyl)-1*H*,8*H*-azeto[2,1-*b*][1,3]benzothiazin-1-one (4c)**
White crystalline powder; mp 199–201 °C.

Anal. Calcd for $C_{21}H_{22}ClNO_6S$ (451.92): C, 55.81; H, 4.91; N, 3.10; S, 7.10. Found: C, 55.69; H, 3.25; N, 3.31; S, 7.21.

***trans*-2-Chloro-2a-(4-fluorophenyl)-2,2a-dihydro-6-methyl-1*H*,8*H*-azeto[2,1-*b*][1,3]benzothiazin-1-one (4e)**
White crystalline powder; mp 133–134 °C.

Anal. Calcd for $C_{17}H_{13}ClFNOS$ (333.81): C, 61.17; H, 3.93;N, 4.20; S, 9.61. Found: C, 61.05; H, 4.11; N, 4.07; S, 9.78.

***trans*-2-Chloro-2,2a-dihydro-6-methyl-2a-(4-methylphenyl)-1*H*,8*H*-azeto[2,1-*b*][1,3]benzothiazin-1-one (4f)**
White crystalline powder; mp 153–154 °C.

Anal. Calcd for $C_{18}H_{16}ClNOS$ (329.84): C, 65.54; H, 4.89; N, 4.25; S, 9.72. Found: C, 65.39; H, 5.02; N, 4.34; S, 9.65.

1,4-Benzothiazepines 7a–f; General Procedure
Azeto-1,3-thiazine **7a**–**f** (0.70 mmol) was dissolved in dry MeOH (40 mL). To this stirred soln, NaOMe (76 mg, 1.40 mmol) was added. The mixture was stirred at reflux for 2 h. The solvent was evaporated and then the residue was dissolved in CH_2Cl_2 (20 mL). The organic phase was extracted with H_2O (10 mL), dried (Na_2SO_4), and evaporated.

Methyl 3-(4-Bromophenyl)-4,5-dihydro-7,8-dimethoxy-1,4-benzothiazepine-2-carboxylate (7a)
Pale yellow crystalline powder; mp 185–186 °C.

Anal. Calcd for $C_{19}H_{18}BrNO_4S$ (436.32): C 52.30; H 4.16; N 3.21; S 7.35. Found: C, 52.15; H, 4.23; N, 3.02; S, 7.51.

Methyl 3-(3-Bromophenyl)-4,5-dihydro-7,8-dimethoxy-1,4-benzothiazepine-2-carboxylate (7b)
Pale yellow crystalline powder; mp 135–137 °C.

Anal. Calcd for $C_{19}H_{18}BrNO_4S$ (436.32): C, 52.30; H, 4.16; N, 3.21; S, 7.35. Found: C, 52.47; H, 4.30; N, 3.31; S, 7.42.

Methyl 4,5-Dihydro-7,8-dimethoxy-3-(3,4,5-trimethoxyphenyl)-1,4-benzothiazepine-2-carboxylate (7c)
Pale yellow crystalline powder; mp 235–236 °C.

Anal. Calcd for $C_{22}H_{25}NO_7S$ (447.50): C, 59.85; H, 5.90; N, 3.03; S, 6.95. Found: C, 60.02; H, 5.77; N, 3.21; S, 7.06.

Methyl 3-(4-Chlorophenyl)-4,5-dihydro-7-methyl-1,4-benzothiazepine-2-carboxylate (7d)
Pale yellow crystalline powder; mp 189–190 °C.

Anal. Calcd for $C_{18}H_{16}ClNO_2S$ (345.84): C, 59.05; H, 5.63; N, 3.13; S, 7.17. Found: C, 59.32; H, 5.76; N, 3.21; S, 7.35.

Methyl 3-(4-Fluorophenyl)-4,5-dihydro-7-methyl-1,4-benzothiazepine-2-carboxylate (7e)
Pale yellow crystalline powder; mp 211–212 °C.

Anal. Calcd for $C_{18}H_{16}FNO_2S$ (329.39): C, 65.63; H, 4.90; N, 4.25; S, 9.74. Found: C, 65.78; H, 5.04; N, 4.43; S, 9.88.

Methyl 4,5-Dihydro-7-methyl-3-(4-methylphenyl)-1,4-benzothiazepine-2-carboxylate (7f)
Pale yellow crystalline powder; mp 165–167 °C.

Anal. Calcd for $C_{19}H_{19}NO_2S$ (325.43): C, 70.12; H, 5.88; N, 4.30; S, 9.85. Found: C, 70.36; H, 6.10; N, 4.17; S, 9.68.

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