# 2-Alkylidene-4-oxothiazolidine Vinyl Bromides: Versatile Precursors for C(5) Functionalization via Pyridine-Assisted Bromine Transfer

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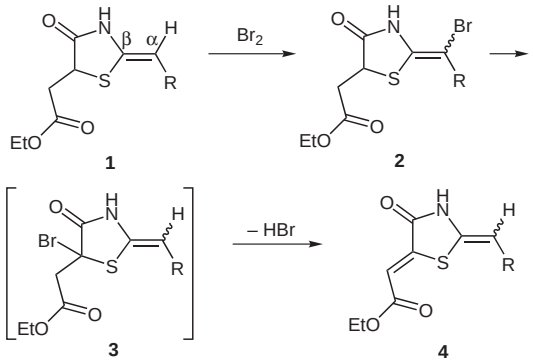
**Abstract:** A series of structurally diverse vinyl bromides, derived from push–pull 2-alkylidene-4-oxothiazolidines, undergoes pyridine-assisted bromine transfer from the C=C bond to the C(5) position, enabling different C(5) functionalization. The type of the product depends on the C(5) substituent and, in some cases, the transformation is affected by the substituent at the C=C bond.

**Key words:** push–pull alkenes, 2-alkylidene-4-oxothiazolidines, pyridine, bromine transfer, functionalization

Vinyl bromides, in which bromine is attached to an α-position of a double bond possessing push–pull character, have been widely used in metal-catalyzed coupling reactions, some being steps toward a synthesis of different biologically active substances.[1–7] Nucleophilic substitution of bromine in compounds of this type has also been reported,[8–11] whereas debromination has been achieved by catalytic hydrogenization,[12,13] or by $Bu_3SnH$.[14] Our recent studies[15,16] on reactivity of push–pull (*Z*)-2-alkylidene-5-ethoxycarbonylmethyl-4-oxothiazolidines **1** have shown that preformed, or in situ formed vinyl bromides **2** undergo an easy cleavage of the C–Br bond and bromine transfer to the C(5) position, yielding, after HBr elimination, 4-oxothiazolidines **4** with two exocyclic double bonds (Scheme 1).




**Scheme 1**

To our knowledge, only one example of an intramolecular bromine migration has been reported, i.e., from uracil to phenyl ring as a side reaction in the *S*→*N*-type Smiles rearrangement of 5-bromo-3-methyl-6-[2-(methylamino)phenylthio]uracil,[17] however, without further examination.

We report herein a generality of this rare bromine transfer reaction by demonstrating its applicability to 2-alkylidene-4-oxothiazolidine vinyl bromides **2**, **5** and **6**, with different substitution pattern at the C(5) position and exocyclic C=C bond. In addition, the synthetic potential of this methodology, affording new pyridinium salts **7** when applied on precursors **5** (Figure 1), was directed towards the preparation of C(5)-functionalized 4-oxothiazolidines by nucleophilic displacement of pyridine as a notoriously poor leaving group.

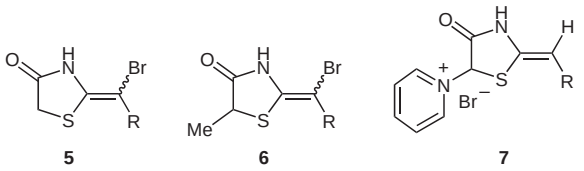



**Figure 1**

Consequently, an efficient regioselective bromination of 5-unsubstituted and 5-methyl-2-alkylidene-4-oxothiazolidines was extended to unreported precursors **5** and **6** (Table 1),[18] by making appropriate changes in the reaction conditions previously employed for the preparation of vinyl bromides **2** (Scheme 1). The regioselectivity is attributed to a higher nucleophilic reactivity of the electron-rich center $C_\alpha$ toward various brominating reagents as compared to the nucleophilic position C(5). According to Satzinger[19,20] and Zaleska[21] the corresponding N-substituted 2-alkylidene-4-oxothiazolidines were brominated exclusively at the C(5) position.

Scheme 2 illustrates the most relevant results obtained in pyridine-assisted bromine transfer of vinyl bromides **2**, **5** and **6**, giving rise to the C(5)-functionalized derivatives **4**, **7** and **8**, respectively, involving also the conversion of the piridinium salts **7** to 5-substituted derivatives **9**–**11**.[22] Referring to our preceding results,[15,16] all vinyl bromides **2**, irrespective of the type of the substituent at the C=C bond, were transformed to the stable 4-oxothiazolidines **4** (Scheme 1). Vinyl bromides **6**, having methyl group at the

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C(5) position, were similarly converted to the less stable 5-methylidene-4-oxothiazolidines **8** (Scheme 2). However, this transformation is restricted to the bromides **6a**,**b** containing an amide substituent at the C=C bond. Compared to the facile rearrangement of 5-ethoxycarbonylmethyl-4-oxothiazolidine vinyl bromides **2**, favored by the easy HBr elimination of the intermediates **3** and formation of the stable derivatives **4**, the analogous reaction of 5-unsubstituted vinyl bromides **5** was rather slow. The presence of an amide, or ester substituent at the C=C bond was necessary for this transformation.

**Table 1** Synthesis of Vinyl Bromides **5** and **6**

| Compound | R | Mp (°C) | Yield (%) |
|---|---|---|---|
| (*Z*)- + (*E*)-**5a** | CONHPh | 139–140 | 91 |
| (*Z*)- + (*E*)-**5b** | $CONH(CH_2)_2Ph$ | 140–142 | 79 |
| (*Z*)- + (*E*)-**5c** | $CO_2Et$ | 103–105 | 76 |
| (*Z*)- + (*E*)-**5d** | COPh | 118–120 | 72 |
| (*Z*)- + (*E*)-**5e** | CN | 163 | 65 |
| (*Z*)- + (*E*)-**6a** | CONHPh | 188–194 | 64 |
| (*Z*)- + (*E*)-**6b** | $CONH(CH_2)_2Ph$ | –[a] | 99[b] |
| (*Z*)- + (*E*)-**6c** | $CO_2Et$ | 75–77 | 68 |
| (*Z*)- + (*E*)-**6d** | COPh | 211–212 | 54 |
| (*Z*)- + (*E*)-**6e** | CN | 124 | 84 |

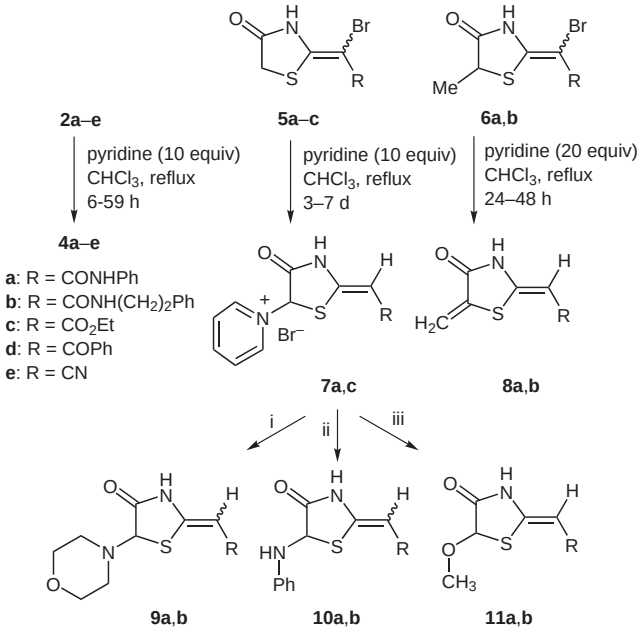
[a] Oily compound.
[b] Yield of the crude product.

Under the conditions defined,[23] **5b** was transformed into a single product, proved convincingly by $^1$H NMR and $^{13}$C NMR data to be the new pyridinium salt, (*Z*)-[4-oxo-5-(pyridinium-1-yl)thiazolidine-2-ylidene)-*N*-(2-phenylethyl)ethanamide bromide (**7b**, Table 2).

The equally slow rearrangement of vinyl bromide **5a** afforded, through visibly progressive precipitation, the corresponding pyridinium salt (*Z*)-**7a**[24] (Table 2), while in the case of the enamino ester **5c** (R = $CO_2Et$) the identical conversion to **7c** took place with low efficiency (14%).

Taking into account the structural similarities of **5** and **7**, the main diagnostic difference in $^1$H NMR and $^{13}$C NMR spectra, apart from the signals of the pyridine ring in **7**, is observed in the position of *H*C(5) and C(5) signals. For example, the *H*C(5) chemical shifts of **5a** and **5b** are observed at δ = 3.86–3.99 and 3.79–3.95 ppm (DMSO-$d_6$), whereas the corresponding downfield shifts in **7a** and **7b** at δ = 7.06 and 7.09 ppm, respectively, indicate the σ-negative effect of the pyridinium ring. In addition, the C(5) signals of **7a** and **7b** at around δ = 72 ppm and upfield chemical shifts (ca. 38 ppm) in the case of **5a** and **5b** fit the above correlation.

The unsubstituted pyridinium salts **7a** and **7b**, with the 4-oxothiazolidine moiety connected through the C(5)–N




**Scheme 2** *Reagents and conditions*: (i) morpholine (excess), $CHCl_3$, r.t., 6.5–25 h; (ii) aniline (excess), MeOH–$H_2O$, r.t., 0.5–1.45 h; (iii) MeOH, $K_2CO_3$, reflux, 24 h.

bond, were then employed as substrates for replacing pyridine by selected nucleophiles (Scheme 2, i–iii).The relevant study by Hutchinson and Tarbell,[25] regarding the determination of the equilibrium constants between *N*-benzyl-*N*-methylpiperidinium halides and pyridine and *N*-benzylpyridinium salts and *N*-methylpiperidine suggested that unsubstituted pyridine in pyridinium salts can be a potential leaving group. A couple of examples involving nucleophilic displacements with pyridine as a leaving group has been reported so far.[26,27]

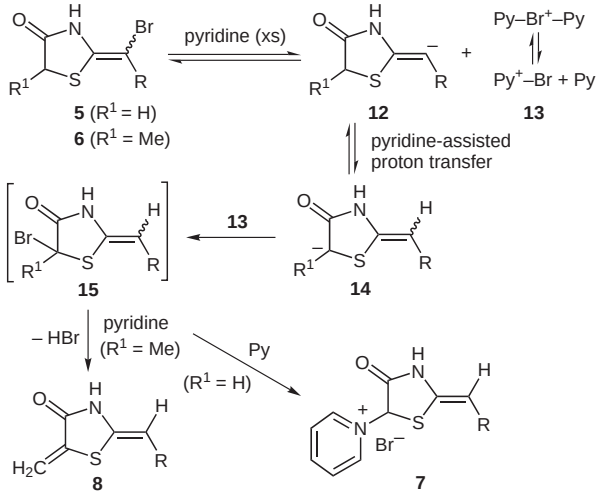
**Table 2** C(5) Functionalization of Parent 4-Oxothiazolidines via Bromine Transfer of Vinyl Bromides **5** and **6**

| Compound | R | Mp (°C) | Yield (%)[a] |
|---|---|---|---|
| (*Z*)-**7a** | CONHPh | 198–200 | 89 |
| (*Z*)-**7b** | $CONH(CH_2)_2Ph$ | 127–128 | 87 |
| (*Z*)-**8a** | CONHPh | –[b] | 7 |
| (*Z*)-**8b** | $CONH(CH_2)_2Ph$ | –[b] | 19 |
| (*Z*)- + (*E*)-**9a** | CONHPh | 160–162 | 91,[c] 82[d] |
| (*Z*)- + (*E*)-**9b** | $CONH(CH_2)_2Ph$ | 114–115 | 87,[c] 69[d] |
| (*Z*)- + (*E*)-**10a** | CONHPh | 180–184 | 63,[c] 57[d] |
| (*Z*)- + (*E*)-**10b** | $CONH(CH_2)_2Ph$ | 189–191 | 86,[c] 68[d] |
| (*Z*)-**11a** | CONHPh | 155–158 | 69,[c] 63[d] |
| (*Z*)-**11b** | $CONH(CH_2)_2Ph$ | 147–149 | 66,[c] 65[d] |

[a] Yield of chromatographed product.
[b] The mp is not sharp.
[c] Yield based on vinyl bromides **5a**,**b**.
[d] Yield based on the parent unbrominated 4-oxothiazolidines.

However, Katritzky et al.[28] reported in a series of papers the substitution of 2,4,6-triphenylpyridine by neutral and anionic nucleophiles from various N-substituted 2,4,6-triphenylpyridinium cations. Within this context, the reaction of unsubstituted pyridinium salts **7a** and **7b** with neutral nucleophiles, such as morpholine, aniline and methanol, forming the substitution products **9**–**11** in good to excellent yields (Table 2), represents an extension of the pyridinium salt chemistry. Spectroscopic data and elemental analyses were consistent with the structures **9**–**11**.[29] Despite the fact that pyridine is a poor leaving group and that the pyridinium ring is susceptible to nucleophilic attack at the 2-, 4- and 6-positions,[30] in some cases followed by ring cleavage,[31,32] we did not observe a decrease in effectiveness of these substitution reactions affording new 5-amino and 5-alkoxy-2-alkylidene-4-oxothiazolidines.

The most likely pathway for the pyridine-assisted vinyl bromide rearrangement of **5** and **6** to the C(5)-functionalized 4-oxothiazolidines is depicted in Scheme 3.

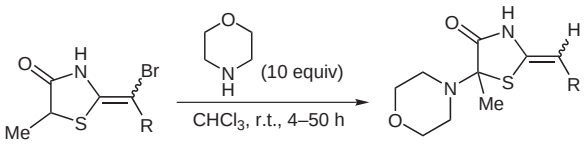



**Scheme 3**

Heterolytic cleavage of the C–Br bond, initiated by pyridine, results in carbanion **12** and bis(pyridine)bromonium cation **13** [in equilibrium with mono(pyridine)bromonium species]. Similar cleavage of C–Br bond, formation of a vinyl anion, represented by an allene-type structure, and its subsequent protonation was reported by Singh et al.[11] in the reaction of α-benzoyl-α-bromoketene *S*,*S*-acetal with morpholine. In the next step, carbanion **14**, formed from **12** by the pyridine-assisted C(5)-proton transfer to the vinylic position, is brominated by bromonium species **13** to form alkyl bromide **15**. After completion of the bromine transfer, the next step depends on the type of the substituent present at the C(5) atom and, in some cases, on the substituent at the exocyclic double bond. In the systems **2** and **6**, bearing $CH_2CO_2Et$ or $CH_3$ group respectively, dehydrobromination occurs and another C=C bond is introduced into the C(5) position. Since elimination is not possible for the intermediate **15**, generated from **5** ($R^1$ = H), then the slow bromide substitution with weakly nucleophilic pyridine leads to synthetically useful pyridinium salts **7**.

Finally, when a better nucleophile, such as morpholine, was used as the bromine transfer agent, 5-methyl derivatives **6a**–**e** were transformed, presumably via the alkyl bromide **15**, into the substitution products 5-methyl-5-morpholino-4-oxothiazolidines **16a**–**e** in high yields (Table 3).

**Table 3** Morpholine-Assisted Bromine Transfer of 2-Alkylidene-5-methyl-4-oxothiazolidine Vinyl Bromides **6**




| Compound | R | Mp (°C) | Yield (%)[a] |
|---|---|---|---|
| (*Z*)- + (*E*)-**16a** | CONHPh | 165-167 | 90 |
| (*Z*)- + (*E*)-**16b** | $CONH(CH_2)_2Ph$ | –[b] | 62 |
| (*Z*)- + (*E*)-**16c** | $CO_2Et$ | –[b] | 90 |
| (*Z*)-**16d** | COPh | 160–162 | 74 |
| (*Z*)-**16e** | CN | –[b] | 78[c] |

[a] Yield of chromatographed product.
[b] Oily compound.
[c] Decomposition occurred during purification.

In conclusion, we have shown that the bromine transfer from the C=C bond to the C(5) position, as a general process for a number of 2-alkylidene-4-oxothiazolidine vinyl bromides, can be efficiently used for the C(5) functionalization of push–pull 2-alkylidene-4-oxothiazolidines. We hope that the synthetic potential and scope of the bromine transfer can be expanded to other structurally related push–pull enaminones and enamino nitriles.

## Acknowledgment

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(18) **Typical Procedure for Synthesis of 2-Bromo-2-(4-oxothiazolidin-2-ylidene)-*N*-(2-phenylethyl)ethanamide (5b).**
To a suspension of 1 mmol of the parent 4-oxothiazolidine in $CHCl_3$ (37 mL) 2% bromine solution in the same solvent (ca. 1 equiv of bromine) was added dropwise under reflux until complete disappearance of the starting material. The progress of the reaction was monitored by TLC. The reaction mixture was evaporated to dryness, EtOH (2–3 mL) and a few drops of $H_2O$ were added and bromide was allowed to crystallize in a freezer. In the case of preparation of vinyl bromides **6a**–**e**, EtOH (50 mL) was used as a solvent and bromine addition was carried out at ca. –5 °C. The reaction mixture was evaporated to several mL, a certain amount of $H_2O$ was added and bromides were allowed to crystallize in a freezer. Only vinyl bromide **6b** was isolated by extraction with $CH_2Cl_2$ and could not be crystallized. All crystallized vinyl bromides **5a**–**e** and **6a**–**e** were isolated as pure substances.
Spectroscopic Data for (*Z*)- and (*E*)-**5b**.
$^1$H NMR (200 MHz, DMSO-$d_6$): δ (*Z* isomer) = 2.78 (t, 2 H, $CH_2$Ph, *J* = 7.3 Hz), 3.33–3.43 (m, 2 H, $NCH_2$), 3.95 (s, 2 H, $CH_2$S), 7.19–7.34 (m, 5 H, Ph), 7.84 (t, 1 H, $NH_{amide}$, *J* = 5.6 Hz), 11.37 (s, 1 H, $NH_{lactam}$); δ (*E*-isomer) = $CH_2$Ph and $NCH_2$ are shielded, 3.79 (s, 2 H, $CH_2$S), Ph is shielded, 7.17 (t, 1 H, $NH_{amide}$, *J* = 5.2 Hz), 10.93 (s, 1 H, $NH_{lactam}$). $^{13}$C NMR (50.3 MHz, DMSO-$d_6$): δ (*Z*-isomer) = 33.2 ($CH_2$S), 35.1 ($CH_2$Ph), 41.4 ($NCH_2$), 84.2 (=CBr), 126.3 (*p*-Ph), 128.6 (*o*-Ph), 128.8 (*m*-Ph), 139.4 (C1–Ph), 152.8 (C=), 163.3 ($CO_{amide}$), 173.3 ($CO_{lactam}$); δ (*E* isomer) = 33.8 ($CH_2$S), 35.4 ($CH_2$Ph), 41.4 ($NCH_2$), 80.0 (=CBr), 126.3 (*p*-Ph), 128.6 (*o*-Ph), 128.8 (*m*-Ph), 139.4 (C1–Ph), 149.9 (C=), 163.3 ($CO_{amide}$), 174.3 ($CO_{lactam}$). IR (KBr, *Z* and *E*): ν = 3360, 3139, 3022, 1723, 1615, 1585, 1517, 1452, 1431, 1350, 1312, 1257, 1219, 1190, 887, 786, 750, 699 cm$^{-1}$. MS (CI): *m/z* = 341/343 [M + 1]. UV (DMSO, *Z* and *E*): $\lambda_{max}$ (ε) = 296.6 nm (18.900). Anal. Calcd for $C_{13}H_{13}BrN_2O_2S$: C, 45.76; H, 3.84; N, 8.21; S, 9.40. Found: C, 45.94; H, 3.90; N, 8.16; S, 9.56.
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(23) **Typical Procedure for Synthesis of (*Z*)-[4-Oxo-5-(pyridinium-1-yl)thiazolidin-2-ylidene]-*N*-(2-phenylethyl)ethanamide Bromide (7b) by Pyridine-Assisted Bromine Transfer Reaction.**
To a suspension of 1.48 mmol of vinyl bromide **5b** (0.505 g) in $CHCl_3$ (31 mL) a tenfold molar excess of pyridine was added and mixture refluxed for 7 d. Reaction mixture was then cooled to r.t. and evaporated to dryness under reduced pressure. Column chromatography ($SiO_2$, MeOH as an eluent) of the crude product yielded **7b** (0.541 g, 87%) as a pale brown solid. $^1$H NMR (200 MHz, DMSO-$d_6$): δ = 2.75 (t, 2 H, $CH_2$Ph, *J* = 7.2 Hz), 3.31–3.40 (m, 2 H, $NCH_2$), 5.94 (s, 1 H, =CH), 7.09 (s, 1 H, CHS), 7.17–7.35 (m, 5 H, Ph), 8.24 (t, 2 H, *m*-pyridine, *J* = 7.2 Hz), 8.33 (t, 1 H, $NH_{amide}$, *J* = 5.4 Hz), 8.75 (t, 1 H, *p*-pyridine, *J* = 7.8 Hz), 9.30 (d, 2 H, *o*-pyridine, *J* = 5.6 Hz), 12.30 (br s, 1 H, $NH_{lactam}$). $^{13}$C NMR (50.3 MHz, DMSO-$d_6$): δ = 35.4 ($CH_2$Ph), 40.4 ($NCH_2$), 71.8 (CHS), 96.5 (=CH), 126.4 (*p*-Ph), 128.6 (*o*-Ph), 128.7 (*m*-pyridine), 128.9 (*m*-Ph), 139.7 (C1–Ph), 144.8 (*o*-pyridine), 146.3 (C=), 148.0 (*p*-pyridine), 166.4 ($CO_{amide}$), 168.2 ($CO_{lactam}$). IR (KBr): ν = 3271, 3051, 3025, 1722, 1656, 1597, 1545, 1484, 1448, 1298, 1246, 1198, 1173, 832, 754, 703 cm$^{-1}$. ESI-MS: *m/z* 340 [M$^+$], 261.
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(29) **Typical Procedure for Synthesis of (*Z*,*E*)-(5-Morpholino-4-oxothiazolidin-2-ylidene)-*N*-(2-phenylethyl)ethanamide (9b).**
A mixture of the crude pyridinium salt **7b** (94.3 mg) and morpholine (0.08 mL, 0.91 mmol) in $CHCl_3$ (8.7 mL) was stirred at r.t. for 6.5 h in dry atmosphere. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography ($SiO_2$, gradient toluene–EtOAc, 4:6 v/v to pure EtOAc) to give a pale yellow solid as a mixture of isomers (*Z*)- and (*E*)-**9b** (69.4 mg, 87% based on vinyl bromide **5b**). $^1$H NMR (200 MHz, DMSO-$d_6$): δ (*Z* isomer) = 2.24–2.30 (m, 2 H, $NCH_{ax}$), 2.62–2.74 (m, 4 H, $NCH_{eq}$ and $CH_2$Ph), 3.24–3.34 (m, 2 H, $NCH_2$), 3.57–3.60 (m, 4 H, $CH_2O$), 5.30 (s, 1 H, CHS), 5.58 (s, 1 H, =CH), 7.16–7.34 (m, 5 H, Ph), 7.90 (t, 1 H, $NH_{amide}$, *J* = 5.5 Hz), 11.42 (s, 1 H, $NH_{lactam}$); δ (*E* isomer) = 2.21–2.31 (m, 2 H, $NCH_{ax}$), 2.57–2.76 (m, 4 H, $NCH_{eq}$ and $CH_2$Ph), $NCH_2$ is shielded, 3.61 (t, 4 H, $CH_2O$, *J* = 4.4 Hz), 5.23 (s, 1 H, =CH), 5.72 (s, 1 H, CHS), 7.16–7.34 (m, 5 H, Ph), 8.02 (t, 1 H, $NH_{amide}$, *J* = 5.6 Hz), 11.70 (s, 1 H, $NH_{lactam}$). $^{13}$C NMR (50.3 MHz, DMSO-$d_6$): δ (*Z* isomer) = 35.6 ($CH_2$Ph), 40.4 ($NHCH_2$), 48.4 ($CH_2$N), 65.9 ($CH_2O$), 72.6 (CHS), 94.5 (=CH), 126.3 (*p*-Ph), 128.6 (*o*-Ph), 128.8 (*m*-Ph), 139.8 (C1–Ph), 148.1 (C=), 166.3 ($CO_{amide}$), 171.7 ($CO_{lactam}$); δ (*E* isomer) = 35.3 ($CH_2$Ph), 40.3 ($NHCH_2$), 48.6 ($CH_2$N), 65.8 ($CH_2O$), 75.1 (CHS), 92.7 (=CH), 126.4 (*p*-Ph), 128.6 (*o*-Ph), 128.8 (*m*-Ph), 139.6 (C1–Ph), 147.7 (C=), 166.8 ($CO_{amide}$), 170.0 ($CO_{lactam}$). IR (KBr, *Z* and *E*): ν = 3437, 3267, 3212, 3077, 1718, 1635, 1565, 1454, 1280, 1249, 1113, 858, 831, 768, 703 cm$^{-1}$. MS (CI): *m/z* 348 [M + 1]. UV (DMSO, *Z* and *E*): $\lambda_{max}$ (ε) = 283.8 nm (25.700). Anal. Calcd for $C_{17}H_{23}N_3O_4S$ (**9b**·$H_2O$): C, 55.87; H, 6.34; N, 11.50; S, 8.77. Found: C, 55.90; H, 6.34; N, 11.42; S, 9.05.
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