Synthesis of 2-(2-Dialkylamino-4*H*-3,1-benzothiazin-4-yl)acetic Acid Derivatives and 2-(2-Thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetic Acid Derivatives

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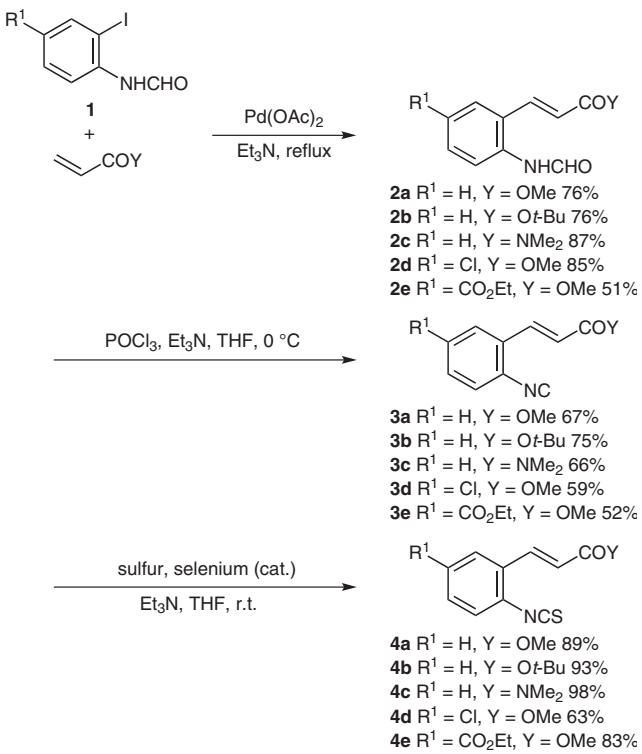
Abstract: An efficient method for the preparation of 2-(4*H*-3,1-benzothiazin-4-yl)acetic acid derivatives and 2-(2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetic acid derivatives has been developed. The reaction of 3-(2-isothiocyanatophenyl)propenoic acid derivatives with secondary amines in methanol at room temperature gave the corresponding thiourea intermediates, which on heating at reflux temperature cyclized by an attack of the sulfur atom on the propenoic moiety in a 1,4-addition manner, to give 2-(2-dialkylamino-4*H*-3,1-benzothiazin-4-yl)acetic acid derivatives in one pot. A similar sequence using primary amines in place of secondary amines afforded 2-[3-alkyl(or aryl)-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl]acetic acid derivatives.

Key words: 4*H*-3,1-benzothiazines, 2-thioxo-1,2,3,4-tetrahydroquinazolines, 3-(2-isothiocyanatophenyl)propenoic acids, thioureas, 1,4-addition

Compounds having the 4*H*-3,1-benzothiazine skeleton have recently attracted much attention because of their biological activities,[1] and a number of efficient methods for their preparation have been reported.[2] In 2000, Miller et al. reported a synthesis of 2-[2-alkyl(or aryl)amino-4*H*-3,1-benzothiazin-4-yl]acetic acid derivatives based on trifluoroacetic acid mediated cyclization of thioureas, prepared by treating 3-(2-aminophenyl)propenoic acid derivatives with isothiocyanates.[2d] We found that 2-(2-dialkylamino-4*H*-3,1-benzothiazin-4-yl)acetic acid derivatives could be obtained by simply heating the respective thiourea intermediates, generated in situ by treating 3-(2-isothiocyanatophenyl)propenoic acid derivatives with secondary amines, in methanol.[3] We describe here the results of our work, which provide an efficient one-pot procedure for the preparation of this type of 4*H*-3,1-benzothiazines. We also found that the use of primary amines in place of secondary amines provided an approach for the construction of a new class of quinazoline derivatives, 2-(2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetic acid derivatives. The 1,2,3,4-tetrahydroquinazoline skeleton is found in many biologically active compounds.[4] Therefore, 2-thioxo-1,2,3,4-tetrahydroquinazoline derivatives are also of potential biological importance. However, few practical methods for the preparation of this class of quinazoline derivatives have been reported.[5] Although Richter et al. have reported the synthesis of 3,4-disubstituted 2-thioxo-1,2,3,4-tetrahydroquinazoline derivatives by the reaction of 2-aminobenzyl alcohols with isothiocyanates, this method suffers from drastic reaction conditions.[5a,b]

The starting materials for our synthesis, 3-(2-isothiocyanatophenyl)propenoic acid derivatives **4**, were prepared by the process illustrated in Scheme 1. Thus, Heck reaction of *N*-(2-iodophenyl)formamides **1** with propenoic acid derivatives afforded 3-(2-formylaminophenyl)propenoic acid derivatives **2**, which were dehydrated with phosphorous oxychloride in the presence of triethylamine to afford 3-(2-isocyanophenyl)propenoic acid derivatives **3**. These isocyanides were converted into the corresponding isothiocyanate **4** on treatment with sulfur in the presence of a catalytic amount of selenium and triethylamine under Fujiwara's conditions.[6]



Scheme 1 Preparation of 3-(2-isothiocyanatophenyl)propenoic acid derivatives

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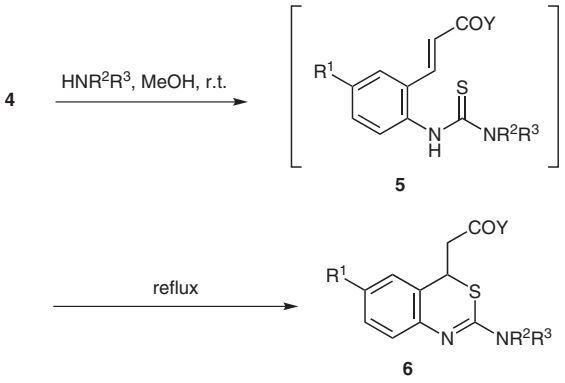
The one-pot synthesis of 2-(2-dialkylamino-4*H*-3,1-benzothiazin-4-yl)acetic acid derivatives **6** from 3-(2-isothiocyanatophenyl)propenoic acid derivatives **4** was conducted as illustrated in Scheme 2. Thus, compounds **4** were treated with secondary amines in methanol at room temperature to generate the corresponding thiourea intermediates **5**, which on heating at reflux temperature cyclized by an attack of the sulfur atom on the propenoic moiety in a 1,4-addition manner. The completion of each step of the sequence could be confirmed by TLC (silica gel) analyses. After cooling, the solutions were concentrated by evaporation and subsequent purification of the residues by column chromatography on silica gel to afford the desired products **6**. The results are summarized in Table 1, which indicates that the yields are generally high, independent of the starting materials **4** and secondary amines used.



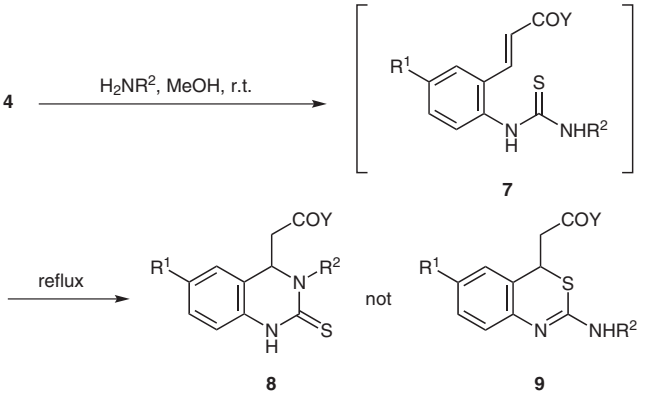
Scheme 2 Preparation of 4*H*-3,1-benzothiazine derivatives

Table 1 2-(2-Dialkylamino-4*H*-3,1-benzothiazin-4-yl)acetic Acid Derivatives **6**

Entry	**4**	HNR^2R^3	Y	**6** (Yield, %)[a]
1	**4a**	pyrrolidine	OMe	**6a** (87)
2	**4a**	piperidine	OMe	**6b** (89)
3	**4a**	morpholine	OMe	**6c** (85)
4	**4b**	*i*-Pr_2NH	O*t*-Bu	**6d** (93)
5	**4c**	Et_2NH	NMe_2	**6e** (98)
6	**4c**	pyrrolidine	NMe_2	**6f** (93)
7	**4c**	4-methylpiperazine	NMe_2	**6g** (88)
8	**4d**	pyrrolidine	OMe	**6h** (89)
9	**4e**	PhNHMe	OMe	**6i** (85)

[a] Isolated yields.

Next, we found that 2-(2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetic acid derivatives **8** were produced in one pot by a similar treatment of 3-(2-isothiocyanatophenyl)propenoic acid derivatives **4** with primary amines in place of secondary amines as illustrated in Scheme 3. Thus, compounds **4** were treated with primary amines under conditions similar to those described for the preparation of **6** to afford **8**. The results are summarized in Table 2, which indicates that the yields are also generally high.



Scheme 3 Preparation of 2-thioxo-1,2,3,4-tetrahydroquinazoline derivatives

Table 2 2-(2-Thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetic Acid Derivatives **8**

Entry	**4**	R^2	Y	**8** (Yield, %)[a]
1	**4b**	Bn	O*t*-Bu	**8a** (96)
2	**4c**	Me	NMe_2	**8b** (95)
3	**4c**	*n*-Pr	NMe_2	**8c** (92)
4	**4c**	4-$MeOC_6H_4$	NMe_2	**8d** (85)
5	**4d**	Et	OMe	**8e** (86)
6	**4d**	Ph	OMe	**8f** (80)

[a] Isolated yields.

In each of the reactions using primary amines, only one of the two possible structural isomers was exclusively obtained. We assigned the structure of the products as quinazoline-2-thiones **8** rather than the isomeric 2-amino-4*H*-benzothiazines **9** on the basis of their spectral data (see Experimental). The assignment was further confirmed by NOE experiments. Thus, for example, an enhancement (10.3%) of the signal at $\delta = 4.97$ assignable to 4-H of compound **8e** was observed when the signal at $\delta = 2.69$ assignable to 3-methylene protons was irradiated.

In conclusion, we have demonstrated that 2-(2-dialkylamino-4*H*-3,1-benzothiazin-4-yl)acetic acid derivatives or 2-(3-alkyl(or aryl)-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetic acid derivatives could be prepared efficiently using one-pot addition/cyclization sequences between 3-(2-isothiocyanatophenyl)acrylic acid derivatives and secondary or primary amines, respectively. The present method must be useful in organic synthesis, because it is operationally very simple and the starting materials are readily available.

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were determined with a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz. The ^{13}C NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Wakogel C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use. Ethyl 4-amino-3-iodobenzoate[7] and *N*-(2-iodophenyl)formamide (**1a**)[8] were prepared according to the reported procedures. All other chemicals used in this study were commercially available.

_N_-(2-Iodophenyl)formamides 1b–e

These compounds were prepared by the treatment of the respective 2-iodoaniline with formic acid in toluene at reflux temperature.[9]

_N_-(4-Chloro-2-iodophenyl)formamide (1d)

Yield: 97%; pale-yellow needles; mp 139–140 °C (hexane–CH_2Cl_2),

IR (KBr): 3273, 1668 cm^{-1}.

^{1}H NMR: δ = 7.13–8.63 (m, 5 H).

Anal. Calcd for C_7H_5ClINO: C, 29.87; H, 1.79; N, 4.98. Found: C, 29.89; H, 1.84; N, 4.97.

Ethyl 4-Formylamino-3-iodobenzoate (1e)

Yield: 90%; beige solid; mp 157–159 °C (hexane–THF).

IR (KBr): 3256, 1713, 1670 cm^{-1}.

^{1}H NMR: δ = 1.40 (t, *J* = 7.3 Hz, 3 H), 4.37 (q, *J* = 7.3 Hz, 2 H), 7.64–8.38 (m, 5 H).

Anal. Calcd for $C_{10}H_{10}INO_3$: C, 37.64; H, 3.16; N, 4.39. Found: C, 37.58; H, 3.18; N, 4.68.

(*E*)-3-(2-Formylaminophenyl)propenoic Acid Derivatives 2

These compounds were prepared by the treatment of *N*-(2-iodophenyl)formamides **1** with propenoic acid derivatives in the presence of a catalytic amount of $Pd(OAc)_2$ in Et_3N at reflux temperature.[10]

Methyl 3-(2-Formylaminophenyl)propenoate (2a)

This is a known compound.[11]

1,1-Dimethylethyl (*E*)-3-(2-Formylaminophenyl)propenoate (2b)

White solid; mp 111–112 °C (hexane–Et_2O).

IR (KBr): 3244, 1705, 1668, 1634 cm^{-1}.

^{1}H NMR: δ = 1.529 and 1.535 (2 s, total 9 H), 6.33–6.37 (m, 1 H), 7.19–8.53 (m, 7 H).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.94; H, 7.18; N, 5.51.

(*E*)-3-(2-Formylaminophenyl)-*N*,*N*-dimethylpropenamide (2c)

Colorless needles; mp 111–113 °C (hexane–CH_2Cl_2).

IR (KBr): 3210, 1674, 1645, 1605 cm^{-1}.

^{1}H NMR: δ = 3.07 (s, 3 H), 3.18 (s, 3 H), 6.81–8.54 (m, 8 H).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.04; H, 6.52; N, 12.74.

Methyl (*E*)-3-(5-Chloro-2-formylaminophenyl)propenoate (2d)

Pale-yellow solid; mp 168–170 °C (hexane–CH_2Cl_2).

IR (KBr): 3219, 1713, 1682, 1657 cm^{-1}.

^{1}H NMR: δ = 3.821 and 3.824 (2 s, total 3 H), 6.40–6.45 (m, 1 H), 7.16–8.47 (m, 6 H).

Anal. Calcd for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; N, 5.84. Found: C, 55.23; H, 4.35; N, 5.83.

Methyl (*E*)-3-(5-Ethoxycarbonyl-2-formylaminophenyl)propenoate (2e)

Pale-yellow solid; mp 96–98 °C (hexane–CH_2Cl_2).

IR (KBr): 3295, 1715, 1696, 1681, 1639 cm^{-1}.

^{1}H NMR: δ = 1.41, 1.43 (2 t, *J* = 7.3 Hz each, total 3 H), 3.62 and 3.84 (2 s, total 3 H), 4.39 and 4.40 (2 q, *J* = 7.3 Hz each, total 2 H), 6.51–8.69 (m, 7 H).

Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.43; H, 5.63; N, 4.83.

(*E*)-3-(2-Isocyanophenyl)propenoic Acid Derivatives 3

These compounds were prepared by treating 3-(2-formylaminophenyl)propenoic acid derivatives **2** with $POCl_3$ in the presence of Et_3N in THF at 0 °C.[12]

Methyl 3-(2-Isocyanophenyl)propenoate (3a)

This is a known compound.[11]

1,1-Dimethylethyl (*E*)-3-(2-Isocyanophenyl)propenoate (3b)

Pale-yellow solid; mp 59–60 °C (hexane).

IR (KBr): 2118, 1713, 1640 cm^{-1}.

^{1}H NMR: δ = 1.55 (s, 9 H), 6.47 (d, *J* = 15.6 Hz, 1 H), 7.39 (td, *J* = 7.3, 1.4 Hz, 1 H), 7.40–7.44 (m, 2 H), 7.65–7.66 (m, 1 H), 7.99 (d, *J* = 15.6 Hz, 1 H).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.24; H, 6.65; N, 6.23.

(*E*)-3-(2-Isocyanophenyl)-*N*,*N*-dimethylpropenamide (3c)

White solid; mp 132–134 °C (hexane–CH_2Cl_2).

IR (KBr): 2124, 1653, 1611 cm^{-1}.

^{1}H NMR: δ = 3.09 (s, 3 H), 3.19 (s, 3 H), 7.06 (d, *J* = 15.6 Hz, 1 H), 7.37 (td, *J* = 7.8, 1.4 Hz, 1 H), 7.40–7.44 (m, 2 H), 7.61 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.83 (d, *J* = 15.6 Hz, 1 H).

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.80; H, 6.05; N, 13.85.

Methyl (*E*)-3-(5-Chloro-2-isocyanophenyl)propenoate (3d)

Pale-yellow solid; mp 121–123 °C (hexane).

IR (KBr): 2114, 1715, 1640 cm^{-1}.

^{1}H NMR: δ = 3.85 (s, 3 H), 6.53 (d, *J* = 16.0 Hz, 1 H), 7.385–7.388 (m, 2 H), 7.64 (s, 1 H), 7.90 (d, *J* = 16.0 Hz, 1 H).

Anal. Calcd for $C_{11}H_8ClNO_2$: C, 59.61; H, 3.64; N, 6.32. Found: C, 59.55; H, 3.89; N, 6.21.

Methyl (*E*)-3-(5-Ethoxycarbonyl-2-isocyanophenyl)propenoate (3e)

White solid; mp 92–93 °C (hexane–Et_2O).

IR (KBr): 2118, 1719, 1637, 1609 cm^{-1}.

^{1}H NMR: δ = 1.42 (t, *J* = 7.3 Hz, 3 H), 3.86 (s, 3 H), 4.42 (q, *J* = 7.3 Hz, 2 H), 6.65 (d, *J* = 16.0 Hz, 1 H), 7.51 (d, *J* = 8.2 Hz, 1 H), 7.98 (d, *J* = 16.0 Hz, 1 H), 8.08 (dd, *J* = 8.2, 1.8 Hz, 1 H), 8.35 (d, *J* = 1.8 Hz, 1 H).

Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.83; H, 5.19; N, 5.32.

(*E*)-3-(2-Isothiocyanatophenyl)propenoic Acid Derivatives 4

These compounds were prepared by treating 3-(2-isocyanophenyl)propenoic acid derivatives **3** with sulfur in the presence of a catalytic amount of selenium and Et_3N in THF at reflux temperature.[6]

Methyl (*E*)-3-(2-Isothiocyanatophenyl)propenoate (4a)

White solid; mp 46–47 °C (hexane).

IR (KBr): 2053, 1701, 1593 cm^{-1}.

^1H NMR: δ = 3.84 (s, 3 H), 6.50 (d, *J* = 16.0 Hz, 1 H), 7.28 (td, *J* = 7.8, 1.4 Hz, 1 H), 7.33 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.37 (td, *J* = 7.8, 1.4 Hz, 1 H), 7.59 (d, *J* = 7.8, 1.4 Hz, 1 H), 7.93 (d, *J* = 16.0 Hz, 1 H).

Anal. Calcd for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14; N, 6.39. Found: C, 60.28; H, 4.28; N, 6.09.

1,1-Dimethylethyl (*E*)-3-(2-Isothiocyanatophenyl)propenoate (4b)

White solid; mp 35–36 °C (hexane).

IR (KBr): 2085, 1707, 1618 cm^{-1}.

^1H NMR: δ = 1.55 (s, 9 H), 6.41 (d, *J* = 16.0 Hz, 1 H), 7.25–7.31 (m, 2 H), 7.35 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 7.84 (d, *J* = 16.0 Hz, 1 H).

Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.20; H, 6.07; N, 5.15.

(*E*)-3-(2-Isothiocyanatophenyl)-*N*,*N*-dimethylpropenamide (4c)

White solid; mp 103–104 °C (hexane–Et_2O).

IR (KBr): 2112, 1651, 1605 cm^{-1}.

^1H NMR: δ = 3.09 (s, 3 H), 3.19 (s, 3 H), 7.00 (d, *J* = 15.6 Hz, 1 H), 7.25–7.29 (m, 1 H), 7.31–7.33 (m, 2 H), 7.55 (d, *J* = 8.2 Hz, 1 H), 7.82 (d, *J* = 15.6 Hz, 1 H).

Anal. Calcd for $C_{12}H_{12}N_2OS$: C, 62.04; H, 5.21; N, 12.06. Found: C, 61.99; H, 5.24; N, 12.04.

Methyl (*E*)-3-(5-Chloro-2-isothiocyanatophenyl)propenoate (4d)

Yellow needles; mp 121–123 °C (hexane–Et_2O).

IR (KBr): 2131, 1713, 1634 cm^{-1}.

^1H NMR: δ = 3.84 (s, 3 H), 6.48 (d, *J* = 16.0 Hz, 1 H), 7.27 (d, *J* = 8.2 Hz, 1 H), 7.35 (dd, *J* = 8.2, 2.3 Hz, 1 H), 7.56 (d, *J* = 2.3 Hz, 1 H), 7.85 (d, *J* = 16.0 Hz, 1 H).

Anal. Calcd for $C_{11}H_8ClNO_2S$: C, 52.08; H, 3.18; N, 5.52. Found: C, 52.15; H, 3.15; N, 5.47.

Methyl (*E*)-3-(5-Ethoxycarbonyl-2-isothiocyanatophenyl)propenoate (4e)

Pale-yellow solid; mp 54–55 °C (hexane–Et_2O).

IR (KBr): 2064, 1722, 1640, 1600 cm^{-1}.

^1H NMR: δ = 1.41 (t, *J* = 7.3 Hz, 3 H), 3.85 (s, 3 H), 4.40 (q, *J* = 7.3 Hz, 2 H), 6.59 (d, *J* = 16.0 Hz, 1 H), 7.39 (d, *J* = 8.7 Hz, 1 H), 7.93 (d, *J* = 16.0 Hz, 1 H), 8.02 (dd, *J* = 8.7, 1.8 Hz, 1 H), 8.28 (d, *J* = 1.8 Hz, 1 H).

Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.81. Found: C, 57.92; H, 4.32; N, 4.60.

Methyl 2-[2-(Pyrrolidin-1-yl)-4*H*-3,1-benzothiazin-4-yl]acetate (6a); Typical Procedure

A mixture of **4a** (0.10 g, 0.46 mmol) and pyrrolidine (32 mg, 0.46 mmol) in MeOH (3 mL) was stirred at r.t. for 5 min. The mixture was then heated at reflux temperature for 10 min. The completion of each step of the sequence could be confirmed by TLC (silica gel) analyses. After cooling to r.t., the resulting mixture was concentrated by evaporation. The residue was purified by column chromatography on silica gel to afford **6a** as a colorless oil; yield: 0.12 g (87%); R_f = 0.58 (THF–hexane, 1:2).

IR (neat): 1738, 1549 cm^{-1}.

^1H NMR: δ = 1.95 (br s, 4 H), 2.71 (dd, *J* = 16.0, 6.4 Hz, 1 H), 2.80 (dd, *J* = 16.0, 9.1 Hz, 1 H), 3.56 (br s, 2 H), 3.68 (s, 3 H), 3.70 (br s, 2 H), 4.43 (dd, *J* = 9.1, 6.4 Hz, 1 H), 6.96 (t, *J* = 7.8 Hz, 1 H), 7.07 (d, *J* = 7.8 Hz, 1 H), 7.10 (d, *J* = 7.8 Hz, 1 H), 7.22 (t, *J* = 7.8 Hz, 1 H).

^{13}C NMR: δ = 25.01, 39.98, 41.66, 47.87, 51.80, 121.29, 122.65, 124.91, 126.07, 128.53, 145.36, 151.25, 170.99.

MS: *m*/*z* (%) = 290 (51, $[M^+]$), 217 (100).

Anal. Calcd for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65. Found: C, 61.87; H, 6.47; N, 9.51.

Methyl 2-[2-(Piperidin-1-yl)-4*H*-3,1-benzothiazin-4-yl]acetate (6b)

Colorless oil; R_f = 0.67 (THF–hexane, 1:3).

IR (neat): 1738, 1549 cm^{-1}.

^1H NMR: δ = 1.60–1.70 (m, 6 H), 2.68 (dd, *J* = 16.0, 6.4 Hz, 1 H), 2.80 (dd, *J* = 16.0, 8.7 Hz, 1 H), 3.68 (s, 3 H), 3.73–3.76 (m, 4 H), 4.47 (dd, *J* = 8.7, 6.4 Hz, 1 H), 6.99 (td, *J* = 7.8, 1.4 Hz, 1 H), 7.09–7.11 (m, 2 H), 7.23 (td, *J* = 7.8, 1.8 Hz, 1 H).

^{13}C NMR: δ = 25.01, 25.97, 40.12, 41.29, 47.86, 51.76, 121.78, 123.07, 124.98, 125.88, 128.42, 145.16, 153.19, 170.96.

MS: *m*/*z* (%) = 304 (57, $[M^+]$), 231 (100).

Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20. Found: C, 63.08; H, 6.28; N, 9.47.

Methyl 2-[2-(Morpholin-4-yl)-4*H*-3,1-benzothiazin-4-yl]acetate (6c)

Pale-yellow oil; R_f = 0.77 (THF–hexane, 1:3).

IR (neat): 1738, 1553 cm^{-1}.

^1H NMR: δ = 2.68 (dd, *J* = 16.0, 6.4 Hz, 1 H), 2.74 (dd, *J* = 16.0, 8.7 Hz, 1 H), 3.68 (s, 3 H), 3.74–3.81 (m, 8 H), 4.50 (dd, *J* = 8.7, 6.4 Hz, 1 H), 7.04 (t, *J* = 7.8 Hz, 1 H), 7.11 (d, *J* = 7.8 Hz, 2 H), 7.24 (t, *J* = 7.8 Hz, 1 H).

^{13}C NMR: δ = 25.59, 41.37, 47.17, 51.84, 66.71, 121.76, 123.81, 125.16, 125.98, 128.58, 144.44, 153.71, 170.76.

MS: *m*/*z* (%) = 306 (61, $[M^+]$), 233 (100).

Anal. Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14. Found: C, 58.72; H, 5.96; N, 8.86.

1,1-Dimethylethyl 2-[2-Bis(1-methylethyl)amino-4*H*-3,1-benzothiazin-4-yl]acetate (6d)

Yellow oil; R_f = 0.35 (Et_2O–hexane, 1:10).

IR (neat): 1732, 1553 cm^{-1}.

^1H NMR: δ = 1.38 (d, *J* = 6.4 Hz, 6 H), 1.41 (d, *J* = 6.4 Hz, 6 H), 1.44 (s, 9 H), 2.60 (dd, *J* = 15.6, 6.4 Hz, 1 H), 2.66 (dd, *J* = 15.6, 8.7 Hz, 1 H), 4.16–4.22 (m, 2 H), 4.38 (dd, *J* = 8.7, 6.4 Hz, 1 H), 6.95 (td, *J* = 7.8, 0.9 Hz, 1 H), 7.08 (d, *J* = 7.8 Hz, 2 H), 7.21 (td, *J* = 7.8, 0.9 Hz, 1 H).

^{13}C NMR: δ = 20.89, 28.07, 40.56, 42.05, 48.95, 80.97, 122.23, 122.49, 124.68, 125.74, 128.13, 145.24, 150.98, 169.87.

MS: *m*/*z* (%) = 362 (25, $[M^+]$), 306 (79), 247 (100).

Anal. Calcd for $C_{20}H_{30}N_2O_2S$: C, 66.26; H, 8.34; N, 7.73. Found: C, 66.25; H, 8.37; N, 7.65.

N,N-Dimethyl-2-(2-diethylamino-4*H*-3,1-benzothiazin-4-yl)acetamide (6e)
Pale-yellow oil; R_f = 0.41 (THF–hexane, 1:2).

IR (neat): 1645, 1549 cm^{-1}.

^1H NMR: δ = 1.20 (t, *J* = 7.3 Hz, 6 H), 2.64 (dd, *J* = 15.1, 6.4 Hz, 1 H), 2.72 (s, 3 H), 2.78 (dd, *J* = 15.1, 8.2 Hz, 1 H), 2.92 (s, 3 H), 3.57 (dq, *J* = 14.2, 7.3 Hz, 2 H), 3.69 (dq, *J* = 14.2, 7.3 Hz, 2 H), 4.60 (dd, *J* = 8.2, 6.4 Hz, 1 H), 6.96 (td, *J* = 7.8, 1.4 Hz, 1 H), 7.08 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.10 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.22 (td, *J* = 7.8, 1.4 Hz, 1 H).

^{13}C NMR: δ = 14.03, 35.45, 37.07, 39.48, 40.43, 43.27, 122.19, 122.68, 124.68, 126.10, 128.27, 145.54, 153.12, 169.88.

MS: *m*/*z* (%) = 305 (53, [M^+]), 219 (100).

Anal. Calcd for $C_{16}H_{23}N_3OS$: C, 62.92; H, 7.59; N, 13.76. Found: C, 62.73; H, 7.72; N, 13.53.

N,N-Dimethyl-2-[2-(pyrrolidin-1-yl)-4*H*-3,1-benzothiazin-4-yl]acetamide (6f)
Pale-yellow solid; mp 105–107 °C (hexane–Et_2O).

IR (KBr): 1645, 1549 cm^{-1}.

^1H NMR: δ = 1.95–1.97 (m, 4 H), 2.71 (s, 3 H), 2.72 (dd, *J* = 15.6, 6.4 Hz, 1 H), 2.78 (dd, *J* = 15.6, 8.2 Hz, 1 H), 2.91 (s, 3 H), 3.55–3.75 (m, 4 H), 4.57 (dd, *J* = 8.2, 6.4 Hz, 1 H), 6.95 (t, *J* = 7.8 Hz, 1 H), 7.08 (d, *J* = 7.8 Hz, 1 H), 7.10 (d, *J* = 7.8 Hz, 1 H), 7.21 (t, *J* = 7.8 Hz, 1 H).

^{13}C NMR: δ = 25.03, 30.29, 35.47, 37.06, 40.33, 47.80, 121.80, 122.66, 124.70, 126.38, 128.38, 145.43, 152.54, 169.88.

MS: *m*/*z* (%) = 303 (32, [M^+]), 217 (100).

Anal. Calcd for $C_{16}H_{21}N_3OS$: C, 63.33; H, 6.98; N, 13.85. Found: C, 63.26; H, 7.13; N, 13.76.

N,N-Dimethyl-2-[2-(4-methylpiperazin-1-yl)-4*H*-3,1-benzothiazin-4-yl]acetamide (6g)
Yellow viscous oil; R_f = 0.18 (THF).

IR (neat): 1643, 1549 cm^{-1}.

^1H NMR: δ = 2.32 (s, 3 H), 2.44 (t, *J* = 5.0 Hz, 4 H), 2.65 (dd, *J* = 15.6, 6.4 Hz, 1 H), 2.73 (s, 3 H), 2.78 (dd, *J* = 15.6, 8.2 Hz, 1 H), 2.92 (s, 3 H), 3.74–3.87 (m, 4 H), 4.64 (dd, *J* = 8.2, 6.4 Hz, 1 H), 7.01 (td, *J* = 7.3, 1.4 Hz, 1 H), 7.10 (dd, *J* = 7.3, 1.4 Hz, 1 H) 7.12 (dd, *J* = 7.3, 1.4 Hz, 1 H), 7.23 (td, *J* = 7.3, 1.4 Hz, 1 H).

^{13}C NMR: δ = 30.29, 35.48, 40.02, 40.38, 46.07, 46.31, 53.94, 122.23, 123.56, 124.92, 126.25, 128.36, 144.79, 154.60, 169.70.

MS: *m*/*z* (%) = 332 (89, [M^+]), 246 (100).

Anal. Calcd for $C_{17}H_{24}N_4OS$: C, 61.41; H, 7.28; N, 16.85. Found: C, 61.16; H, 7.41; N, 16.80.

Methyl 2-[6-Chloro-2-(pyrrolidin-1-yl)-4*H*-3,1-benzothiazin-4-yl]acetate (6h)
Yellow viscous oil; R_f = 0.47 (EtOAc–hexane, 1:3).

IR (neat): 1738, 1549 cm^{-1}.

^1H NMR: δ = 1.93–1.98 (m, 4 H), 2.69 (dd, *J* = 16.0, 6.4 Hz, 1 H), 2.80 (dd, *J* = 16.0, 9.1 Hz, 1 H), 3.55 (br s, 2 H), 3.68 (br s, 2 H), 3.70 (s, 3 H), 4.38 (dd, *J* = 9.1, 6.4 Hz, 1 H), 7.02 (d, *J* = 8.7 Hz, 1 H), 7.07 (d, *J* = 2.3 Hz, 1 H), 7.16 (dd, *J* = 8.7, 2.3 Hz, 1 H).

^{13}C NMR: δ = 24.99, 39.63, 41.43, 47.96, 51.91, 122.60, 125.94, 126.13, 126.94, 128.50, 144.13, 151.37, 170.67.

MS: *m*/*z* (%) = 324 (54, [M^+]), 251 (100).

Anal. Calcd for $C_{15}H_{17}ClN_2O_2S$: C, 55.46; H, 5.28; N, 8.62. Found: C, 55.41; H, 5.20; N, 8.82.

Methyl 2-[6-Ethoxycarbonyl-2-methyl(phenyl)amino-4*H*-3,1-benzothiazin-4-yl]acetate (6i)
Pale-yellow solid; mp 124–125 °C (hexane–CH_2Cl_2).

IR (KBr): 1732, 1713, 1531 cm^{-1}.

^1H NMR: δ = 1.39 (t, *J* = 7.3 Hz, 3 H), 4.35 (dd, *J* = 15.5, 6.4 Hz, 1 H), 4.73 (dd, *J* = 15.5, 9.1 Hz, 1 H), 3.59 (s, 3 H), 3.62 (s, 3 H), 4.35 (q, *J* = 7.3 Hz, 2 H), 4.41 (dd, *J* = 9.1, 6.4 Hz, 1 H), 7.21–7.23 (m, 3 H), 7.34 (tt, *J* = 7.3, 1.4 Hz, 1 H), 7.40 (dd, *J* = 7.8, 7.3 Hz, 2 H), 7.82 (d, *J* = 1.8 Hz, 1 H), 7.95 (dd, *J* = 8.2, 1.8 Hz, 1 H).

^{13}C NMR: δ = 14.38, 39.75, 40.50, 41.29, 51.81, 60.68, 121.70, 124.99, 125.09, 127.80, 127.87, 128.00, 129.27, 129.99, 144.10, 149.01, 154.96, 166.41, 170.35.

MS: *m*/*z* (%) = 398 (39, [M^+]), 325 (100).

Anal. Calcd for $C_{21}H_{22}N_2O_4S$: C, 63.30; H, 5.56; N, 7.03. Found: C, 63.29; H, 5.67; N, 6.94.

1,1-Dimethylethyl 2-(3-Phenylmethyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (8a)
Colorless crystals; mp 175–177 °C (hexane–CH_2Cl_2).

IR (KBr): 3185, 1722, 1481, 1148 cm^{-1}.

^1H NMR: δ = 1.37 (s, 9 H), 2.56 (dd, *J* = 15.1, 8.7 Hz, 1 H), 2.62 (dd, *J* = 15.1, 5.0 Hz, 1 H), 4.59 (d, *J* = 15.1 Hz, 1 H), 4.92 (dd, *J* = 8.7, 5.0 Hz, 1 H), 6.07 (d, *J* = 15.1 Hz, 1 H), 6.85 (d, *J* = 8.2 Hz, 1 H), 6.96–6.99 (m, 2 H), 7.21–7.36 (m, 6 H), 8.69 (s, 1 H).

^{13}C NMR: δ = 27.93, 40.33, 54.91, 55.63, 81.57, 113.53, 121.07, 123.69, 125.74, 127.86 (2 C), 128.76, 128.96, 134.11, 135.91, 169.12, 177.54.

MS: *m*/*z* (%) = 368 (38, [M^+]), 312 (41), 253 (100).

Anal. Calcd for $C_{21}H_{24}N_2O_2S$: C, 68.45; H, 6.56; N, 7.60. Found: C, 68.18; H, 6.79; N, 7.48.

N,N-Dimethyl-2-(3-methyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetamide (8b)
Pale-yellow solid; mp 172–173 °C (hexane–CH_2Cl_2).

IR (KBr): 3233, 1616, 1485, 1125 cm^{-1}.

^1H NMR: δ = 2.68 (dd, *J* = 15.1, 8.2 Hz, 1 H), 2.75 (s, 3 H), 2.77 (dd, *J* = 15.1, 5.5 Hz, 1 H), 2.91 (s, 3 H), 3.51 (s, 3 H), 5.18 (dd, *J* = 8.2, 5.5 Hz, 1 H), 6.86 (d, *J* = 7.8 Hz, 1 H), 7.03 (t, *J* = 7.8 Hz, 1 H), 7.20 (d, *J* = 7.8 Hz, 1 H), 7.23 (t, *J* = 7.8 Hz, 1 H), 8.87 (s, 1 H).

^{13}C NMR: δ = 35.59, 37.27, 37.34, 40.86, 59.55, 113.27, 121.32, 123.66, 126.02, 128.85, 134.25, 168.99, 176.91.

MS: *m*/*z* (%) = 263 (49, [M^+]), 177 (100).

Anal. Calcd for $C_{13}H_{17}N_3OS$: C, 59.29; H, 6.51; N, 15.96. Found: C, 59.28; H, 6.57; N, 15.90.

N,N-Dimethyl-2-(3-propyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetamide (8c)
Pale-yellow solid; mp 164–165 °C (hexane–CH_2Cl_2).

IR (KBr): 3210, 1628, 1483, 1134 cm^{-1}.

^1H NMR: δ = 0.92 (t, *J* = 7.8 Hz, 3 H), 1.75 (sext, *J* = 7.8 Hz, 2 H), 2.68 (dd, *J* = 15.1, 5.0 Hz, 1 H), 2.71 (s, 3 H), 2.76 (dd, *J* = 15.1, 8.2 Hz, 1 H), 2.89 (s, 3 H), 3.29–3.35 (m, 1 H), 4.58–4.64 (m, 1 H), 5.15 (dd, *J* = 8.2, 5.0 Hz, 1 H), 6.88 (d, *J* = 7.8 Hz, 1 H), 7.03 (t, *J* = 7.8 Hz, 1 H), 7.22 (d, *J* = 7.8 Hz, 1 H), 7.24 (t, *J* = 7.8 Hz, 1 H), 8.92 (s, 1 H).

^{13}C NMR: δ = 11.01, 20.99, 35.53, 37.21, 37.51, 53.89, 57.45, 113.29, 121.56, 123.59, 125.99, 128.80, 134.41, 169.02, 176.60.

MS: *m*/*z* (%) = 291 (53, [M^+]), 205 (100).

Anal. Calcd for $C_{15}H_{21}N_3OS$: C, 61.82; H, 7.26; N, 14.42. Found: C, 61.75; H, 7.39; N, 14.18.

***N*,*N*-Dimethyl-2-[3-(4-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl]acetamide (8d)**
Pale-yellow solid; mp 224–226 °C (hexane–CH_2Cl_2).

IR (KBr): 3187, 1647, 1494, 1233 cm^{-1}.

^1H NMR: δ = 2.65 (s, 3 H), 2.80 (s, 3 H), 2.84 (dd, *J* = 15.1, 3.7 Hz, 1 H), 3.04 (dd, *J* = 15.1, 10.1 Hz, 1 H), 3.83 (s, 3 H), 5.33 (dd, *J* = 10.1, 3.7 Hz, 1 H), 6.94–6.96 (m, 3 H), 7.03 (td, *J* = 7.8, 1.4 Hz, 1 H), 7.22–7.27 (m, 2 H), 7.29–7.32 (m, 2 H), 9.45 (s, 1 H).

^{13}C NMR: δ = 35.40, 37.10, 37.21, 55.40, 61.49, 113.65, 114.51, 121.53, 123.61, 126.48, 128.92, 129.36, 134.46, 136.69, 158.98, 168.56, 177.56.

MS: *m*/*z* (%) = 355 (47, [M^+]), 269 (100).

Anal. Calcd for $C_{19}H_{21}N_3O_2S$: C, 64.20; H, 5.95; N, 11.82. Found: C, 64.22; H, 6.03; N, 11.73.

Methyl 2-(6-Chloro-3-ethyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (8e)
Yellow crystals; mp 140–141 °C (hexane–Et_2O).

IR (KBr): 3179, 1734, 1487, 1234 cm^{-1}.

^1H NMR: δ = 1.30 (t, *J* = 7.3 Hz, 3 H), 2.69 (dd, *J* = 15.6, 8.7 Hz, 1 H), 2.75 (dd, *J* = 15.6, 5.0 Hz, 1 H), 3.42–3.49 (m, 1 H), 3.68 (s, 3 H), 4.59–4.66 (m, 1 H), 4.97 (dd, *J* = 8.7, 5.0 Hz, 1 H), 6.75 (d, *J* = 8.7 Hz, 1 H), 7.15 (d, *J* = 2.3 Hz, 1 H), 7.22 (dd, *J* = 8.7, 2.3 Hz, 1 H), 8.37 (s, 1 H).

^{13}C NMR: δ = 12.88, 39.10, 47.42, 52.15, 55.79, 114.79, 122.38, 125.65, 128.56, 129.16, 132.93, 170.18, 176.32.

MS: *m*/*z* (%) = 298 (39, [M^+]), 225 (100).

Anal. Calcd for $C_{13}H_{15}ClN_2O_2S$: C, 52.26; H, 5.06; N, 9.38. Found: C, 52.26; H, 5.20; N, 9.33.

Methyl 2-(6-Chloro-3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (8f)
Pale-yellow needles; mp 99 °C (dec.) (hexane–Et_2O).

IR (KBr): 3173, 1732, 1495, 1229 cm^{-1}.

^1H NMR: δ = 2.86 (dd, *J* = 15.6, 8.7 Hz, 1 H), 2.94 (dd, *J* = 15.6, 4.5 Hz, 1 H), 3.59 (s, 3 H), 5.21 (dd, *J* = 8.7, 4.5 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 1 H), 7.16 (d, *J* = 2.3 Hz, 1 H), 7.24 (dd, *J* = 8.7, 2.3 Hz, 1 H), 7.37–7.50 (m, 5 H), 8.99 (s, 1 H).

^{13}C NMR: δ = 39.24, 52.05, 60.43, 115.13, 122.29, 125.98, 128.48, 128.53, 128.83, 129.33, 129.58, 133.04, 143.48, 169.65, 177.21.

MS: *m*/*z* (%) = 346 (39, [M^+]), 273 (100).

Anal. Calcd for $C_{17}H_{15}ClN_2O_2S$: C, 58.87; H, 4.36; N, 8.08. Found: C, 58.84; H, 4.45; N, 8.16.

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