Notes

2-Alkylthio-4-oxo-3-quinazolineacetonitriles and Analogous Thieno[3,2-*d*]pyrimidineacetonitriles: Reaction with Thiols via Trapped Thioimidates

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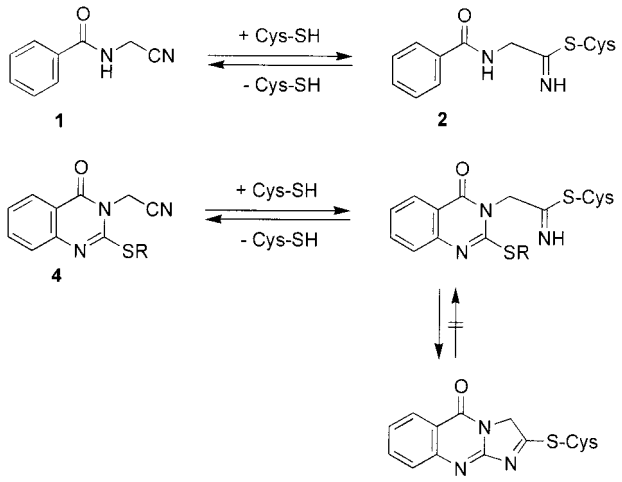
Introduction

Cysteine proteases, a group of proteolytic enzymes, play important roles in a multitude of physiological as well as pathological processes including lysosomal function, bone resorption, hormone biosynthesis and inactivation, apoptosis, and certain viral and protozoal infections. Therefore, cysteine proteases constitute prime targets for the design of specific inhibitors[1] to block the activity of cathepsins, calpains,[2] caspases,[3] and viral cysteine proteases.[4] A characteristic feature of cysteine proteases is the nucleophilic deprotonated active-site cysteine.[1,5] Since cysteine and serine proteases show similarities in their catalytic mode of action, the development of inhibitors specific for cysteine proteases presents a serious problem[1a] and, thus, a special challenge in designing inhibitors.[1,5,6]

Amino acid and dipeptide-derived nitriles have been reported to inactivate papain, cathepsin C, and cathepsin B.[6−9] Papain, a prototype cysteine protease, reacts reversibly with hippuronitrile **1** to form a thioimidate covalent intermediate **2** (Scheme 1).[7,10,11] Dipeptide-derived nitriles, such as *N*-(*N*-acetyl-L-phenylalanyl)-aminoacetonitrile are stronger transition-state analogue inhibitors toward papain.[6] The reversible formation of a covalent thioimidate intermediate was demonstrated by NMR studies and binding kinetics.[8,11,12] Notably, amino acid or peptide-derived nitriles did show some selectivity for cysteine over serine proteases.[1a,6,8] Conceptually, an ideal nitrile inhibitor would prevent release of the active-site thiol and dissociation of the enzyme−inhibitor complex after formation of the intermediate thioimidate enzyme−inhibitor adduct. The goal of the present work was the design of compounds that contain an additional nucleofuge situated at a favorable distance from the nitrile function. Such nitriles could react with the active-site cysteine residue of a cysteine protease to yield a thioimidate that might be trapped by an adjacent electrophilic carbon. Since heterocyclic alkylthio substituents are excellent leaving groups, the 2-alkylthiopyrimidinone structure was chosen. The lead structure **4** resembles the papain inhibitor hippuronitrile **1**, and the possible reaction course with a cysteine protease, in principle, is outlined in Scheme 1.

Scheme 1



In this paper, we report the reaction of a series of 2-alkylthio-4-oxo-3-quinazolineacetonitriles and analogous thieno[3,2-*d*]pyrimidine-3-acetonitriles with thiolates. This mechanistic study was performed in order to investigate whether such compounds react via thioimidates and undergo a subsequent trapping reaction to form imidazoquinazolines and imidazothienopyrimidines, respectively.

Results and Discussion

The synthesis of quinazolineacetonitriles **4** and thieno[3,2-*d*]pyrimidineacetonitriles **7** is shown in Scheme 2. Compounds **4a**,**b** and **7a**,**b** were prepared in good yields by base-catalyzed treatment of **3** or **6** with 1-bromopropane and benzyl chloride, respectively, in aqueous ac-

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(2) (a) Wang, K. K.; Yueng, P. W. *Trends Pharmacol. Sci.* **1994**, *15*, 412. (b) Li, Z.; Ortega-Vilain, A.- C.; Patil, G. S.; Chu, D.-L.; Foreman, J. E.; Eveleth, D. D.; Powers, J. C. *J. Med. Chem.* **1996**, *39*, 4089.

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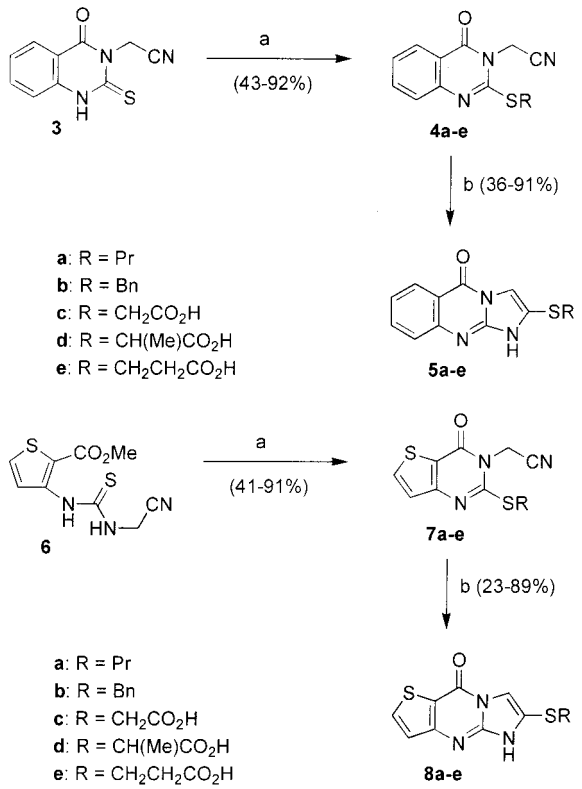
Scheme 2



[a] Reactions and conditions: (a) RX, 1 M NaOH, acetone, rt (**a**, **b**); or RCl, KI, Na_2CO_3, DMF, 100 °C, 90 min (**c**−**e**); (b) RSH, *t*-BuOH, *t*-BuOK, rt, 24 h (**a**, **b**); or RSH, 1 M NaOH, 0 °C, 10 min (**c**, **d**); or $HSCH_2CH_2CO_2H$, 1 M NaOH, rt, 4 h (**e**).

etone at room temperature. To obtain the thienopyrimidines **7**, a one-pot reaction involving S-alkylation and cyclocondensation was employed.[13] However, these conditions were not suitable for the preparation of the carboxyalkyl substituted compounds **4c**−**e** and **7c**−**e**, and their preparation was accomplished in moderate yields using the respective chloroacetic or chloropropionic acid under conditions of the Finkelstein reaction (KI, DMF).

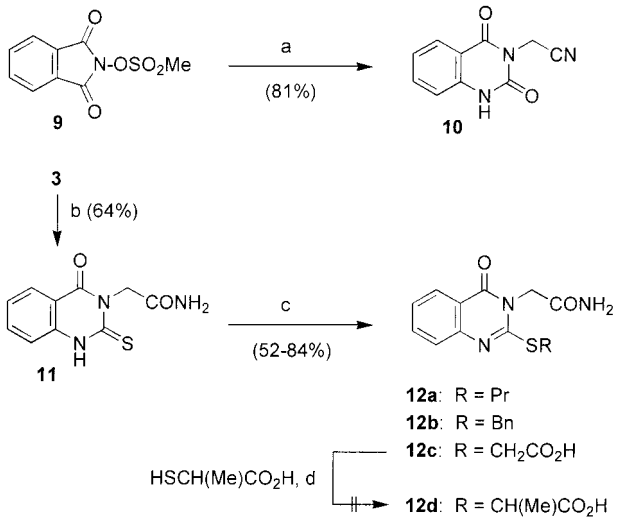
The base-catalyzed reaction of compounds **4** and **7** with thiols was studied in order to prove the concept of trapping thioimidates by an adjacent electrophilic site. We chose to utilize those thiols that had already been incorporated into the alkylthio function of each of the starting compounds. All reactions were performed using a 1:10:5 ratio (nitrile/thiol/base).

The reactions of the propylthio- and benzylthio-substituted heterocycles (**4a**,**b** and **7a**,**b**) with propyl mercaptan and benzyl mercaptan, respectively, were performed in *tert*-butyl alcohol with potassium *tert*-butoxide at room temperature. The desired imidazo derivates **5a**,**b** and **8a**,**b** were obtained in low yields after column chromatography.

The reaction of the carboxyalkylthio quinazolinones **4c**−**e** with mercaptoacetic acid, thiolactic acid, and 3-mercaptopropionic acid, respectively, in aqueous alkali afforded the carboxyalkylthio imidazoquinazolinones **5c**−**e**. The reaction to produce **5e** was carried out at room temperature, whereas the reactions of **4c** with mercaptoacetic acid and **4d** with thiolactic acid occurred rapidly and were completed after 10 min at 0 °C. The resulting

(13) Gütschow, M.; Powers, J. C. *J. Heterocycl. Chem.*, in press.

Scheme 3



[a] Reactions and conditions: (a) aminoacetonitrile bisulfate, pyridine, rt, 24 h; (b) 0.5 M NaOH, acetone, rt, 15 h; (c) RX, 1 M NaOH, acetone, rt (**a**, **b**), or $ClCH_2CO_2H$, KI, Na_2CO_3, DMF, 100 °C, 90 min (**c**); (d) 1 M NaOH, 0 °C, 10 min.

imidazo[2,1-*b*]quinazolin-5-ones **5c**−**e** were obtained as pure compounds in excellent yields. In an analogous manner, treatment of the carboxyalkylthio thienopyrimidinones **7c**−**e** with mercaptoacids readily provided the imidazo[1,2-*a*][3,2-*d*]pyrimidin-9-ones **8c**−**e**.

When the reactions of **4a** (with propyl mercaptan) or **4b** (with benzyl mercaptan) in a solution of sodium hydroxide in 50% acetone at room temperature were performed, they were found to be much slower compared to those of the carboxyalkylthio derivatives described above.[14] The resulting product mixtures were analyzed by TLC using the reference substances **10**,[16] **12a**, and **12b**. The preparation of these reference substances is shown in Scheme 3. When **4a** was treated with propyl mercaptan in aqueous acetone in the presence of sodium hydroxide at room temperature over 5 days, the reaction mixture contained the quinazolineacetamide **12a**, together with starting material and **5a**. Similarly, **4b** and benzyl mercaptan gave a mixture of the amide **12b**, starting material, and **5b**. However, the quinazolinedione **10**, which would result from hydrolysis at the C(2) carbon of **4a** and **4b**, was not detected. This showed that the nitrile group is more reactive than the C(2) electrophile under basic aqueous conditions.

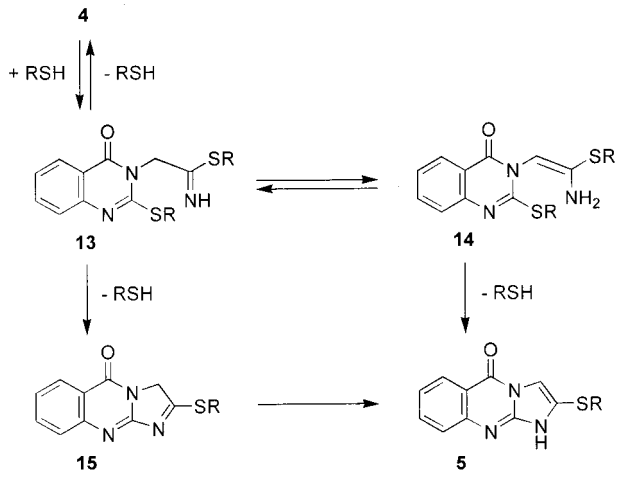
It might be assumed that the treatment of compounds **4** and **7** with thiols could occur by an *initial* attack of the thiolate at the C(2) carbon. In the case of the parent compounds **4** and **7**, reaction at the C(2) rather than at the nitrile group would give starting material, and the products **5** and **8** could be formed subsequently. To test the reactivity of the C(2) electrophilic site, the acetamide **12c** was reacted with thiolactic acid (Scheme 3). The reaction was performed under the same conditions that have been applied for the conversion of the nitriles **4c** and **4d** into the corresponding imidazo compounds **5c** and

(14) The greater nucleophilicity of mercaptoalkylcarboxylate dianions compared to simple thiolate anions is the likely explanation for this difference; see ref 15.

(15) Friedman, M.; Cavins, J. F.; Wall, J. S. *J. Am. Chem. Soc.* **1965**, *87*, 3672.

(16) For the reaction of *N*-(sulfonyloxy)phthalimides with nucleophiles, see ref 17 and references therein.

Scheme 4



5d. However, no formation of the C(2) reaction product **12d** was observed. Instead, pure starting material **12c** was obtained in quantitative yield. This indicated that the thiolate prefers to attack at the nitrile function and not at the electrophilic site at C(2) of **4** and **7**.

The structures **5** and **8** were established by elemental analyses and spectral data. In particular, the ^{1}H NMR spectra of **5** and **8** showed a sharp singlet in the range of 7.50−7.60 ppm for the CH of the imidazole.[18] Mass spectra of **5** and **8** were characterized by a typical fragmentation pattern.[19]

As shown for the quinazoline series in Scheme 4, the formation of the tricyclic compounds **5** involves the attack of the thiolate anion at the nitrile function of **4** followed by rapid protonation to give the neutral thioimidates **13**. Thioimidates are known to undergo a base-catalyzed decomposition;[12,20] an equilibrium between nitriles **4** and thioimidates **13** is therefore assumed. However, attack of the thioimidate nitrogen at the C(2) carbon followed by displacement of the alkylthio leaving group affords **15**. Tautomeric rearrangement to the more stable[21] ketene-S,N-acetals **5** probably occurs in a subsequent step. However, we cannot exclude the rearrangement to **14** *prior* to cyclization.

In summary, it was demonstrated that fused 2-alkylthio-4-oxopyrimidine-3-acetonitriles undergo an irreversible ring closure upon treatment with thiols via thioimidate intermediates. Thioimidates were trapped by attack of the thioimidate nitrogen at an adjacent electrophilic site contained within the heterocyclic structure. To the best of our knowledge, the synthesis of **5** and **8** is the first report of an in situ cyclization of thioimidates to form fused nitrogen heterocycles. This "trapped thioimidate" cyclization should also be applicable to other types of heterocyclic compounds. Furthermore, the trapped thioimidate strategy might be useful in the design of new inhibitors of cysteine proteases. For such an approach, the heterocyclic structure should be utilized as a scaffold onto which amino acid or peptidic moieties could be introduced to provide specific recognition in the active site of the targeted cysteine protease.

Experimental Section

Melting points are not corrected. ^{1}H NMR spectra (300 MHz) were recorded in DMSO-d_6. Mass spectra were performed using electron impact ionization (EI, 70 eV), unless otherwise stated. Thin-layer chromatography was performed on Merck aluminum sheets, silica gel 60 F_{254}. The solvent systems used for TLC were toluene/ethyl acetate (2:1, 1:1) and 1-propanol/30% NH_3 (10:1). Column chromatography was performed on silica gel (32−63 μm) using ethyl acetate/hexane (1:1). Elemental analyses were performed by Atlanta Microlab Inc., Norcross, GA.

1,4-Dihydro-4-oxo-2-thioxo-3(2*H*)-quinazolineacetonitrile (**3**) and methyl 3-[3-(cyanomethyl)thioureido]thiophene-2-carboxylate (**6**) were prepared as reported.[13] 2-(Propylthio)-4-oxo-3(4*H*)-quinazolineacetonitrile (**4a**)[13] was prepared from **3** and 1-bromopropane in 88% yield. 2-(Benzylthio)-4-oxo-3(4*H*)-quinazolineacetonitrile (**4b**)[13] was prepared from **3** and benzyl chloride in 92% yield. 2-(Propylthio)-4-oxothieno[3,2-*d*]pyrimidine-3(4*H*)-acetonitrile (**7a**)[13] was prepared from **6** and 1-bromopropane in 91% yield. 2-(Benzylthio)-4-oxothieno[3,2-*d*]pyrimidine-3(4*H*)-acetonitrile (**7b**)[13] was prepared from **6** and benzyl chloride in 71% yield.

General Procedure for the Preparation of Carboxyalkylthio Derivatives 4c−e and 7c−e. A mixture of compound **3** or **6** (5 mmol), Na_2CO_3 (2.12 g, 20 mmol), KI (1.66 g, 10 mmol), DMF (25 mL), and the appropriate chloro-substituted acid (10 mmol) was stirred at 100 °C for 90 min and poured into H_2O (200 mL). The pH was adjusted to 7.5, and the solution was extracted with ethyl acetate (200 mL), followed by hexane (150 mL). The aqueous layer was acidified with 1 M HCl, and the mixture was cooled. The precipitate that formed was collected by filtration, dried, and recrystallized from acetonitrile after charcoal treatment.

[[3-(Cyanomethyl)-3,4-dihydro-4-oxo-2-quinazolinyl]-thio]acetic Acid (4c). Treatment of compound **3** with chloroacetic acid gave **4c** as white crystals in 70% yield: mp 191−192 °C; ^{1}H NMR δ 4.16 (s, 2H), 5.20 (s, 2H), 7.48−7.54 (m, 2H), 7.81−7.87 (m, 1H); EIMS (*m*/*z*) 275 (M^+, 51), 231 ($M^+ - CO_2$, 50), 191 (100). Anal. Calcd for $C_{12}H_9N_3O_3S$: C, 52.36; H, 3.30; N, 15.26. Found: C, 52.40; H, 3.32; N, 15.16.

(*R,S*)-2-[[3-(Cyanomethyl)-3,4-dihydro-4-oxo-2-quinazolinyl]thio]propionic Acid (4d). Compound **3** was reacted with 2-chloropropionic acid to obtain **4d** as a white solid in 43% yield: mp 175−176 °C; ^{1}H NMR δ 1.62 (d, J = 7.3 Hz, 3H), 4.60 (q, J = 7.3 Hz, 1H), 5.16 (s, 2H), 7.48−7.53 (m, 2H), 7.82−7.88 (m, 1H), 8.09−8.12 (m, 1H); EIMS (*m*/*z*) 289 (M^+, 57), 245 ($M^+ - CO_2$), 162 ($C_6H_4(CO)NCS$, 100). Anal. Calcd for $C_{13}H_{11}N_3O_3S$: C, 53.97; H, 3.83; N, 14.52. Found: C, 54.19; H, 3.89; N, 14.76.

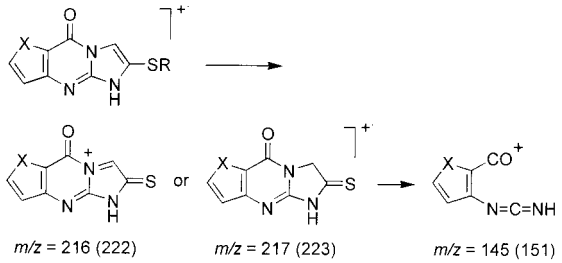
3-[[3-(Cyanomethyl)-3,4-dihydro-4-oxo-2-quinazolinyl]-thio]propionic Acid (4e). Compound **3** was reacted with 3-chloropropionic acid to obtain **4e** as white crystals in 58% yield: mp 159−160 °C; ^{1}H NMR δ 2.80 (t, J = 6.7 Hz, 2H), 3.49 (t, J = 6.7 Hz, 2H), 5.13 (s, 2H), 6.47−7.59 (m, 2H), 7.81−7.87 (m, 1H), 8.08−8.11 (m, 1H); EIMS (*m*/*z*) 289 (M^+, 14), 217 (100), 162 ($C_6H_4(CO)NCS$, 44). Anal. Calcd for $C_{13}H_{11}N_3O_3S$: C, 53.97; H, 3.83; N, 14.52. Found: C, 54.06; H, 3.80; N,14.58.

[[3-(Cyanomethyl)-3,4-dihydro-4-oxothieno[3,2-*d*]pyrimidin-2-yl]thio]acetic Acid (7c). Treatment of compound **6**

(17) Gütschow, M. *J. Org. Chem*. **1999**, *64*, 5109.

(18) Compounds **5** and **8** showed signals for S−CH_2 methylene at 0.33−0.39 ppm upfield compared to the S−CH_2 protons of the corresponding bicyclic compounds **4** and **7**. Similarly, the methine signals of **5d** and **8d** were upfield 0.60−0.63 ppm compared to **4d** and **7d**.

(19) MS fragmentation of compounds of **5** (X = −CH=CH−) and **8** (X = S, *m*/*z* values in parentheses) is shown below. Relative intensities are noted in the Experimental Section. Additionally, carboxyalkyl derivatives **5c−e** and **8c−e** underwent an initial loss of H_2O.



(20) Chatuvedi, R. K.; MacMahon, A. E.; Schmir, G. L. *J. Am. Chem. Soc*. **1967**, *89*, 6984.

(21) Hino, T.; Nakagawa, M.; Yamaji, N.; Miwa, Y.; Tsuneoka, K.; Akaboshi, S. *Tetrahedron* **1971**, *27*, 775.

with chloroacetic acid gave **7c** as white crystals in 47% yield: mp 180−181 °C; ^{1}H NMR δ 4.16 (s, 2H), 5.22 (s, 2H), 7.29 (d, J = 5.2 Hz, 1H), 8.25 (d, J = 5.2 Hz, 1H); EIMS (m/z) 281 (M^+, 46), 237 ($M^+ - CO_2$, 40), 168 ($C_4H_2S(CO)NCS$, 100). Anal. Calcd for $C_{10}H_7N_3O_3S_2$: C, 42.70; H, 2.51; N, 14.94. Found: C, 42.62; H, 2.46; N, 14.85.

(*R,S*)-2-[[3-(Cyanomethyl)-3,4-dihydro-4-oxothieno[3,2-*d*]pyrimidin-2-yl]thio]propionic Acid (7d). Compound **6** was reacted with 2-chloropropionic acid to obtain **7d** as colorless crystals in 41% yield: mp 127−128 °C; ^{1}H NMR δ 1.61(d, J = 7.3 Hz, 3H), 4.58 (q, J = 7.3 Hz, 1H), 5.19 (s, 2H), 7.30 (d, J = 5.4 Hz, 1H), 8.26 (d, J = 5.4 Hz, 1H); EIMS (m/z) 295 (M^+, 31), 223 (100), 168 ($C_4H_2S(CO)NCS$, 73). Anal. Calcd for $C_{11}H_9N_3O_3S_2$: C, 44.74; H, 3.07; N, 14.23. Found: C, 44.45; H, 3.01; N, 14.06.

3-[[3-(Cyanomethyl)-3,4-dihydro-4-oxothieno[3,2-*d*]pyrimidin-2-yl]thio]propionic Acid (7e). Compound **6** was reacted with 3-chloropropionic acid to obtain **7e** as a slightly yellow solid in 57% yield: mp 172−173 °C; ^{1}H NMR δ 2.78 (t, J = 6.7 Hz, 2H), 3.46 (t, J = 6.7 Hz, 2H), 5.16 (s, 2H), 7.36 (d, J = 5.3 Hz, 1H), 8.25 (d, J = 5.3 Hz, 1H); EIMS (m/z) 295 (M^+, 34), 251 ($M^+ - CO_2$, 14), 168 ($C_4H_2S(CO)NCS$, 100). Anal. Calcd for $C_{11}H_9N_3O_3S_2$: C, 44.74; H, 3.07; N, 14.23. Found: C, 44.91; H, 3.11; N, 14.23.

General Procedure for the Preparation of Alkylthio Imidazo[2,1-*b*]quinazolinones and Imidazo[1,2-*a*]thieno-[3,2-*d*]pyrimidinones 5a,b and 8a,b. Potassium *tert*-butoxide (560 mg, 5 mmol) was added to a mixture of compound **4** or **7** (1 mmol), *t*-BuOH (80 mL), and the appropriate thiol (10 mmol). The reaction mixture was stirred at room temperature for 24 h, diluted with brine (400 mL), and extracted with ethyl acetate (2 × 100 mL). The organic layer was washed with H_2O (400 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was washed with cold hexane (40 mL) and purified by column chromatography.

2-(Propylthio)imidazo[2,1-*b*]quinazolin-5(1*H*)-one (5a). Compound **4a** was reacted with 1-propanethiol to give **5a** in 36% yield as a light brown solid: mp >164 °C dec; ^{1}H NMR δ 0.97 (t, 3H), 1.64 (sextet, 2H), 2.59 (t, 2H), 7.24−7.30 (m, 1H), 7.40−7.44 (m, 1H), 7.53 (s, 1H), 7.72−7.78 (m, 1H), 8.12−8.15 (m, 1H); EIMS (m/z)[19] 259 (M^+, 62), 217 (100), 145 (26). Anal. Calcd for $C_{13}H_{13}N_3OS$: C, 60.21; H, 5.05; N, 16.20; S, 12.36. Found: C, 60.47; H, 5.28; N, 16.11; S, 12.28.

2-(Benzylthio)imidazo[2,1-*b*]quinazolin-5(1*H*)-one (5b). Compound **5b** was obtained from **4b** and benzyl mercaptan in 41% yield as slightly yellow crystals: mp 242−243 °C; ^{1}H NMR δ 4.26 (s, 2H), 7.22−7.45 (m, 7H), 7.50 (s, 1H), 7.73−7.79 (m, 1H), 8.10−8.14 (m, 1H); EIMS (m/z)[19] 307 (M^+, 37), 216 (15), 145 (22), 91 ($C_7H_7^+$, 100). Anal. Calcd for $C_{17}H_{13}N_3OS$: C, 66.43; H, 4.26; N, 13.67. Found: C, 66.27; H, 4.21; N, 13.59.

6-(Propylthio)imidazo[1,2-*a*]thieno[3,2-*d*]pyrimidin-9(5*H*)-one (8a). Compound **7a** was treated with 1-propanethiol to obtain **8a** in 23% yield as yellow crystals: mp >150 °C dec; ^{1}H NMR δ 0.95 (t, 3H), 1.59 (sextet, 2H), 2.94 (t, 2H), 7.19 (d, J = 5.4 Hz, 1H), 7.62 (s, 1H), 8.14 (d, J = 5.4 Hz, 1H); EIMS (m/z)[19] 265 (M^+, 75), 223 (100), 151 (56). Anal. Calcd for $C_{11}H_{11}N_3OS_2 \cdot 0.5\ H_2O$: C, 48.16; H, 4.41; N, 15.32. Found: C, 48.10; H, 4.02; N 15.36.

6-(Benzylthio)imidazo[1,2-*a*]thieno[3,2-*d*]pyrimidin-9(5*H*)-one (8b). Compound **7b** was reacted with benzyl mercaptan to give **8b** in 27% yield as yellow crystals: mp >170 °C dec; ^{1}H NMR δ 4.24 (s, 2H), 7.19 (d, J = 5.4 Hz, 1H), 7.23−7.33 (m, 5H), 7.50 (s, 1H), 8.14 (d, J = 5.4 Hz, 1H); EIMS (m/z)[19] 313 (M^+, 65), 222 (14), 151 (25), 91 ($C_7H_7^+$, 100). Anal. Calcd for $C_{15}H_{11}N_3OS_2 \cdot 0.5$ AcOEt: C, 57.12; H, 4.23; N, 11.76. Found: C, 57.15; H, 4.26; N, 11.71.

General Procedure for the Preparation of Carboxyalkylthio Imidazo[2,1-*b*]quinazolinones and Imidazo[1,2-*a*]thieno[3,2-*d*]pyrimidinones 5c,d and 8c,d. A mixture of compound **4** or **7** (2 mmol) and mercaptoacetic acid (1.84 g, 20 mmol) or thiolactic acid (2.12 g, 20 mmol) was cooled to 0 °C and 1 M NaOH (30 mL, previously cooled to 0 °C) was added. The mixture was stirred for 10 min in an ice-bath and then acidified with 1 M HCl (45 mL). After the mixture was cooled for 6 h, the precipitate was collected by filtration and washed with *i*-PrOH to obtain pure products. Analytical samples were obtained by recrystallization from *i*-PrOH.

[(1,5-Dihydro-5-oxoimidazo[2,1-*b*]quinazolin-2-yl)thio]-acetic Acid (5c). Compound **4c** was reacted with mercaptoacetic acid to give **5c** as white crystals in 86% yield: mp >265 °C dec; ^{1}H NMR δ 3.83 (s, 2H), 7.24−7.30 (m, 1H), 7.40−7.44 (m, 1H), 7.53 (s, 1H), 7.73−7.78 (m, 1H), 8.11−8.14 (m, 1H); EIMS (m/z)[19] 275 (M^+, 10), 257 ($M^+ - H_2O$, 100), 216 (18), 145 (23). Anal. Calcd for $C_{12}H_9N_3O_3S$: C, 52.36; H, 3.30; N, 15.26. Found: C, 51.99; H, 3.28; N, 14.91.

(*R,S*)-2-[(1,5-Dihydro-5-oxoimidazo[2,1-*b*]quinazolin-2-yl)thio]propionic Acid (5d). Compound **4d** was treated with thiolactic acid to afford **5d** in 84% yield as a white solid: mp 255−257 °C; ^{1}H NMR δ 1.44 (d, J = 7.1 Hz, 3H), 3.97 (q, J = 7.1 Hz, 1H), 7.23−7.30 (m, 1H), 7.40−7.44 (m, 1H), 7.63 (s, 1H), 7.73−7.79 (m, 1H), 8.11−8.15 (m, 1H); EIMS (m/z)[19] 289 (M^+, 4), 271 ($M^+ - H_2O$, 100), 216 (17), 145 (37). Anal. Calcd for $C_{13}H_{11}N_3O_3S$: C, 53.97; H, 3.83; N, 14.52. Found: C, 53.93; H, 3.86; N, 14.39.

[(5,9-Dihydro-9-oxoimidazo[1,2-*a*]thieno[3,2-*d*]pyrimidin-6-yl)thio]acetic Acid (8c). Compound **7c** was treated with mercaptoacetic acid to obtain **8c** as a white solid in 82% yield: mp 242−245 °C; ^{1}H NMR δ 3.84 (s, 2H), 7.18 (d, J = 5.4 Hz, 1H), 7.60 (s, 1H), 8.16 (d, J = 5.4 Hz, 1H); EIMS (m/z)[19] 281 (M^+, 9), 263 ($M^+ - H_2O$, 100), 222 (7), 151 (12). Anal. Calcd for $C_{10}H_7N_3O_3S_2$: C, 42.70; H, 2.51; N, 14.94. Found: C, 42.46; H, 2.55; N, 14.66.

(*R,S*)-2-[(5,9-Dihydro-9-oxoimidazo[1,2-*a*]thieno[3,2-*d*]-pyrimidin-6-yl)thio]propionic Acid (8d). Compound **7d** was reacted with thiolactic acid to give **8d** as a white solid in 86% yield. An analytic sample was obtained by washing the product with hot *i*-PrOH: mp 262−266 °C; ^{1}H NMR δ 1.41 (d, J = 7.1 Hz, 3H), 3.89 (q, J = 7.1 Hz, 1H), 7.19 (d, J = 5.4 Hz, 1H), 7.70 (s, 1H), 8.16 (d, J = 5.4 Hz, 1H); EIMS (m/z)[19] 295 (M^+, 2), 277 ($M^+ - H_2O$, 100), 223 (10), 151 (21). Anal. Calcd for $C_{11}H_9N_3O_3S_2 \cdot 0.5\ H_2O$: C, 43.41; H, 3.31; N, 13.81. Found: C, 43.25; H, 2.99; N, 13.50.

General Procedure for the Preparation of Carboxyethylthio Derivatives 5e and 8e. A mixture of compound **4e** or **7e** (2 mmol), 3-mercaptopropionic acid (2.12 g, 20 mmol), and 1 M NaOH (30 mL) was stirred at room temperature for 4 h. The mixture was acidified with 1 M HCl (45 mL) and cooled. The precipitate was collected by filtration and washed with cold H_2O to obtain pure products.

3-[(1,5-Dihydro-5-oxoimidazo[2,1-*b*]quinazolin-2-yl)thio]-propionic Acid (5e). Compound **5e** was obtained from compound **4e** in 91% yield. Recrystallization from *i*-PrOH afforded slightly yellow crystals: mp >235 °C dec; ^{1}H NMR δ 2.63 (t, J = 7.0 Hz, 2H), 3.13 (t, J = 7.0 Hz, 2H), 7.24−7.30 (m, 1H), 7.40−7.44 (m, 1H), 7.59 (s, 1H), 7.72−7.79 (m, 1H), 8.11−8.15 (m, 1H); EIMS (m/z)[19] 289 (M^+, 28), 271 ($M^+ - H_2O$, 50), 216 (100), 145 (20). Anal. Calcd for $C_{13}H_{11}N_3O_3S$: C, 53.97; H, 3.83; N, 14.52. Found: C, 53.97; H, 3.93; N, 14.41.

3-[(5,9-Dihydro-9-oxoimidazo[1,2-*a*]thieno[3,2-*d*]pyrimidin-6-yl)thio]propionic Acid (8e). Compound **8e** was obtained from compound **7e** in 89% yield. Recrystallization from *i*-PrOH afforded colorless crystals: mp 229−230 °C; ^{1}H NMR δ 2.59 (t, J = 7.0 Hz, 2H), 3.11 (t, J = 7.0 Hz, 2H), 7.19 (d, J = 5.4 Hz, 1H), 7.65 (s, 1H), 8.14 (d, J = 5.4 Hz, 1H); EIMS (m/z)[19] 295 (M^+, 6), 277 ($M^+ - H_2O$, 73), 223 (100), 151 (19). Anal. Calcd for $C_{11}H_9N_3O_3S_2$: C, 44.74; H, 3.07; N, 14.23. Found: C, 44.51; H, 3.19; N, 14.00.

1,4-Dihydro-2,4-dioxo-3(2*H*)-quinazolineacetonitrile (10). Compound **9**[22] (2.42 g, 10 mmol), aminoacetonitrile bisulfate (1.74 g, 11.3 mmol), and pyridine (50 mL) were stirred at room temperature for 24 h. The precipitate that formed was separated, and the filtrate was evaporated under reduced pressure to obtain a yellow oil. Ice−water (150 mL) was added, and the precipitate was collected by filtration to give **10** (1.63 g, 81%). Recrystallization from EtOH/H_2O afforded colorless crystals: mp 250−251 °C; ^{1}H NMR δ 4.89 (s, 2H), 7.19−7.28 (m, 2H), 7.68−7.74 (m, 1H), 7.95−7.99 (m, 1H), 11.76 (s, 1H); EIMS (m/z) 201 (M^+, 100). Anal. Calcd for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.84; H, 3.58; N, 20.93.

1,4-Dihydro-4-oxo-2-thioxo-3(2*H*)-quinazolineacetamide (11). Compound **3** (870 mg, 4 mmol) was dissolved in a

(22) Kühle, E.; Wegler, R. *Liebigs Ann. Chem.* **1958**, *616*, 183.

mixture of 0.5 M NaOH (16 mL) and acetone (8 mL), stirred at room temperature for 15 h, and poured into 0.5 M HCl (20 mL). The precipitate was collected by filtration to afford **11** (605 mg, 64%). Recrystallization from acetic acid gave colorless crystals: mp >280 °C dec; ^{1}H NMR δ 4.99 (s, 2H), 7.10 (s, br, 1H), 7.32−7.45 (m, 2H), 7.58 (s, br, 1H), 7.73−7.79 (m, 1H), 7.93−7.97 (m, 1H); EIMS (*m*/*z*) 235 (M^+, 50), 218 (100). Anal. Calcd for $C_{10}H_9N_3O_2S$: C, 51.05; H, 3.86; N, 17.86. Found: C, 51.22; H, 3.83; N, 17.64.

2-(Propylthio)-4-oxo-3(4*H*)-quinazolineacetamide (12a). 1-Bromopropane (615 mg, 5 mmol) and 1 M NaOH (4.4 mL) were added to a mixture of compound **11** (940 mg, 4 mmol) and acetone (10 mL). This was stirred at room temperature for 24 h, diluted with H_2O, and cooled. The precipitate was collected to obtain **12a** (895 mg, 81%): mp 216−217 °C (acetone/H_2O); ^{1}H NMR δ 0.99 (t, 3H), 1.72 (sextet, 2H), 3.24 (t, 2H), 4.67 (s, 2H), 7.30 (s, br, 1H), 7.41−7.48 (m, 1H), 7.53−7.57 (m, 1H), 7.72 (s, br, 1H), 7.76−7.83 (m, 1H), 8.30−8.80 (m, 1H); EIMS (*m*/*z*) 277 (M^+, 17), 260 ($M^+ - OH$, 22), 218 ($M^+ - OH - C_3H_6$, 100). Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15. Found: C, 56.46; H, 5.36; N, 15.15.

2-(Benzylthio)-4-oxo-3(4*H*)-quinazolineacetamide (12b). Benzyl chloride (633 mg, 5 mmol) and 1 M NaOH (4.4 mL) were added to a mixture of compound **11** (940 mg, 4 mmol) and acetone (10 mL). The mixture was stirred at room temperature for 24 h, diluted with H_2O, and cooled. The precipitate was collected to afford **12b** (1.09 g, 84%): mp 228−229 °C (ethyl acetate/cyclohexane); ^{1}H NMR δ 4.54 (s, 2H), 4.65 (s, 2H), 7.26−7.35 (m, 4H), 7.47−7.52 (m, 3H), 7.63−7.66 (m, 1H), 7.72 (s, br, 1H), 7.80−7.85 (m, 1H), 8.05−8.08 (m, 1H); EIMS (*m*/*z*) 325 (M^+, 19), 308 ($M^+ - OH$), 91 ($C_7H_7^+$, 100). Anal. Calcd for $C_{17}H_{15}N_3O_2S$: C, 62.75; H, 4.65; N, 12.91. Found: C, 62.54; H, 4.67; N, 13.01.

[[3-(Carbamoylmethyl)-3,4-dihydro-4-oxo-2-quinazolinyl]-thio]acetic Acid (12c). A mixture of compound **11** (1.18 g, 5 mmol), Na_2CO_3 (2.12 g, 20 mmol), KI (1.66 g, 10 mmol), DMF (25 mL), and chloroacetic acid (945 mg, 10 mmol) was stirred at 100 °C for 90 min and poured into H_2O (200 mL). The pH was adjusted to 7.5 and the solution was extracted with ethyl acetate (200 mL), followed by hexane (150 mL). The aqueous layer was acidified with 1 M HCl, and the mixture was cooled. The precipitate that formed was collected by filtration, dried, and recrystallized from acetic acid to give **12c** (760 mg, 52%): mp 227−228 °C; ^{1}H NMR δ 4.07 (s, 2H), 4.69 (s, 2H), 7.35 (s, br, 1H), 7.43−7.50 (m, 2H), 7.76−7.83 (m, 2H), 8.04−8.07 (m, 1H); MS (FAB) 294 (MH^+). Anal. Calcd for $C_{12}H_{11}N_3O_4S$: C, 49.14; H, 3.78; N, 14.33. Found: C, 49.21; H, 3.76; N, 14.33.

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