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ONE-POT SYNTHESIS OF DENSELY FUNCTIONALIZED THIAZOLES AND *SYN*-3-THIOACRYLATES

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Abstract – A sequential one-pot, two-step reaction has been established for efficient synthesis of densely functionalized thiazoles and *syn*-3-thioacrylates. Treatment of cyanoacetamide with isothiocyanates gave rise to 2-cyano-3-mercaptoacrylamides, trapped by but-2-ynedioates through [3+2] cyclization to access functionalized thiazoles. Using propiolates to replace but-2-ynedioates, the reaction resulted in highly substituted *syn*-3-thioacrylates. The present green synthesis shows several advantages including operational simplicity and fast reaction rates, which makes it a useful and attractive process of library generation for drug discovery.

INTRODUCTION

Thiazoles and their analogues, being as an important class of bioactive heterocycles, present in naturally occurring and non-naturally products, which show a wide spectrum of pharmacological properties[1] such as antidiabetic, antibiotic, and antifungal activities.[2–6] Particularly, thiazoles can serve as antidiabetic agents that increase the insulin sensitivity of target tissues, and they also acted as potent and selective activators of peroxisome proliferator-activated receptor γ (PPARγ).[7] Owing to the biological significance of these molecules, the synthesis of thiazoles has attracted considerable attentions. For instance, Obydennov and co-workers reported the synthesis of 3-oxothien-2-ylidenes or 4-oxothiazol-2,5-ylidenes

through a reaction of thioacetamides with dimethyl acetylenedicarboxylate but involved the narrow substrate scope.[8] Basheer and co-workers employed cyanoacetamide to react with isothiocyanates, followed by treating cycloketones to generate several 1,3-thiazine derivatives, but demanded a two-step process.[9] Although these limited syntheses, the explorations of a facile and practical protocol toward new thiazoles with diversity in their substituents is highly desirable. Recently, we developed a sequential one-pot, two-step reaction for efficient synthesis of spiro-substituted 1,3-thiazine library.[10] In this report, 2-cyano-3-mercaptoacrylamides (Figure 1), derived from cyanoacetamide and isothiocyanatobenzene, were subjected with cyclic ketones through [5+1] cyclizations, affording spiro-substituted 1,3-thiazines. S1,N5-binucleophilic sites of 2-cyano-3-mercaptoacrylamides were involved in this transformation. Enlightened by cyclization reactions, we envisioned that [3+2] cyclization can be realized in a one-pot, two-step process using 1,2-bielectrophiles to react with S1,N3-binucleophilic sites of compounds **A**. As a continuation of our research devoted to domino reactions,[11] in this paper, we would like to report a one-pot, two-step reaction for the domino synthesis of thiazole derivatives using cyanoacetamide **1**, isothiocyanates **2** and but-2-ynedioates **3a-b** as starting materials. The syntheses were achieved by reacting cyanoacetamide with isothiocyanates to yield 2-cyano-3-mercaptoacrylamides **A**, which are trapped by but-2-ynedioates through [3+2] cyclization, providing multi-functionalized thiazole derivatives **4**. With exchanging but-2-ynedioates **3a-b** for propiolates **3c-d**, the reaction gave an unexpected 3-thioacrylates **6** with *syn*-selectivity (only *syn* isomer) (Scheme 1).

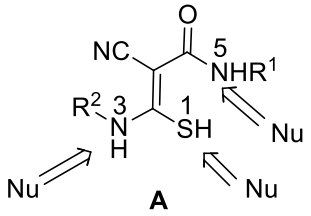
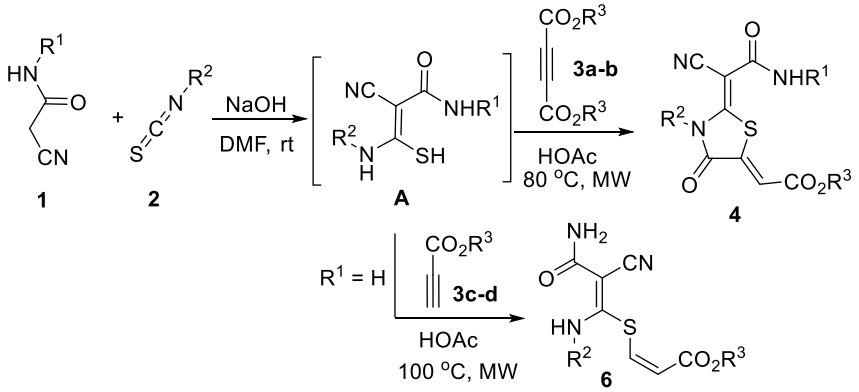


Figure 1. The reactivity of 2-cyano-3-mercaptoacrylamides



Scheme 1. Chemoselective synthesis of thiazoles **4** and *syn*-3-thioacrylates **6**

RESULTS AND DISCUSSION

We firstly chose dimethyl but-2-ynedioate (DMAD) as 1,2-bielectrophiles to explore the feasibility of this reaction in one-pot two-step manner. Upon treatment with isothiocyanates and cyanoacetamide in the presence of sodium hydroxide in DMF at room temperature gave 2-cyano-3-mercaptoacrylamides in quantitative chemical yields. Without isolation, excess of HOAc (2.0 mL) was added into the above reaction system, followed by dimethyl but-2-ynedioate (DMAD) **3a**, due to HOAc can promote the [3+2] cyclization. The new reaction system was heating at 60 ºC under microwave irradiation (MWI) for 20 min. The pale yellow solid was obtained in 52% chemical yield (Table 1, entry 1). Its characterization by NMR and IR spectra indicated that the structure of resultant solid was thiazoles **4a**. Next, we screened reaction temperatures and solvents for the reaction. The identical reaction was repeated many times at reaction temperatures ranging from 60 ºC to 100 ºC. The best result was obtained (**4a**, 78% yield, entry 2) when the reaction was conducted at 80 ºC in HOAc. Increasing reaction temperature to 100 ºC did not improve chemical yields (entry 3). Other solvents such as ethanol, formic acid (HCO_2H), and propionic acid ($EtCO_2H$) were inferior to HOAc in terms of reaction yields (entries 4-6).

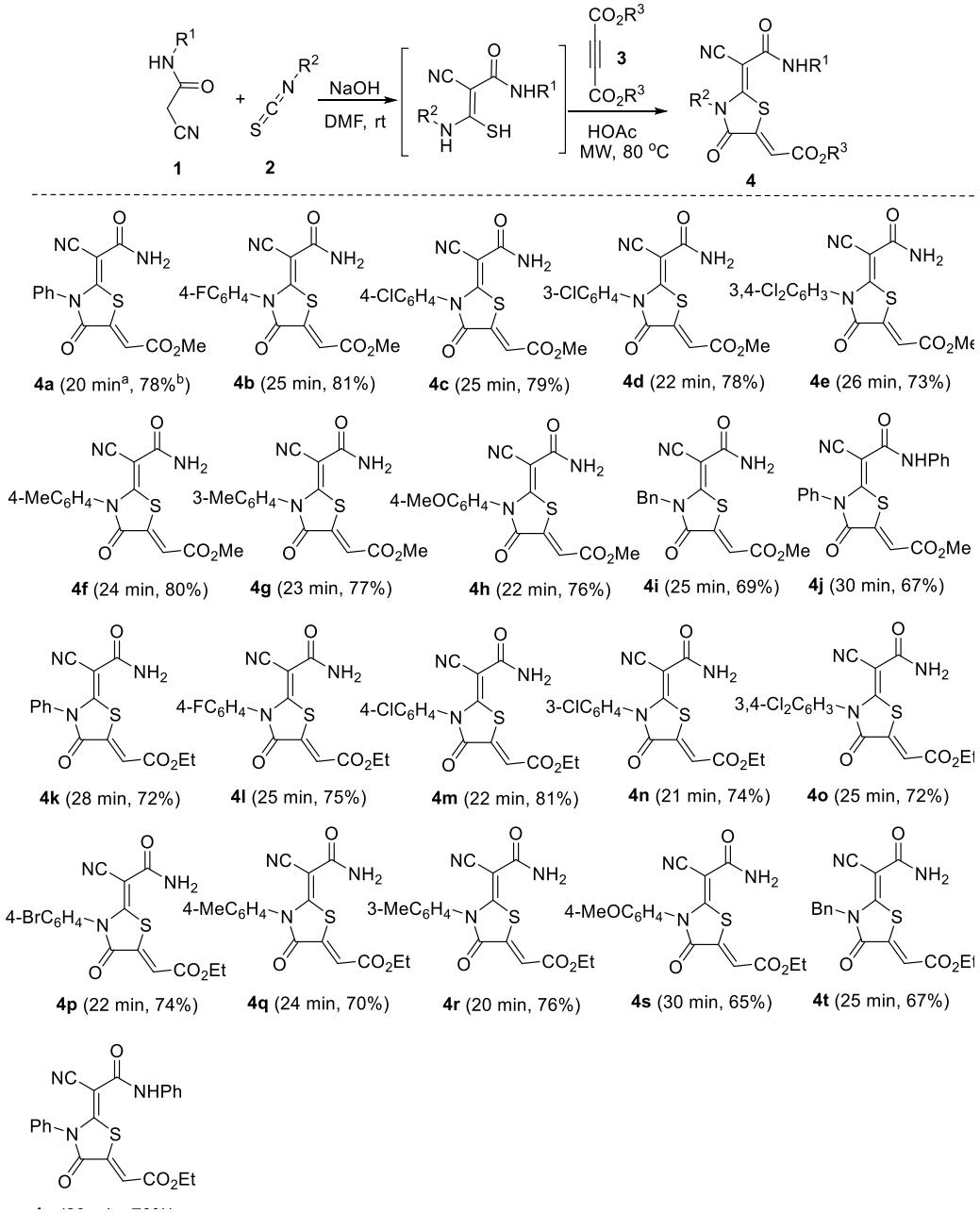
Table 1. Optimization of reaction conditions under MWI

Entry	Solvent	T/ ºC	Yield [a]/%
1	HOAc	60	52
2	HOAc	80	78
3	HOAc	100	70
4	EtOH	80	14
5	HCO_2H	80	56
6	$EtCO_2H$	80	68

[a] Isolated yield

With this result in hand, we went on to study the scope of the methodology. Using the optimized reaction conditions, a variety of structurally diverse isothiocyanates **2** were investigated and a series of new thiazole derivatives **4** were afforded in good yields through one-pot two-step strategy. As shown in Scheme 2, at the beginning, we made a search for the isothiocyanate substrate scope, cyanoacetamide **1** and DMAD **3a** were used as model substrates, and the results indicated that arylated isothiocyanates bearing electron-withdrawing (fluoro, chloro) or electron-donating (methyl, methoxy) groups were found to be suitable for the synthesis of compound **4**, giving good to excellent yields ranging from 73-81% (**4b**-**4h**). Notably, aliphatic counterparts such as benzyl group also exhibited a high reactivity, allowing [3+2] cyclization toward the formation of the corresponding densely functionalized thiazoles **4i** in a 69%

yield. Alternatively, *N*-phenyl-cyanoacetamide **1b** was successfully engaged in this transformation, affording highly substituted thiazoles **4j** in a 67% yield. Replacement of diethyl but-2-ynedioate **3b** with substrate **3a** delivered a wide range of polysubsituted thiazoles **4k-4u** in acceptable yields. The electronic property of arylated isothiocyanates shows no deducible impact on the reaction results. The structural elucidation and the attribution of stereoselectivity were unequivocally determined by NMR spectroscopic analysis and X-ray diffraction of single crystals that was obtained by slow evaporation of the solvent, as in the case of thiazole **4m** (Figure 2).



Scheme 2. Domino synthesis of products **4**. [a]Second-step reaction times under MWI. [b]Isolated yield.

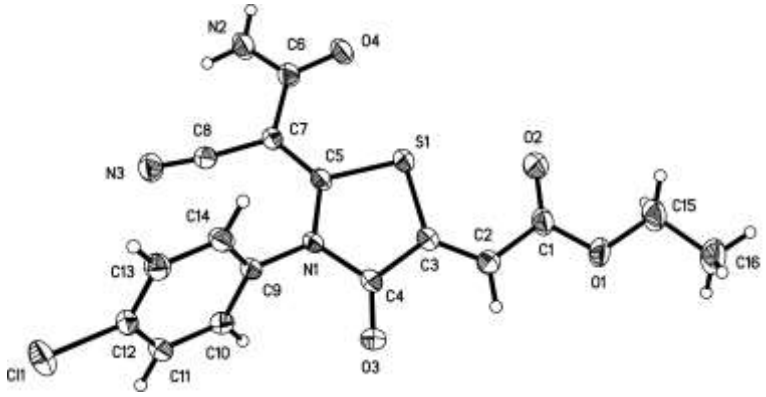
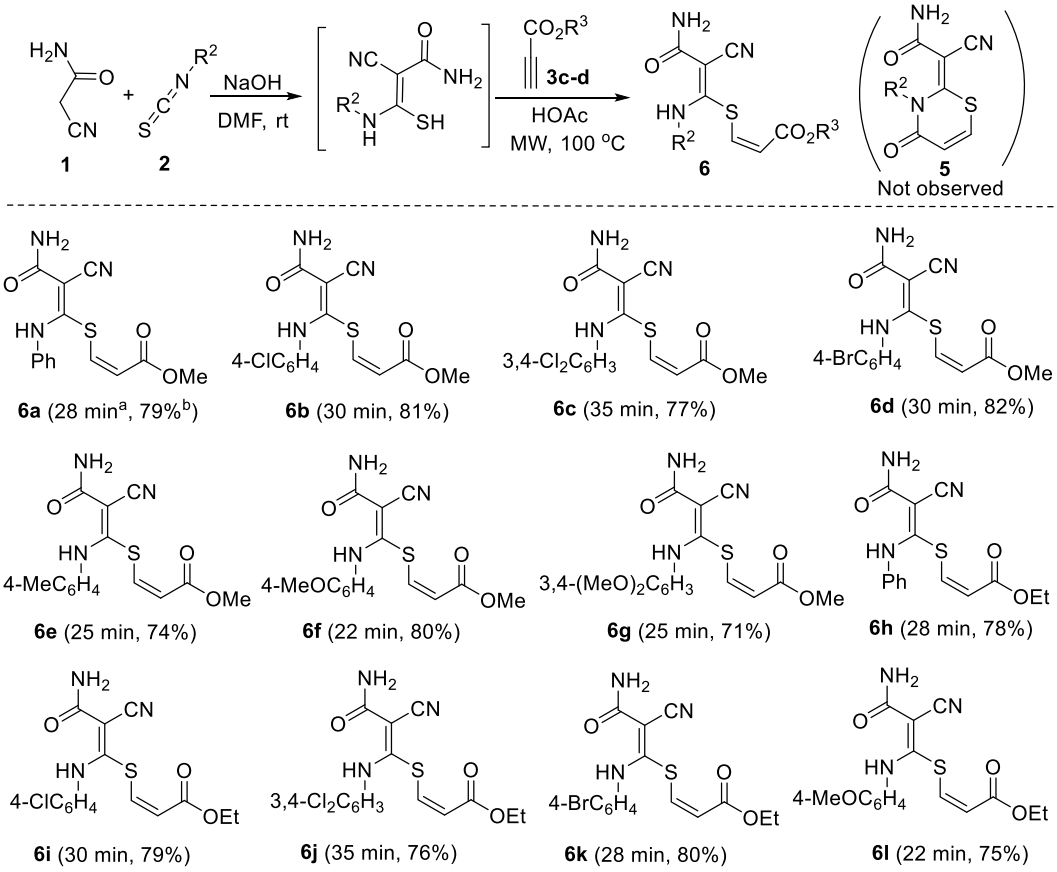


Figure 2. X-Ray structure of compound **4m**[12]



Scheme 3. Synthesis of *syn*-3-thioacrylates **6.** [a]Second-step reaction times under MWI. [b]Isolated yield

In view of our success with one-pot/two-step protocol for the synthesis of functional thiazoles **4**, we envisioned this reaction can proceed to yield 1,3-thiazin-4(3*H*)-ones **5** through [3+3] cyclization using propiolates **3c-d** to replace substrates **3a-b**. Unexpectedly, instead of 1,3-thiazin-4(3*H*)-ones **5**, the reaction underwent another direction to form the *syn*-adducts **6** (Scheme 3). A range of isothiocyanates containing a variety of different functional groups, such as methyl, methoxy, chloride and bromide were tolerated leading to the corresponding *syn*-3-thioacrylates **6** with good yields (71%-82%). The results

revealed that the electronic nature of the substituents on the benzene ring of isothiocyanates had no significant influence on the reactivity. In order to determine the stereochemistry of 3-thioacrylates **6**, the single crystal of **6a** was obtained by slow evaporation of the solvent. Its relative stereo-configuration was established by X-ray diffraction as shown in Figure 3.

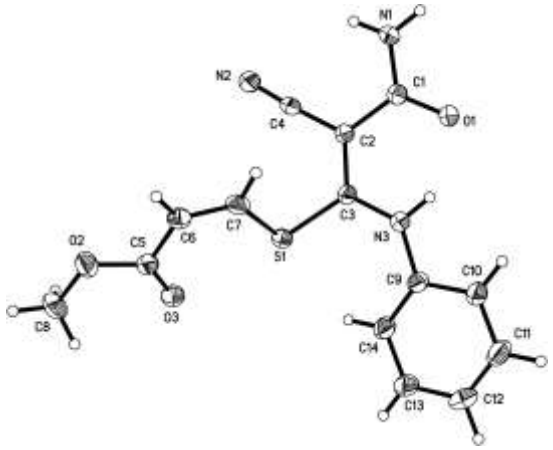
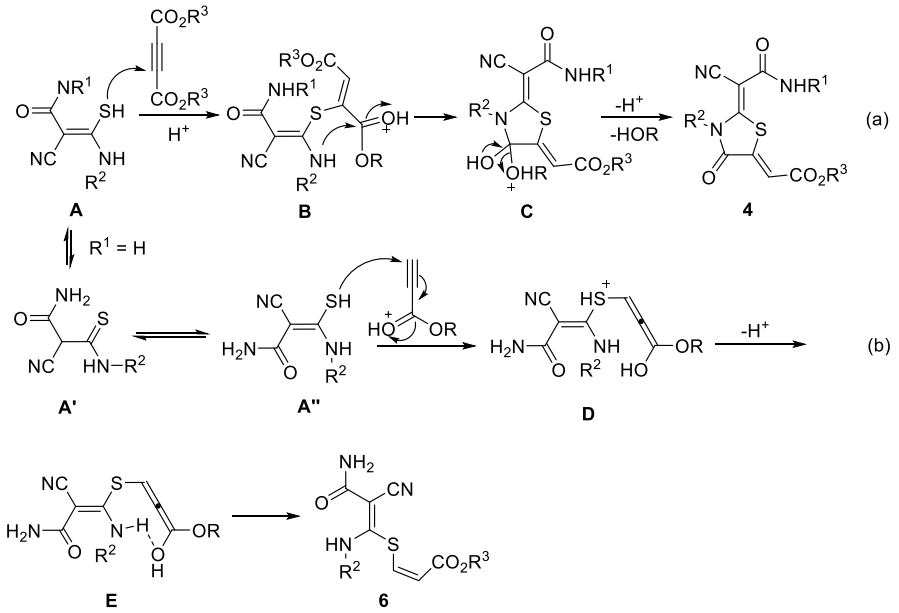


Figure 3. X-Ray structure of compound **6a**[13]

In general, the present two new reactions showed the following attractive characteristics: (1) the reactions proceed efficiently with formation of alcohols as a major by-product under air conditions, which belongs to environmentally friendly chemistry; (2) the convenient workup is needed *via* simple filtration since the products directly precipitate out of solution after the reaction system is diluted with cold water, which belongs to GAP chemistry;[14] (3) Excellent stereoselectivity of both reactions was achieved without using any metal catalysts.



Scheme 4. Proposed mechanism for products **4** and **6**

On the basis of the above results, possible mechanisms have been proposed for the formation of products **4** and **6** as shown in Scheme 4. The formation of thiazoles **4** involved a successive *S*-addition / *N*-addition and elimination of alkoxy group sequence (Scheme 4(a)). Similar to the former reaction, the latter underwent tautomerization, *S*-addition and *syn*-tautomerization of enols to generate the final 3-thioacrylates **6** (Scheme 4(b)). The *syn*-selectivity may be attributed the intramolecular hydrogen bonds. In conclusion, we have developed one-pot two-step practical reactions for the efficient synthesis of densely functionalized thiazoles and *syn*-3-thioacrylates under microwave irradiation using commercially available starting materials. The reaction showed high stereoselectivity and broad scopes of substrates which can employ a wide range of common commercial starting materials. A new mechanism has been proposed to explain the reaction process and stereoselectivity. Both reactions feature mild conditions, simple operation, easy accessibility of reactants and workup procedure as well as metal-free catalysts. Further investigation on the biological evaluation of these resultant products is underway.

EXPERIMENTAL

Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage Company, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 with chemical shift (δ) given in ppm relative to TMS as internal standard. HRMS (ESI) was determined by using microTOF-QⅡ HRMS/MS instrument (BRUKER). X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer

General Procedure for the Synthesis of Compounds 4a

Typically, in a 10 mL Initiator reaction vial, phenyl isothiocyanate (1.0 mmol) with cyanoacetamide (1.0 equiv) was performed in DMF catalyzed by sodium hydroxide (0.2 equiv) for 30 min at room temperature, and then HOAc (2.0 mL, excess) and dimethyl but-2-ynedioate (1.2 equiv) were added into the reaction system. Subsequently, the mixture was irradiated by microwave at 80 ^oC for 20 min. The automatic mode stirring helped the mixing and uniform heating of the reactants. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and diluted with cold water, which then was filtered to give the crude products. The crude products were further purified by recrystallization from 95% EtOH as a pale yellow solid

(Z)-Methyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-4-oxo-3-phenylthiazolidin-5-ylidene)acetate (4a)

A pale yellow solid; Mp >300 ^oC; IR (KBr, ν, cm^{-1}): 3469, 3355, 3319, 3248, 3168, 2210, 1731, 1699, 1667, 1591, 1536, 1493, 1446, 1373, 1326, 1245, 1202, 1014, 869; ^1H NMR (400 MHz, DMSO-d_6) (δ,

ppm): 7.77 (s, 1H, NH_2), 7.58-7.53 (m, 5H, Ar-H), 7.36 (s, 1H, NH_2), 6.80 (s, 1H,CH), 3.82 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.9, 164.7, 164.6, 161.6, 141.4, 134.5, 130.7, 129.4, 129.3, 116.9, 112.8, 81.4, 52.6. HRMS (ESI): *m/z* calcd for $C_{15}H_{11}N_3NaO_4S$, 352.0368 $[M+Na]^+$; found: 352.0344.

(*Z*)-Methyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(4-fluorophenyl)-4-oxothiazolidin-5-ylidene)-acetate (4b)

A pale yellow solid; Mp 288-289 ºC; IR (KBr, ν, cm^{-1}): 3509, 3430, 3404, 3337, 3293, 3242, 3196, 2202, 1737, 1715, 1666, 1602, 1536, 1508, 1437, 1373, 1229, 1262, 1053, 1026, 859, 706; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.78 (s, 1H, NH_2), 7.64-7.61 (m, 2H, Ar-H), 7.42 (s, 1H, NH_2), 3.79 (d, J = 8.4 Hz, 2H, Ar-H), 6.81 (s, 1H, CH), 3.35 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.8, 164.7, 164.5, 162.0, 141.4, 132.0, 131.9, 130.8, 117.0, 116.5, 116.2, 112.9, 81.3, 52.6. HRMS (ESI): *m/z* calcd for $C_{15}H_{10}FN_3NaO_4S$, 370.0274 $[M+Na]^+$; found: 370.0270.

(*Z*)-Methyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(4-chlorophenyl)-4-oxothiazolidin-5-ylidene)-acetate (4c)

A pale yellow solid; Mp: 265-267 ºC; IR (KBr, ν, cm^{-1}): 3473, 3331, 3285, 3209, 3072, 2203, 1744, 1674, 1526, 1476, 1392, 1330, 1224, 1195, 1014, 875; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.78 (s, 1H, NH_2), 7.65-7.58 (m, 4H, Ar-H), 7.37 (s, 1H, NH_2), 6.81 (s, 1H, CH), 3.82 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.8, 164.6, 164.5, 161.7, 141.3, 135.5, 133.4, 131.4, 129.5, 117.0, 113.0, 81.2, 52.6. HRMS (ESI): *m/z* calcd for $C_{15}H_{10}ClN_3NaO_4S$, 385.9978 $[M+Na]^+$; found: 385.9984.

(*Z*)-Methyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(3-chlorophenyl)-4-oxothiazolidin-5-ylidene)-acetate (4d)

A pale yellow solid; Mp >300 ºC; IR (KBr, ν, cm^{-1}): 3473, 3339, 3285, 3208, 3173, 2204, 1744, 1695, 1677, 1524, 1438, 1330, 1219, 1054, 1014, 875; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.80 (s, 1H, NH_2), 7.76 (s, 1H, Ar-H), 7.69-7.66 (m, 1H, Ar-H), 7.60-7.55 (m, 2H, Ar-H), 7.43 (s, 1H, NH_2), 6.82 (s, 1H, CH), 3.82 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.8, 164.6, 164.4, 161.5, 141.2, 135.7, 133.4, 130.8(8), 130.8(6), 129.5, 128.5, 117.0, 113.0, 81.3, 52.6. HRMS (ESI): *m/z* calcd for $C_{15}H_{10}ClN_3NaO_4S$, 385.9978 $[M+Na]^+$; found: 385.9965.

(*Z*)-Methyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(3,4-dichlorophenyl)-4-oxothiazolidin-5-ylidene)acetate (4e)

A pale yellow solid; Mp >300 ºC; IR (KBr, ν, cm^{-1}): 3466, 3345, 3267, 3168, 3061, 2983, 2938, 2204, 1744, 1677, 1615, 1529, 1475, 1392, 1377, 1357, 1229, 1201, 1137, 919, 866; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.00 (d, J = 2.0 Hz, 1H, NH_2), 7.87 (d, J = 8.8 Hz, 1H, Ar-H), 7.80 (s, 1H, Ar-H), 7.64-7.61 (m, 1H, Ar-H), 7.43 (s, 1H, NH_2), 6.83 (s, 1H, CH), 3.83 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.8, 164.5, 164.3, 161.5, 141.1, 134.2, 133.8, 131.6(9), 131.6(7), 131.3, 130.2,

117.2, 113.2, 81.2, 52.7. HRMS (ESI): *m/z* calcd for $C_{15}H_9Cl_2N_3NaO_4S$, 419.9589 $[M+Na]^+$; found: 419.9583.

(*Z*)-Methyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-4-oxo-3-(*p*-tolyl)thiazolidin-5-ylidene)acetate (4f)

A pale yellow solid; Mp 293-295 ºC; IR (KBr, ν, cm^{-1}): 3486, 3352, 3324, 3260, 3179, 3079, 3039, 2204, 1741, 1683, 1599, 1532, 1448, 1371, 1326, 1238, 1205, 1009, 899, 858, 831; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.75 (s, 1H, NH_2), 7.38 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.34-7.31 (m, 3H, NH_2 and Ar-H), 7.43 (s, 1H, NH_2), 6.79 (s, 1H, CH), 3.82 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.9, 164.7, 164.6, 161.8, 141.4, 140.4, 131.9, 129.8, 129.1, 116.9, 112.9, 81.3, 52.6, 21.0. HRMS (ESI): *m/z* calcd for $C_{16}H_{13}N_3NaO_4S$, 366.0524 $[M+Na]^+$; found: 366.0522.

(*Z*)-Methyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-4-oxo-3-(*m*-tolyl)thiazolidin-5-ylidene)acetate (4g)

A pale yellow solid; Mp 284-286 ºC; IR (KBr, ν, cm^{-1}): 3472, 3314, 3165, 3064, 2949, 2202, 1744, 1698, 1602, 1539, 1439, 1332, 1245, 1058, 1017, 947, 915, 893, 857; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.75 (s, 1H, NH_2), 7.41 (d, 2H, *J* = 7.2 Hz , Ar-H), 7.33-7.30 (m, 3H, NH_2 and Ar-H), 6.79 (s, 1H, CH), 3.82 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.9, 164.7, 164.6, 161.6, 141.4, 138.9, 134.3, 131.4, 129.6, 129.1, 126.4, 116.9, 112.8, 81.4, 52.6, 20.8. HRMS (ESI): *m/z* calcd for $C_{16}H_{13}N_3NaO_4S$, 366.0524 $[M+Na]^+$; found: 366.0530.

(*Z*)-Methyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(4-methoxyphenyl)-4-oxothiazolidin-5-ylidene)-acetate (4h)

A pale yellow solid; Mp 265-266 ºC; IR (KBr, ν, cm^{-1}): 3440, 3349, 3320, 3262, 3193, 2204, 1744, 1678, 1605, 1599, 1509, 1445, 1376, 1325, 1235, 1170, 1018, 943, 899; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.75 (s, 1H, NH_2), 7.43 (d, *J* = 9.2 Hz, 2H, Ar-H), 7.32 (s, 1H, NH_2), 7.06 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.79 (s, 1H, CH), 3.82 (s, 6H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.9, 164.7, 164.6, 162.3, 160.8, 141.5, 130.7, 126.9, 116.8, 114.5, 113.0, 81.3, 55.5, 52.6. HRMS (ESI): *m/z* calcd for $C_{16}H_{13}N_3NaO_5S$, 382.0474 $[M+Na]^+$; found: 382.0475.

(*Z*)-Methyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-benzyl-4-oxothiazolidin-5-ylidene)acetate (4i)

A pale yellow solid; Mp 268-269 ºC; IR (KBr, ν, cm^{-1}): 3451, 3338, 3282, 3204, 3171, 3059, 2199, 1738, 1688, 1674, 1603, 1520, 1433, 1347, 1321, 1218, 1077; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.86 (s, 1H, NH_2), 7.58 (s, 1H, NH_2), 7.37 (t, *J* = 7.2 Hz, 2H, Ar-H), 7.29 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.18 (d, *J* = 7.6 Hz, 2H, Ar-H), 6.86 (s, 1H, CH), 5.48 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.8, 165.4, 164.3, 161.4, 140.1, 134.9, 128.7, 127.4, 125.8, 117.8, 115.3, 80.6, 52.6, 47.5. HRMS (ESI): *m/z* calcd for $C_{16}H_{13}N_3NaO_4S$, 366.0524 $[M+Na]^+$; found: 366.0502.

(*Z*)-methyl 2-(2-(1-cyano-2-oxo-2-(phenylamino)ethylidene)-4-oxo-3-phenylthiazolidin-5-ylidene)-

acetate (4j)

A pale yellow solid; Mp 271-273 ºC; IR (KBr, ν, cm^{-1}): 3468, 3435, 3285, 3200, 3063, 2203, 1731, 1693, 1654, 1600, 1531, 1442, 1364, 1321, 1219, 912, 869; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.81 (s, 1H, NH_2), 7.58 (s, 7H, Ar-H), 7.34 (s, 2H, Ar-H), 7.14 (s, 1H, Ar-H), 6.85 (s, 1H, CH), 6.85 (s, 1H, CH), 3.83 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.8, 164.7, 162.4, 161.9, 140.7, 137.7, 134.4, 130.8, 129.4(2), 129.3(7), 128.5, 124.5, 121.3, 117.4, 112.5, 82.0, 52.7. HRMS (ESI): *m/z* calcd for $C_{21}H_{15}N_3NaO_4S$, 428.0681 $[M+Na]^+$; found: 428.0681.

(*Z*)-Ethyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-4-oxo-3-phenylthiazolidin-5-ylidene)acetate (4k)

A pale yellow solid; Mp: 248-249 ºC; IR (KBr, ν, cm^{-1}): 3460, 3358, 3322, 3240, 3172, 2204, 1720, 1699, 1660, 1598, 1539, 1493, 1444, 1379, 1326, 1245, 1200, 1011, 868; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.70 (s, 1H, NH_2),7.60-7.53 (m, 3H, Ar-H), 7.49-7.46 (m, 2H, NH_2 and Ar-H), 6.78 (s, 1H, CH), 4.28 (m, 2H, CH_2) , 1.31 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.3, 164.6, 164.5, 161.7, 140.8, 134.2, 130.8, 129.3, 129.2, 117.6, 112.8, 81.4, 61.5, 13.9. HRMS (ESI): *m/z* calcd for $C_{16}H_{13}N_3NaO_4S$, 366.0524 $[M+Na]^+$; found: 366.0520.

(*Z*)-Ethyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(4-fluorophenyl)-4-oxothiazolidin-5-ylidene)-acetate (4l)

A pale yellow solid; Mp 262-263 ºC; IR (KBr, ν, cm^{-1}): 3477, 3341, 3285, 3200, 3167, 2203, 1742, 1675, 1525, 1371, 1325, 1227, 1195, 1027, 883; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.78 (s, 1H, NH_2), 7.64-7.60 (m, 2H, Ar-H), 7.40 (t, *J* = 8.8 Hz, 3H, NH_2 and Ar-H), 6.78 (s, 1H, CH), 4.31-4.26 (m, 2H, CH_2), 1.28 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.4, 164.7, 164.5, 162.0, 141.2, 132.0, 131.9, 130.8, 117.3, 116.5, 116.2, 113.0, 81.2, 61.5, 14.0. HRMS (ESI): *m/z* calcd for $C_{16}H_{12}FN_3NaO_4S$, 384.0430 $[M+Na]^+$; found: 384.0418.

(*Z*)-Ethyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(4-chlorophenyl)-4-oxothiazolidin-5-ylidene)-acetate (4m)

A pale yellow solid; Mp 251-252 ºC; IR (KBr, ν, cm^{-1}): 3448, 3289, 3207, 3056, 2205, 1735, 1692, 1653, 1609, 1530, 1493, 1393, 1361, 1320, 1229, 1195, 1090, 1019, 850; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.78 (s, 1H, NH_2), 7.63 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.59 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.39 (s, 1H, NH_2), 6.77 (s, 1H, CH), 4.31-4.26 (m, 2H, CH_2), 1.28 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.3, 164.6, 164.5, 161.7, 141.2, 135.5, 133.4, 131.4, 129.4, 117.3, 113.0, 81.2, 61.5, 14.0. HRMS (ESI): *m/z* calcd for $C_{16}H_{12}ClN_3NaO_4S$, 400.0135 $[M+Na]^+$; found: 400.0122.

(*Z*)-Ethyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(3-chlorophenyl)-4-oxothiazolidin-5-ylidene)-acetate (4n)

A pale yellow solid; Mp >300 ºC; IR (KBr, ν, cm^{-1}): 3494, 3418, 3289, 3208, 2205, 1708, 1601, 1508, 1453, 1371, 1294, 1226, 1135, 1053, 860; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.78 (s, 1H, NH_2),

7.76 (d, *J* = 1.6 Hz, 1H, Ar-H), 7.69-7.66 (m, 1H, Ar-H), 7.60-7.54 (m, 2H, Ar-H), 7.42 (s, 1H, NH_2), 6.78 (s, 1H, CH), 4.31-4.26 (m, 2H, CH_2), 1.28 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.3, 164.6, 164.4, 161.5, 141.1, 135.7, 133.4, 130.9, 129.5, 128.5, 117.4, 113.0, 81.3, 61.6, 14.0. HRMS (ESI): *m/z* calcd for $C_{16}H_{12}ClN_3NaO_4S$, 400.0135 $[M+Na]^+$; found: 400.0135.

(*Z*)-Ethyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(3,4-dichlorophenyl)-4-oxothiazolidin-5-ylidene) acetate (4o)

A pale yellow solid; Mp >300 ºC; IR (KBr, ν, cm^{-1}): 3476, 3344, 3286, 3166, 3061, 2992, 2938, 2205, 1744, 1677, 1605, 1529, 1473, 1392, 1371, 1327, 1229, 1201, 1127, 1137, 919, 864; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.99 (d, *J* = 0.8 Hz, 1H, NH_2), 7.87 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.80 (s, 1H, Ar-H), 7.64-7.61 (m, 1H, Ar-H), 7.43 (s, 1H, NH_2), 6.80 (s, 1H, CH), 4.32-4.26 (m, 2H, CH_2), 1.28 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.3, 164.5, 164.3, 161.6, 141.0, 134.3, 133.8, 131.7, 131.3, 130.2, 117.5, 113.2, 81.2, 61.6, 14.0. HRMS (ESI): *m/z* calcd for $C_{16}H_{11}Cl_2N_3NaO_4S$, 433.9745 $[M+Na]^+$; found: 433.9738.

(*Z*)-Ethyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(4-bromophenyl)-4-oxothiazolidin-5-ylidene)-acetate (4p)

A pale yellow solid; Mp 258-259 ºC; IR (KBr, ν, cm^{-1}): 3448, 3341, 3287, 3208, 3178, 2203, 1733, 1692, 1607, 1582, 1529, 1490, 1371, 1319, 1229, 1195, 1112, 1015, 847; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.78 (s, 2H, Ar-H), 7.76 (s, 1H, NH_2), 7.52 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.39 (s,1H, NH_2), 6.77 (s, 1H, CH), 4.31-4.26 (m, 2H, CH_2), 1.28 (t, *J* = 14.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.3, 164.6, 164.4, 161.7, 141.2, 133.8, 132.4, 131.7, 124.1, 117.3, 113.0, 81.2, 61.6, 14.0. HRMS (ESI): *m/z* calcd for $C_{16}H_{12}BrN_3NaO_4S$, 443.9630 $[M+Na]^+$; found: 443.9643.

(*Z*)-Ethyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-4-oxo-3-(*p*-tolyl)thiazolidin-5-ylidene)acetate (4q)

A pale yellow solid; Mp 259-261 ºC; IR (KBr, ν, cm^{-1}): 3476, 3337, 3266, 2200, 1750, 1688, 1590, 1536, 1444, 1369, 1321, 1234, 1003, 899, 858, 829, 761; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.76 (s, 1H, NH_2), 7.38 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.34-7.19 (m, 3H, NH_2 and Ar-H), 6.76 (s, 1H, CH), 4.30-4.26 (m, 2H, CH_2), 2.39 (s, 3H, CH_3) , 1.28 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.4, 164.7, 164.6, 161.9, 141.4, 140.4, 131.9, 129.8, 129.1, 117.1, 112.9, 81.3, 61.5, 20.9, 14.0. HRMS (ESI): *m/z* calcd for $C_{17}H_{15}N_3NaO_4S$, 380.0681 $[M+Na]^+$; found: 380.0668.

(*Z*)-Ethyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-4-oxo-3-(*m*-tolyl)thiazolidin-5-ylidene)acetate (4r)

A pale yellow solid; Mp 277-279 ºC; IR (KBr, ν, cm^{-1}): 3480, 3342, 3266, 3164, 3060, 2991, 2199, 1742, 1675, 1613, 1524, 1491, 1453, 1371, 1324, 1223, 1032, 914, 888; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.74 (s, 1H, NH_2), 7.43-7.38 (m, 2H, Ar-H), 7.33-7.30 (m, 3H, NH_2 and Ar-H), 6.75 (s, 1H, CH), 4.31-4.25 (m, 2H, CH_2), 2.36 (s, 3H, CH_3) , 1.28 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz,

DMSO-d_6) (δ, ppm): 165.4, 164.7, 164.6, 161.7, 141.3, 138.8, 134.3, 131.3, 129.6, 129.1, 126.4, 117.2, 112.9, 81.3, 61.5, 20.8, 14.0. HRMS (ESI): *m/z* calcd for $C_{17}H_{15}N_3NaO_4S$, 380.0681 $[M+Na]^+$; found: 380.0659.

(*Z*)-Ethyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(4-methoxyphenyl)-4-oxothiazolidin-5-ylidene)-acetate (4s)

A pale yellow solid; Mp 257-259 ºC; IR (KBr, ν, cm^{-1}): 3480, 3431, 3390, 3254, 3176, 2205,1731, 1694, 1530, 1368, 1320, 1228, 1193, 1022, 885; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.76 (s, 1H, NH_2), 7.42 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.32 (s, 1H, NH_2), 7.06 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.75 (s, 1H, CH), 4.31-4.26 (m, 2H, CH_2), 3.82 (s, 3H, OCH_3), 1.28 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.4, 164.8, 164.6, 162.3, 160.8, 141.4, 130.7, 126.9, 117.1, 114.5, 113.0, 81.3, 61.5, 55.5, 14.0. HRMS (ESI): *m/z* calcd for $C_{17}H_{15}N_3NaO_5S$, 396.0630 $[M+Na]^+$; found: 396.0630.

(*Z*)-Ethyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-benzyl-4-oxothiazolidin-5-ylidene)acetate (4t)

A pale yellow solid; Mp 232-233 ºC; IR (KBr, ν, cm^{-1}): 3471, 3342, 3287, 3169, 3062, 2201, 1735, 1676, 1607, 1528, 1372, 1352, 1219, 1184, 1029, 964; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.85 (s, 1H, NH_2), 7.57 (s, 1H, NH_2), 7.37 (t, *J* = 7.2 Hz, 2H, Ar-H), 7.29 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.18 (d, *J* = 7.6 Hz, 2H, Ar-H), 6.83 (s, 1H, CH), 5.48 (s, 2H, CH_2), 4.30-4.25 (m, 2H, CH_2), 1.28 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.4, 165.3, 164.3, 161.4, 140.0, 134.9, 128.7, 127.4, 125.8, 118.1, 115.4, 80.6, 61.6, 47.5, 14.0. HRMS (ESI): *m/z* calcd for $C_{17}H_{15}N_3NaO_4S$, 380.0681 $[M+Na]^+$; found: 380.0667.

(*Z*)-Ethyl 2-(2-(1-cyano-2-oxo-2-(phenylamino)ethylidene)-4-oxo-3-phenylthiazolidin-5-ylidene)-acetate (4u)

A pale yellow solid; Mp 221-222 ºC; IR (KBr, ν, cm^{-1}): 3544, 3479, 3468, 3391, 3050, 2196, 1726, 1687, 1661, 1521, 1441, 1367, 1319, 1221, 1018, 931, 886; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.81 (s, 1H, NH_2), 7.57-7.55 (m, 7H, Ar-H), 7.33 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.12 (t, *J* = 7.2 Hz, 1H, Ar-H) , 6.81 (s, 1H, CH), 4.31-4.26 (m, 2H, CH), 1.28 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 165.3, 164.7, 162.4, 161.9, 140.6, 137.7, 134.4, 130.8, 129.4(3), 129.3(5), 128.5, 124.5, 121.3, 117.6, 112.5, 81.9, 61.6, 14.0. HRMS (ESI): *m/z* calcd for $C_{22}H_{17}N_3NaO_4S$, 442.0837 $[M+Na]^+$; found: 442.0838.

General Procedure for the Synthesis of Compounds 6a

Typically, in a 10 mL Initiator reaction vial, phenyl isothiocyanate (1.0 mmol) with cyanoacetamide (1.0 equiv) was performed in DMF catalyzed by sodium hydroxide (0.2 equiv) for 30 min at room temperature, and then HOAc (2.0 mL, excess) and methyl propiolate (1.5 equiv) were added into the reaction system. Subsequently, the mixture was irradiated by microwave at 100 ºC for 28 min. The automatic mode stirring helped the mixing and uniform heating of the reactants. Upon completion, monitored by TLC, the

reaction mixture was cooled to room temperature and filtered to give the crude products, which were further purified by recrystallization from 95% EtOH as a pale yellow solid.

(*Z*)-Methyl 3-((3-amino-2-cyano-3-oxo-1-(phenylamino)prop-1-en-1-yl)thio)acrylate (6a)

A pale yellow solid; Mp 156-157 °C; IR (KBr, ν, cm^{-1}) : 3524, 3501, 3479, 3468, 3430, 2198, 1707, 1675, 1559, 1411, 1325, 1232, 1166, 1034, 883; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) : 12.54 (s, 1H, NH), 7.39-7.35 (m, 2H, Ar-H), 7.28-7.26 (m, 2H, Ar-H), 7.22 (d, *J* = 7.6 Hz, 2H, NH), 6.94 (d, *J* = 9.6 Hz, 1H, CH=), 3.73 (s, 3H, CH_3), 1.60 (s, 1H, CH=); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 168.0, 166.0, 163.4, 143.2, 137.6, 129.1, 126.5, 125.4, 118.1, 114.9, 80.6, 51.6. HRMS (ESI): *m/z* calcd for $C_{14}H_{13}N_3NaO_3S$, 326.0575 $[M+Na]^+$; found: 326.0578.

(*Z*)-Methyl 3-(1-(4-chlorophenylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6b)

A pale yellow solid; Mp 173-175 °C; IR (KBr, ν, cm^{-1}): 3189, 2201, 1720, 1552, 1217, 1179, 828; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm) : 12.48 (s, 1H, NH), 7.45-7.43 (m, 2H, Ar-H), 7.35 (m, 2H, Ar-H), 7.33 (d, *J* = 4.4 Hz, 1H, CH=), 6.04 (d, *J* = 9.8 Hz, 1H, CH=), 3.65 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 168.1, 166.5, 163.6, 143.6, 137.3, 131.1, 129.5, 127.6, 118.4, 115.6, 81.9, 52.1. HRMS (ESI): *m/z* calcd for $C_{14}H_{12}ClN_3NaO_3S$, 360.0186 $[M+Na]^+$; found: 326.0578.

(Z)-Methyl 3-(1-(3,4-dichlorophenylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6c)

A dark yellow solid; Mp 173-175 °C; IR (KBr, ν, cm^{-1}): 3192, 2198, 1694, 1525, 1215, 1167, 823; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm) : 12.34 (s, 1H, NH), 7.66-7.62 (m, 2H, Ar-H), 7.36 (d, *J* = 9.8 Hz, 1H, CH=), 7.32 (d, *J* = 11.2 Hz, 1H, Ar-H), 6.08 (d, *J* = 9.8 Hz, 1H, CH=), 3.66 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 168.1, 166.1, 163.7, 143.4, 137.3, 131.1, 129.5, 127.5, 118.4, 115.9, 81.8, 60.9, 14.5. HRMS (ESI): *m/z* calcd for $C_{14}H_{11}Cl_2N_3NaO_3S$, 393.9796 $[M+Na]^+$; found: 326.0578.

(Z)-Methyl 3-(1-(4-bromophenylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6d)

A white solid; Mp 159-161 °C; IR (KBr, ν, cm^{-1}): 3186, 2201, 1719, 1557, 1217, 1175, 811; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm) : 12.46 (s, 1H, NH), 7.58-7.56 (m, 2H, Ar-H), 7.35 (d, *J* = 9.8 Hz, 1H, CH=), 7.28-7.26 (m, 2H, Ar-H), 6.04 (d, *J* = 9.8 Hz, 1H, CH=), 3.65 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 168.1, 166.5, 163.4, 143.6, 137.7, 132.4, 127.8, 119.4, 118.4, 115.6, 82.0, 52.1. HRMS (ESI): *m/z* calcd for $C_{14}H_{12}BrN_3NaO_3S$, 403.968 $[M+Na]^+$; found: 326.0578.

(*Z*)-Methyl 3-(1-(*p*-tolylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6e)

A pale yellow solid; Mp 135-137 °C; IR (KBr, ν, cm^{-1}): 3191, 2218, 1711, 1544, 1242, 1169, 818; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm) : 12.55 (s, 1H, NH), 7.35 (d, *J* = 9.8 Hz, 1H, CH=), 7.18 (s, 4H, Ar-H), 6.01 (d, *J* = 9.8 Hz, 1H, CH=), 3.64 (s, 3H, CH_3), 1.91 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 168.6, 166.5, 164.1, 144.0, 136.5, 135.6, 130.1, 125.8, 115.3, 80.5, 52.1, 31.2, 21.5, 21.0. HRMS (ESI): *m/z* calcd for $C_{15}H_{15}N_3NaO_3S$, 340.0732 $[M+Na]^+$; found: 326.0578.

(*Z*)-Methyl 3-(1-(4-methoxyphenylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6f)

A gray solid; Mp: 139-141 ºC; IR (KBr, ν, cm^{-1}): 3109, 2193, 1702, 1559, 1224, 1162, 804; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm) : 12.49 (s, 1H, NH), 7.36 (d, J = 9.8 Hz, 1H, CH=), 7.23-7.21 (m, 2H, Ar-H), 6.95-6.93 (m, 2H, Ar-H), 6.01 (d, J = 9.8 Hz, 1H, CH=), 3.75 (s, 3H, CH_3), 3.64 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 168.7, 166.5, 164.6, 158.2, 144.1, 130.9, 127.7, 115.2, 114.8, 79.9, 55.8, 52.1. HRMS (ESI): *m/z* calcd for $C_{15}H_{15}N_3NaO_4S$, 356.0681 $[M+Na]^+$; found: 326.0578.

(*Z*)-Methyl 3-(1-(3,4-dimethoxyphenylamino)-2-carbamoyl-2-cyanovinylthio) acrylate (6g)

A yellow solid; Mp 215-217 ºC; IR (KBr, ν, cm^{-1}): 3183, 2193, 1701, 1574, 1224, 1169, 812; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm) : 12.50 (s, 1H, NH), 7.38 (d, J = 9.8 Hz, 1H, CH=), 6.95 (m, 2H, Ar-H), 6.83-6.80 (m, 1H, Ar-H), 6.02 (d, J = 9.8 Hz, 1H. CH=), 3.74 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 3.64 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 168.7, 166.5, 164.4, 149.2, 147.9, 144.1, 131.0, 118.8, 118.4, 115.1, 112.0, 110.6, 80.0, 56.1, 56.0, 52.1. HRMS (ESI): *m/z* calcd for $C_{16}H_{17}N_3NaO_5S$, 386.0787 $[M+Na]^+$; found: 326.0578.

(*Z*)-Ethyl 3-((3-amino-2-cyano-3-oxo-1-(phenylamino)prop-1-en-1-yl)thio)acrylate (6h)

A pale yellow solid; Mp 146-147 ºC; IR (KBr, ν, cm^{-1}): 3528, 3511, 3474, 3469, 3422, 2203, 1706, 1675, 1559, 1424, 1343, 1229, 1159, 1036, 888; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) : 12.54 (s, 1H, NH), 7.39-7.37 (m, 2H, Ar-H), 7.27 (s, 3H, Ar-H), 7.22 (d, J = 7.6 Hz, 2H, NH), 6.93 (d, J = 10.0 Hz, 1H, CH=), 5.92 (d, J = 8.0 Hz, 1H, CH=) 4.21-4.15 (m, 2H, CH_2), 1.27 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 168.0, 165.5, 163.5, 142.9, 137.6, 129.1, 126.4, 125.3, 118.0, 115.2, 80.5, 60.3, 14.0. HRMS (ESI): *m/z* calcd for $C_{15}H_{15}N_3NaO_3S$, 340.0732 $[M+Na]^+$; found: 340.0726.

(*Z*)-Ethyl 3-(1-(4-chlorophenylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6i)

A white solid; Mp 164-167 ºC; IR (KBr, ν, cm^{-1}): 3178, 2201, 1713, 1558, 1215, 1174, 832; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm) : 12.47 (s, 1H, NH), 7.45-7.43 (m, 2H, Ar-H), 7.34-7.33 (m, 2H, Ar-H), 7.32 (d, J = 4.8 Hz, 1H, CH=), 6.02 (d, J = 9.8 Hz, 1H, CH=), 4.11 (q, J = 7.2 Hz, 2H, CH_2), 1.19 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 168.1, 166.1, 163.7, 143.4, 143.4, 137.3, 133.8, 131.1, 130.5, 129.5, 127.9, 127.5, 127.4, 118.4, 118.2, 115.9, 81.8, 60.9, 14.5. HRMS (ESI): *m/z* calcd for $C_{15}H_{14}ClN_3NaO_3S$, 374.0342 $[M+Na]^+$; found: 326.0578.

(*Z*)-Ethyl 3-(1-(3,4-dichlorophenylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6j)

A pale yellow solid; Mp 170-172 ºC; IR (KBr, ν, cm^{-1}): 3197, 2199, 1697, 1549, 1223, 1172, 815; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm) : 12.34 (s, 1H, NH), 7.66-7.62 (m, 2H, Ar-H), 7.35-7.32 (m, 1H, Ar-H), 7.31 (d, J = 2.6 Hz, 1H, CH=), 6.05 (d, J = 9.8 Hz, 1H, CH=), 4.12 (q, J = 7.2 Hz, 2H, CH_2), 1.20 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 167.6, 166.1, 163.1, 143.2, 138.6, 131.6, 131.2, 128.8, 127.4, 125.9, 118.3, 116.2, 83.1, 60.9, 14.5. HRMS (ESI): *m/z* calcd for $C_{15}H_{13}Cl_2N_3NaO_3S$, 407.9952 $[M+Na]^+$; found: 326.0578.

(*Z*)-Ethyl 3-(1-(4-bromophenylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6k)

A white solid; Mp 166-168 ºC; IR (KBr, ν, cm^{-1}): 3177, 2203, 1712, 1552, 1212, 1179, 817; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm) : 12.45 (s, 1H, NH), 7.58-7.56 (m, 2H, Ar-H), 7.34-7.31 (m, 2H, Ar-H), 7.27 (d, *J* = 8.8 Hz, 1H, CH=), 6.02 (d, *J* = 9.8 Hz, 1H, CH=), 4.11 (q, *J* = 7.2 Hz, 2H, CH_2), 1.19 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 168.1, 166.1, 163.6, 143.4, 137.7, 132.4, 127.8, 119.4, 118.4, 116.0, 81.9, 60.9, 14.5. HRMS (ESI): *m/z* calcd for $C_{15}H_{14}BrN_3NaO_3S$, 417.9837 $[M+Na]^+$; found: 326.0578.

(*Z*)-Ethyl 3-(1-(4-methoxyphenylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6l)

A gray solid; Mp 134-136 ºC; IR (KBr, ν, cm^{-1}): 3142, 2196, 1693, 1530, 1214, 1186, 810; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm) : 12.49 (s, 1H, NH), 7.34-7.21 (m, 4H, Ar-H), 6.94 (d, *J* = 9.0 Hz, 1H, CH=), 5.98 (d, *J* = 9.8 Hz, 1H, CH=), 4.09 (q, *J* = 7.2 Hz, 2H, CH_2), 3.75 (s,3H, CH_3), 1.18 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 168.7, 166.1, 164.7, 158.2, 143.9, 130.9, 127.7, 118.8, 115.5, 114.8, 79.9, 60.8, 55.8, 14.5. HRMS (ESI): *m/z* calcd for $C_{16}H_{17}N_3NaO_4S$, 370.0837 $[M+Na]^+$; found: 326.0578.

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12. Crystal data for **4m**: $C_{16}H_{12}ClN_3O_4S$, pale yellow, block, Triclinic, space group *P*-1, a = 5.1991(9) Å, b = 10.9259(13) Å, c = 14.8466(16) Å, α = 86.570(2)°, β = 81.3180(10)°, γ = 84.3840(10)°, V = 828.8(2) Å^3, Mr = 377.80, Z = 2, Dc = 1.514 Mg/m^3, λ = 0.71073 Å, μ(Mo Kα) = 0.384 mm^{-1}, F(000) = 388, R = 0.0547, wR_2 = 0.0963, largest diff. Peak and hole: 0.315 and -0.353 e/Å^3.
13. Crystal data for **6a**: $C_{14}H_{13}N_3O_3S$, pale yellow, block, Monoclinic, space group c2/c, a = 30.309(3) Å, b = 9.2416(8) Å, c = 10.0704(9) Å, $\alpha = \gamma$ = 90°, β = 96.2810(10)°, V = 2803.8(4) Å^3, Mr = 303.33, Z = 8, Dc = 1.437 Mg/m^3, λ = 0.71073 Å, μ(Mo Kα) = 0.245 mm^{-1}, F(000) = 1264, R = 0.0470, wR_2 = 0.1029, largest diff. Peak and hole: 0.283 and-0.246 e/Å^3.
14. This reaction joins the family of GAP chemistry (Group-Assistant-Purification chemistry) processes which can avoid the use of traditional chromatography and recrystallization (a) P. Kaur, S. Pindi, W. Wever, T. Rajale, and G. Li, *Chem. Commun.*, 2010, 4330; (b) P. Kaur, S. Pindi, W. Wever, T. Rajale, and G. Li, *J. Org. Chem.*, 2010, **75**, 5144; (c) S. Pindi, J. Wu, and G. Li, *J. Org. Chem.*, 2013, **78**, 4006; (d) S. Pindi, P. Kaur, G. Shakya, and G. Li, *Chem. Biol. Drug Des.*, 2011, **77**, 20; (e) G. An, C. Seiferta, and G. Li, *Org. Biomol. Chem.*, 2015, **13**, 1600; (f) C. W. Seifert, S. Pindi, and G. Li, *J. Org. Chem.*, 2015, **80**, 447.