Transformations of dimethyl acetone-1,3-dicarboxylate. The synthesis of (4-oxo-4*H*-pyrido[1,2-a]pyrimidin-3-yl)thiazole-5-carboxylates

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Dedicated to Professor Henk van der Plas on the occasion of his 80th anniversary

Abstract
Methyl 2-amino-4-(2-methoxy-2-oxo-ethyl)thiazole-5-carboxylate (**2a**), prepared from dimethyl acetone-1,3-dicarboxylate (**1**), sulfuryl chloride and thiourea according to a known procedure, was transformed in two steps into (4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)thiazole-5-carboxylates (**6**).

Keywords: Dialkyl acetone-1,3-dicarboxylates, 2-amino-4-(2-alkoxy-2-oxoethyl)thiazole-5-carboxylates, 4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)thiazole-5-carboxylates, 7-oxo-6,7-dihydro-thiazolo[5,4-*c*]pyridine-4-carboxylate

Introduction

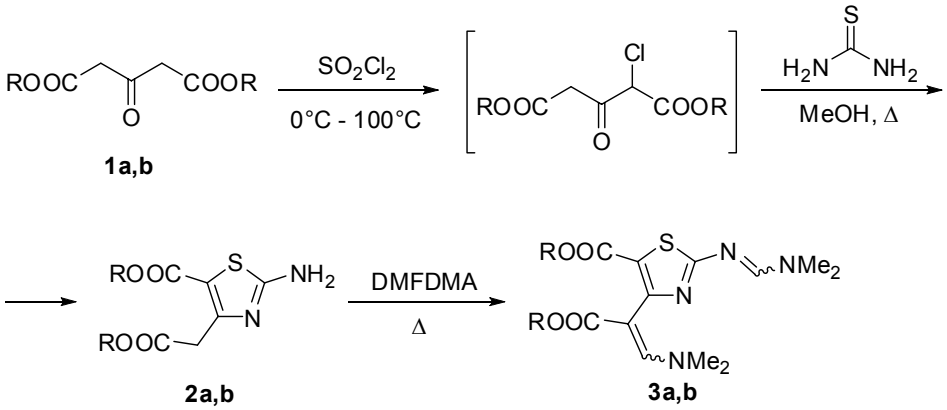
There are many methods described in the literature for the synthesis of pyridopyrimidines.[1-3] Recently, they have been prepared from 4-amino-6-chloro-5-phenyl-2-methylthiopyrimidine,[4] and from 4-amino-1-benzyl 1,2,5,6-tetrahydropyridine-3-carboxylate.[5] They are well-known pharmacophores,[6,7] PDE- inhibitors,[8] and inhibitors of tyrosine kinase activity in the epidermal growth factor receptor.[9,10]

In connection with our interest in enaminones and related compounds as building blocks for the preparation of various heterocyclic systems,[11] including also some natural products,[12,13] dialkyl acetone-1,3-dicarboxylates have recently been employed for the synthesis of hetero-aryl substituted pyrimidines,[14] dialkyl 1-substituted 4-oxo-1,4-dihydropyridine-3,5-dicarboxylates,[15] pyrazolo[4,3-*d*]pyridine 7-carboxylates,[16] pyrazole-substituted pyridopyrimidines, pyranopyran-diones, chromenediones,[17] and pyrazolo[4,3-*d*][1,2]diazepines.[18,19] We recently reported an efficient method for the preparation and functionalization of highly substituted 1-aminopyrroline, 1-aminopyrrole and oxazoline-pyrroline fused systems from 1,2-diaza-1,3-butadienes and 3-

dimethylaminopropenoates,[20] and the regio- and stereoselective one-pot synthesis of oxazoline-fused pyridazine *via* a, "Michael addition-pyridazine-cyclization-oxazoline cyclization" cascade reaction.[21] Many fused pyrimidines are formed by cyclization of 3-hetero-arylaminopropenoates, derived from 2-substituted 3-(dimethylamino)propenoates and heterocyclic α-amino compounds.[11,22] We now report a simple synthesis of (4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)thiazole-5-carboxylates from dimethyl acetone-1,3-dicarboxylate *via* 2-amino-4-(2-methoxy-2-oxoethyl)thiazole-5-carboxylate.

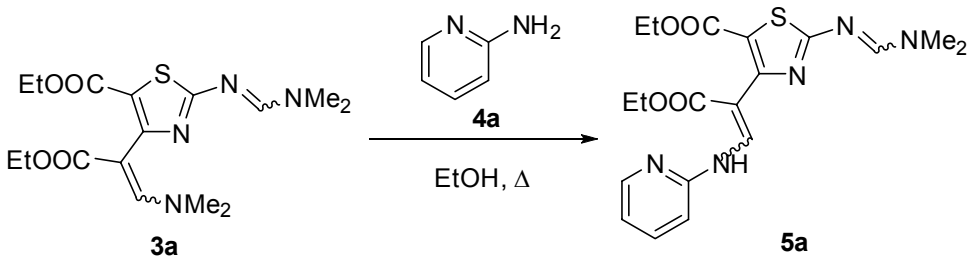
Results and Discussion

Ethyl 2-amino-4-(2-ethoxy-2-oxoethyl)thiazole-5-carboxylate (**2a**), prepared from diethyl acetone-1,3-dicarboxylate (**1a**), sulfuryl chloride and thiourea according to the procedure described in the literature,[23] was transformed with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) into ethyl 4-[1-(dimethylamino)-3-ethoxy-3-oxoprop-1-en-2-yl]-2-[(dimethylamino)methyleneamino]thiazole-5-carboxylate (**3a**) in 77 % yield. (Scheme 1). This compound was treated with 2-aminopyridine **(4a)** by heating in ethanol to yield intermediate **5a**, which exists in two isomeric forms in ratio 3:1, due to the orientation around the exocyclic double bond. No attempts were made in order to determine which is which. (Scheme 2). On the other hand, when compound **3b** was heated with α-amino-heterocycles **4b-g** in acetic acid under reflux for 1-4 h, the cyclization occurred to give substituted (4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)thiazole-5-carboxylates **6b-g**. No attempts were made to isolate the intermediates **5b-g** (Scheme 3).

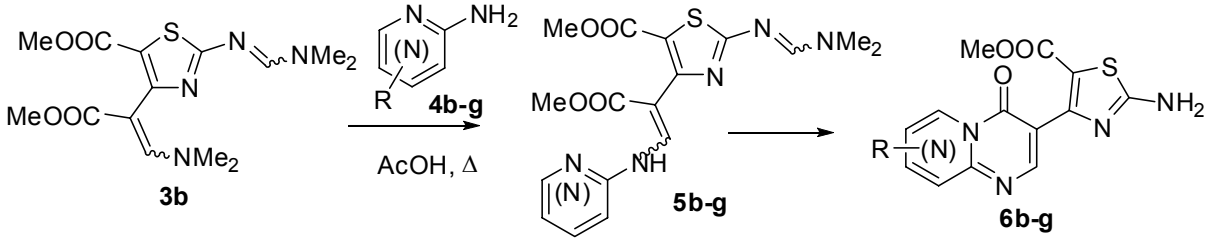


	R	**2**, yield (%)	**3**, yield (%)	**3**, time (h)
a	Et	86	77	15
b	Me	85	96	8

Scheme 1. The synthesis of alkyl 4-(1-(dimethylamino)-3-ethoxy-3-oxoprop-1-en-2-yl)-2-((dimethylamino)methyleneamino)thiazole-5-carboxylates **3a,b.**



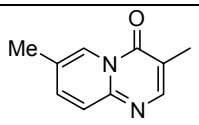
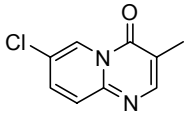
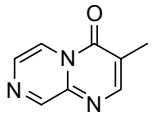
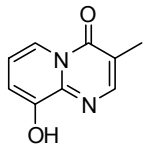
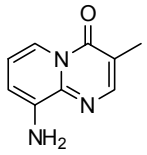
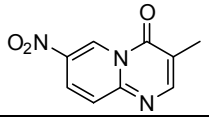
Scheme 2. Synthesis of ethyl 2-((dimethylamino)methyleneamino)-4-(3-ethoxy-3-oxo-1-(pyridin-2-ylamino)prop-1-en-2-yl)thiazole-5-carboxylate, **5a**.

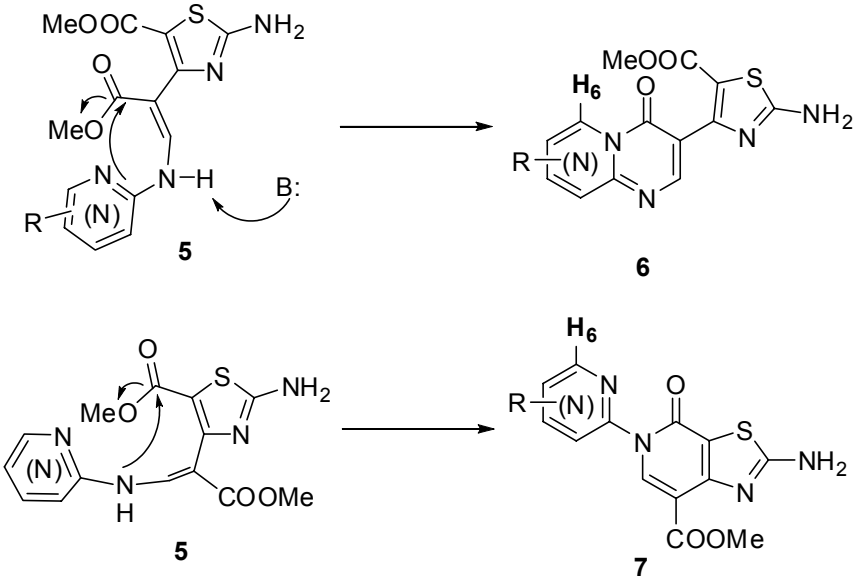


Scheme 3. Synthesis of methyl 2-amino-4-(7-methyl-4-oxo-4*H*-azino[1,2-*a*]pyrimidin-3-yl)thiazole-5-carboxylates, **6b-g**.

Structure determination

The structures of the products were determined on the basis of elemental analysis for C, H, and N, and IR, ^{1}H NMR, and mass spectra. Two types of products could be formed, depending on the ester group which is involved in cyclization. If the cyclization is taking place to the ester group of the side chain attached at the 4 position of the thiazole ring, the corresponding fused azinopyrimidinone derivatives **6** would be formed. On the other hand, if the cyclization is taking place to the ester group at 5 position of the thiazole ring, then the azinyl substituted thiazolo[5,4-*c*]pyridine derivatives **7** would have been formed**.** (Scheme 4). One can differentiate between these two structures on the basis of comparison of ^{1}H NMR spectral characteristics. Namely, the chemical shifts of the protons at the 6 position in compounds of the types **6** and **7** are of significant values. The protons at position 6 in compounds **6** are shifted downfield, δ = 8.04–8.70 ppm, similarly to other derivatives of this bicyclic system.[23] On the other hand, the chemical shifts of protons at position 6 in the starting 2-aminopyridine derivatives, δ = 7.28–7.87 ppm, are similar to those reported for the corresponding proton in other N-substituted pyridine derivatives.[24] Accordingly, similar values could be expected for the protons at the 6 position in compounds of the type **7** (Table 1).

Compound		Yield (%)	Time (h)
6b		36	4
6c		47	1
6d		28	1
6e		23	1
6f		52	4
6g		23	4



Scheme 4. Possible cyclizations of **5** to give either **6** or **7.**

Table 1. Chemical shifts, δ_{H6}, in compounds **4** and **6**

Product	Chemical shift, δ_{H6}	Hetero-arylamine	Chemical shift, δ_{H6}
6b	8.44	**4b**	7.73
6c	8.70	**4c**	7.87
6d	8.69-8.82	**4d**	7.89
6e	8.04	**4e**	7.43
6f	8.04	**4f**	7.28
6g	9.43	**4g**	8.85

Experimental Section

General Procedures. Melting points were taken with a Kofler micro hot stage. The ^{1}H NMR spectra (300 MHz) spectra were obtained with a Bruker Avance DPX 300 (300 MHz) spectrometer with $CDCl_3$ as solvent and Me_4Si as internal standard. IR spectra were recorded with a Perkin-Elmer Spectrum BX FTIR spectrophotometer (KBr discs). The microanalyses for C, H, and N were obtained with a Perkin-Elmer CHN Analyzer 2400. Reactions were followed by TLC using Merck, Alufolien Kieselgel 60 F 254, 0.2 mm. Ethyl 2-amino-4-(2-ethoxy-2-oxoethyl)thiazole-5-carboxylate (**2a**) was prepared according to the literature procedure.[25]

Methyl 2-amino-4-(2-methoxy-2-oxoethyl)thiazole-5-carboxylate (2b). Methyl 2-amino-4-(2-methoxy-2-oxoethyl)thiazole-5-carboxylate (**2b**) was prepared according to the literature procedure for ethyl 2-amino-4-(2-methoxy-2-oxoethyl)thiazole-5-carboxylate.[25] Sulfuryl chloride (6.75 g, 0.05 mol) was slowly added to dimethyl acetone-1,3-dicarboxylate (**1b**) (10.1 g, 0.05 mol) at 0°C. Then the reaction mixture was heated on a steam bath until the gas stopped evolving. The reaction mixture was then added to a suspension of thiourea (3.8 g, 0.05 mol) in MeOH (25 mL) and the mixture was refluxed for 30 minutes. The solution was poured onto 150 mL of ice and water and neutralized by K_2CO_3. The white precipitate was filtered under reduced pressure. Yield: 9.86 g (85 %); mp 127-129°C. IR (KBr, cm^{-1}): 3415, 3339, 3291, 3119, 3001, 2948, 1718, 1694, 1646, 1541, 1516, 1435, 1401, 1371, 1342, 1281, 1217, 1186, 1217, 1186, 1171, 1100; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.59 (s, 3H, Me), 3.68 (s, 3H, Me), 3.89 (s, 2H, CH_2), 7.85 (s, 2H, NH_2). Anal. Calcd for $C_8H_{10}N_2O_4S$: C 41.73, H 4.38, N 12.17. Found: C, 41.36, H 4.34, N 11.93%.

Ethyl 4-(1-(dimethylamino)-3-ethoxy-3-oxoprop-1-en-2-yl)-2[(dimethylamino)-methyleneamino]-thiazole-5-carboxylate (3a). A mixture of ethyl 2-amino-4-(2-ethoxy-2-oxoethyl)thiazole-5-carboxylate (**2a**) (2.58 g, 10 mmol) and DMF–DMA (8.5 mL, 100 mmol) was refluxed for 15 hours. Volatile components were evaporated *in vacuo* and water (20-30 mL) was added to the residue. Precipitated product was filtered under reduced pressure and washed with water. The product was recrystallized from a mixture of toluene and heptane. Yield: 2.83 g (77%) of yellow–orange crystals; mp 119–121°C. IR (KBr, cm^{-1}): 3546, 3474, 3414, 1704, 1677,

1621, 1594, 1460, 1374, 1298, 1248, 1218, 1085. ^{1}H NMR ($CDCl_3$): δ=1.16 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.28 (t, J = 7.1 Hz, 3H, CH_2CH_3), 2.79 (s, 6H, N-$(CH_3)_2$), 3.09 (s, 3H, N-CH_3), 3.11 (s, 3H, N-CH_3), 4.00-4.17 (m, 2H, CH_2CH_3), 4.23 (q, J = 7.1 Hz, 2H, CH_2CH_3), 7.56 (s, 1H, C*H*), 8.39 (s, 1H, C*H*). Anal. Calcd for $C_{16}H_{24}N_4O_4S$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.20; H, 6.59; N, 15.19%.

Methyl 4-(1-(dimethylamino)-3-methoxy-3-oxoprop-1-en-2-yl)-2-[(dimethylamino)-methyleneamino]thiazole-5-carboxylate (3b). A mixture of methyl 2-amino-4-(2-methoxy-2-oxoethyl)thiazole-5-carboxylate (**2b**) (5 g, 14.6 mmol) and DMFDMA (12.48 mL, 147 mmol) was refluxed for 8 hours. The yellow precipitate was collected by filtration under reduced pressure and washed with water. Yield: 4.8 g (96 %); mp 160-162°C. IR (KBr, cm^{-1}): 3457, 3001, 2949, 2805, 1705, 1674, 1623, 1597, 1492, 1508, 1465, 1426, 1370, 1304, 1242, 1132, 1089; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.72 (br s, 6H, NMe_2), 2.98 (s, 3H, NMe), 3.13 (s, 3H, NMe), 3.44 (s, 3H, Me), 3.64 (s, 3H, Me), 7.41 (s, 1H, CH), 8.41 (s, 1H, CH). Anal. Calcd for $C_{14}H_{20}N_4O_4S$: C 49.40, H 5.92, N 16.46. Found: C 49.30, H 6.02, N 16.35%; MS (ESI) *m*/*z*: 341 (MH^+).

Ethyl 2-[(dimethylamino)methyleneamino]-4-(3-ethoxy-3-oxo-1-(pyridin-2-ylamino)prop-1-en-2-yl)thiazole-5-carboxylate (5a). Ethyl 4-(1-(dimethylamino)-3-ethoxy-3-oxoprop-1-en-2-yl)-2-((dimethylamino)methyleneamino)thiazole-5-carboxylate (**3a**) (0.368 g, 1 mmol) was added to a solution of 2-aminopyridine (**4a**) (0.197 g, 2 mmol) and concentrated HCl (6 drops) in EtOH (2 mL). The mixture was refluxed for 5 hours. The white precipitate was collected by filtration under reduced pressure and washed with ethanol. Yield: 0.095 g (23 %); mp 188-190°C. IR (KBr, cm^{-1}): 3443, 1707, 1676, 1627, 1616, 1574, 1472, 1431, 1392, 1287, 1259, 1234; ^{1}H NMR (300 MHz, DMSO-d_6): major isomer: δ = 1.18-1.33 (m, 6H, 2×CH_3), 3.12 (s, 3H, NMe), 3.14 (s, 3H, NMe), 4.14-4.28 (m, 4H, 2×CH_2), 6.79-6.90 (m, 2H, 3'-H and 5'-H), 7.52-7.61 (m, 1H, 4'-H), 8.21-8.26 (m, 1H, 6'-H), 8.32 (s, 1H, C<u>H</u>NMe_2), 8.46 (d, 1H, CH), 8.69 (d, 1H, NH); minor isomer: δ = 1.18-1.33 (m, 6H, 2×CH_3), 3.09-3.17 (m, 6H, 2×NMe), 4.14-4.28 (m, 4H, 2×CH_2), 6.75 (d, 1H, 5'-H), 6.79-6.89 (m, 1H, 3'-H), 7.52-7.61 (m, 1H, 4'-H), 8.21-8.26 (m, 1H, 6'-H), 8.36 (d, 1H, CH), 8.39 (s, 1H, C<u>H</u>NMe_2), 10.49 (d, 1H, NH); *Anal.* Calcd for $C_{19}H_{23}N_5O_4S$: C 54.66, H 5.55, N 16.78; found C 54.54, H 5.49, N 16.58; MS (ESI) *m*/*z*: 418 (MH^+); HRMS-ESI Calcd $C_{19}H_{24}N_5O_4S$: 418.1549; found 418.1533.

General procedure for the preparation of pyrido[1,2-*a*]pyrimidines 6b,c,e,f,g and pyrazino[1,2-*a*]pyrimidine 6d

A mixture of methyl 4-(1-(dimethylamino)-3-methoxy-3-oxoprop-1-en-2-yl)-2-((dimethylamino) methyleneamino)thiazole-5-carboxylate (**3b**) and amine **4b-g** was refluxed in acetic acid. The product, which precipitated after 24 hours at room temperature, was collected by filtration under reduced pressure and washed with methanol. The product was recrystallized from a mixture of toluene and DMF.

Methyl 2-amino-4-(7-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)thiazole-5-carboxylate (6b). Prepared from methyl 4-(1-(dimethylamino)-3-methoxy-3-oxoprop-1-en-2-yl)-2-((dimethylamino)methyleneamino)thiazole-5-carboxylate (**3b**) (0.170 g, 0.5 mmol) and 2-amino-5-methylpyridine (**4b**) (0.108 g, 1 mmol) in acetic acid (2 mL), 4 hours to give colorless crystals. Yield: 0.058 g (36 %); mp 318-322°C. IR (KBr, cm^{-1}): 3475, 3268, 3177, 3108, 1728, 1698, 1674, 1638, 1552, 1509, 1485, 1416, 1384, 1337, 1316, 1268, 1121, 1063; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.38 (s, 3H, Me), 3.79 (s, 3H, COOMe), 7.69-7.90 (m, 2H, 8'-H and 9'-H), 8.37 (s, 2H, NH_2), 8.43-8.47 (m, 1H, 6'-H), 8.48 (s, 1H, 2'-H); *Anal.* Calcd for $C_{14}H_{12}N_4O_3S$: C 53.16, H 3.82, N 17.71; found C 52.91, H 3.80, N 17.46; MS (EI) *m*/*z*: 316 (M^+); HRMS-EI Calcd $C_{14}H_{12}N_4O_3S$: 316.0630; found 316.0640.

Methyl 2-amino-4-(7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)thiazole-5-carboxylate (6c). Prepared from methyl 4-(1-(dimethylamino)-3-methoxy-3-oxoprop-1-en-2-yl)-2-((dimethylamino)methyleneamino)thiazole-5-carboxylate (**3b**) (0.340 g, 1 mmol) and 2-amino-5-chloropyridine (**4c**) (0.257 g, 2 mmol) in acetic acid (2 mL), 1 hour. Yield: 0.149 g (47 %) of colorless crystals; mp 302-307°C. IR (KBr, cm^{-1}): 3445, 3268, 3106, 1741, 1676, 1630, 1577, 1544, 1490, 1461, 1422, 1375, 1331, 1307, 1259, 1123, 848; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.79 (s, 3H, COOMe), 7.91 (dd, *J* = 8.7, 0.5 Hz, 1H, 9'-H), 8.16 (dd, *J* = 8.7, 2.6 Hz, 1H, 8'-H), 8.42 (s, 2H, NH_2), 8.52 (s, 1H, 2'-H), 8.70 (dd, *J* = 2.6, 0.5 Hz, 1H, 6'-H). Anal. Calcd for $C_{13}H_9ClN_4O_3S$: C 46.37, H 2.69, N 16.64; found C 46.00, H 3.04, N 15.72; MS (ESI) *m*/*z*: 337 (MH^+); HRMS-ESI Calcd for $C_{13}H_{10}ClN_4O_3S$: 337.0150. Found 337.0162.

Methyl 2-amino-4-(4-oxo-4*H*-pyrazino[1,2-*a*]pyrimidin-3-yl)thiazole-5-carboxylate (6d). Prepared from methyl 4-(1-(dimethylamino)-3-methoxy-3-oxoprop-1-en-2-yl)-2-((dimethylamino)methyleneamino)thiazole-5-carboxylate (**3b**) (0.340 g, 1 mmol) and 2-aminopyrazine (**4d**) (0.190 g, 2 mmol) in acetic acid (2 mL), 1 hour. Yield: 0.085 g (28 %) of colorless crystals; mp 343-348°C. IR (KBr, cm^{-1}): 3309, 3102, 1713, 1702, 1662, 1646, 1528, 1479, 1411, 1342, 1299, 1259. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.83 (s, 3H, COOMe), 8.45 (br s, 2H, NH_2), 8.55 (s, 1H, 2'-H), 8.69-8.82 (m, 2H, 7'-H and 6'-H), 9.15 (d, *J* = 1.2 Hz, 1H, 9'-H). Anal. Calcd for $C_{12}H_9N_5O_3S$: C 47.52; H 2.99; N 23.09. Found: C, 47.38; H, 3.19; N, 23.36. MS (EI) *m*/*z*: 303 (M^+); HRMS-EI Calcd for $C_{12}H_9N_5O_3S$: 303.0430. Found: 303.0426.

Methyl 2-amino-4-(9-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)thiazole-5-carboxylate (6e). Prepared from methyl 4-(1-(dimethylamino)-3-methoxy-3-oxoprop-1-en-2-yl)-2-((dimethylamino)methyleneamino)thiazole-5-carboxylate (**3b**) (0.340 g, 1 mmol) and 2-amino-3-hydroxypyridine (**4e**) (0.220 g, 2 mmol) in acetic acid (2 mL), 1 hour. Yield, 0.075 g (23 %) of colorless crystals; mp 320-322°C. IR (KBr, cm^{-1}): 3476, 3244, 3089, 1735, 1654, 1621, 1568, 1538, 1489, 1474, 1419, 1333, 1311, 1257, 1109, 774; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.77 (s, 3H, COOMe), 7.41-7.46 (m, 2H, 7'-H and 8'-H), 8.04 (dd, *J* = 3.8, 2.3 Hz, 1H, 6'-H), 8.10 (s, 1H, 2'-H), 8.33 (br s, 2H, NH_2), 10.50 (s, 1H, OH). Anal. Calcd for $C_{13}H_{10}N_4O_4S$: C, 49.05; H, 3.17; N, 17.60. Found: C, 48.94; H 3.22, N, 17.39. MS (EI) *m*/*z*: 318 (M^+); HRMS-EI, Calcd for $C_{13}H_{10}N_4O_4S$: 318.0430, Found 318.0422.

Methyl 2-amino-4-(9-amino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)thiazole-5-carboxylate (6f). Prepared from methyl 4-(1-(dimethylamino)-3-methoxy-3-oxoprop-1-en-2-yl)-2-((dimethylamino)methyleneamino)thiazole-5-carboxylate (**3b**) (0.170 g, 0.5 mmol) and 2,3-diaminopyridine (**4f**) (0.095 g, 1 mmol) in acetic acid (2 mL), 4 hours. Yield: 0.082 g (52 %) of colorless crystals; mp 305-308°C. IR (KBr, cm^{-1}): 3337, 3197, 1723, 1651, 1633, 1547, 1485, 1420, 1337, 1301, 1277, 1207, 1119, 985, 778; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.75 (s, 3H, COOMe), 6.04 (br s, 2H, NH_2), 6.65 (dd, *J* = 7.6, 4.9 Hz, 1H, 7'-H), 7.45 (dd, *J* = 7.6, 1.7 Hz, 1H, 8'-H), 7.92 (s, 1H, 2'-H), 8.04 (dd, *J* = 4.9, 1.7 Hz, 1H, 6'-H), 8.24 (br s, 2H, NH_2). Anal. Calcd for $C_{13}H_{11}N_5O_3S$: C; 49.21; H 3.49; N 22.07. Found: C, 49.03; H, 3.79; N, 21.73. MS (EI) *m*/*z*: 317 (M^+). HRMS-EI Calcd for $C_{13}H_{11}N_5O_3S$: 317.0591. Found: 317.0582.

Methyl 2-amino-4-(7-nitro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)thiazole-5-carboxylate (6g). Prepared from methyl 4-(1-(dimethylamino)-3-methoxy-3-oxoprop-1-en-2-yl)-2-((dimethylamino)methyleneamino)thiazole-5-carboxylate (**3b**) (0.170 g, 0.5 mmol) and 2-amino-5-nitropyridine (**4g**) (0.139 g, 1 mmol) in acetic acid (2 mL), 4 hours. Yield: 0.030 g (23 %) of colorless crystals; mp 284-289°C. IR (KBr, cm^{-1}): 3140, 3331, 3179, 1707, 1668, 1606, 1571, 1529, 1486, 1435, 1355, 1253; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.81 (s, 3H, COOMe), 8.23 (dd, *J* = 9.0, 0.5 Hz, 1H, 9'-H), 8.48 (br s, 2H, NH_2), 8.68 (s, 1H, 2'-H), 8.79 (dd, *J* = 9.0, 2.8 Hz, 1H, 8'-H), 9.43 (dd, *J* = 2.7, 0.5, 1H, 6'-H). Anal. Calcd for $C_{13}H_9N_5O_5S$: C, 44.96; H, 2.61; N, 20.16. Found: C, 44.75; H, 2.74; N, 19.82. MS (EI) *m*/*z*: 347 (M^+). HRMS-EI Calcd $C_{13}H_9N_5O_5S$: 347.0330. Found: 347.032440.

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