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SYNTHESIS OF NOVEL BENZOFURO-FUSED THIAZOLO[3,2-*a*]-PYRIMIDINONES *VIA* PICTET-SPENGLER REACTION

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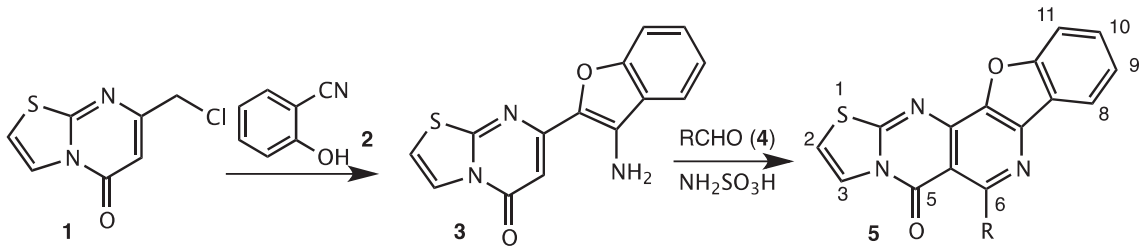
Abstract – An efficient method for the preparation of novel benzofuro-[3',2':2,3]pyrido[4,5:*d*]thiazolo[3,2-*a*]pyrimidin-5-ones **5** is described. The key intermediate, 7-(3-amino-2-benzofuran)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**3**), was synthesized from 7-(chloromethyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**1**) with salicylonitrile (**2**) by Thorpe-Ziegler isomerization. Subsequent reaction of the intermediate amine with aromatic aldehydes *via* Pictet-Spengler reaction provided benzofuro-fused thiazolo[3,2-*a*]pyrimidines under sulfamic acid as catalyst in good yields.

Thiazolo[3,2-*a*]pyrimidine heterocyclic systems are the key chemical building blocks for numerous compounds that play important roles in the functioning of biologically active molecules.[1] As one type of those heterocyclic rings, 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones are considered a promising class of bioactive heterocyclic compounds encompassing a diverse range of biological activities such as anticancer,[2] antitumor,[3] antiinflammatory,[4] antinociceptive,[5] antiviral,[6] and antibiofilm properties.[7] Owing to these remarkably broad pharmacological properties, a variety of synthetic methods have been reported for the preparation of thiazolo[3,2-*a*]pyrimidinone derivatives.[6-10]

In addition, benzofuran derivatives have attracted widespread interest in view of their presence in natural products, and their biological and pharmacological activities.[11] The benzofuran nucleus is a central component of a diverse class of heterocyclic natural and synthetic products that possess a broad range of biological activities.[12]

As part of our continuing interest on the development of new synthetic methods for heterocyclic compounds,[13] herein we report the synthesis of some new fused heterocyclic systems: benzofuro-[3',2':2,3]pyrido[4,5:*d*]thiazolo[3,2-*a*]pyrimidin-5-ones by the application of Pictet-Spengler reaction

(Scheme 1).[14]



Scheme 1. Syntheses of benzofuro-fused thiazolopyrimidines

In this study, the key intermediate amine, 7-(3-amino-2-benzofuran)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**3**) was obtained by the condensation of 7-(chloromethyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one[15] (**1**) with salicylonitrile (**2**) *via* Thorpe-Ziegler isomerization,[16] in 80% yield. Elemental analysis ($C_{14}H_9N_3O_2S$) and spectral data supported its structure. Its IR spectrum contains absorption peaks at 3450-3362 and 1682 cm^{-1}, demonstrating the presence of NH_2 and C=O funcitions, respecticely. Its ^1H NMR spectrum (DMSO-d_6) shows the presence of a D_2O exchangeable broad singlet at δ 6.56 ppm (2H) which can be attributed to the NH_2 protons and singlet peak at δ 6.16 corresponding to C_6-H of thiazolo[3,2-*a*]-pyrimidine nucleus. The multiplet between 7.27-8.01 ppm (6H) corresponding to the aromatic protons of benzene and thiazole nucleus.

In an initial endeavor, we selected benzadehyde **4a** as model aromatic aldehyde to react with equimolar amounts of intermediate amine **3a** for the preparation of benzofuro[3',2':2,3]pyrido[4,5:*d*]thiazolo[3,2-*a*]-pyrimidin-5-one **5a** and investigated the optimal reaction conditions. The reaction was carried out under neat conditions at 120 °C without and with different acid catalysts such as *p*-toluenesulfonic acid (*p*-TsOH), trifluoroacetic acid (TFA), and sulfamic acid (SA) each 10 mol% in DMF. The maximum yield was obtained using SA. It can be seen that the reaction did not proceed even after 24 h in the absence of this catalyst (Table 1, entry 1). Although a lower catalyst loading of 5 mol% accomplished this condensation, 10 mol% of SA was optimal in terms of reaction time and isolated yield (Table 1, entry 4). Increasing the amount from 10 to 15 mol% has no effect on the product yield and reaction time (Table 1, entry 6).

In addition, various solvents such as HOAc, DMSO, glycol, toluene, and MeCN were screened for the optimal reaction conditions. The best catalytic activity was observed in DMF compared to other organic solvents (Table 1, entries 7-11).

Table 1. Optimization of reaction conditions on the synthesis of **5a***

Entry	Catalyst / (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	none	DMF	120	24	trace
2	*p*-TsOH (10)	DMF	120	12	68
3	TFA (10)	DMF	120	12	72
4	SA (10)	DMF	120	9	82
5	SA (5)	DMF	120	12	73
6	SA (15)	DMF	120	9	80
7	SA (10)	HOAc	120	12	76
8	SA (10)	DMSO	120	10	65
9	SA (10)	Glycol	120	15	60
10	SA (10)	toluene	110	20	53
11	SA (10)	MeCN	80	16	60

* Reaction conditions: **3** (1.0 mmol), benzaldehyde (**4a**, 1.0 mmol), solvent (20 mL).

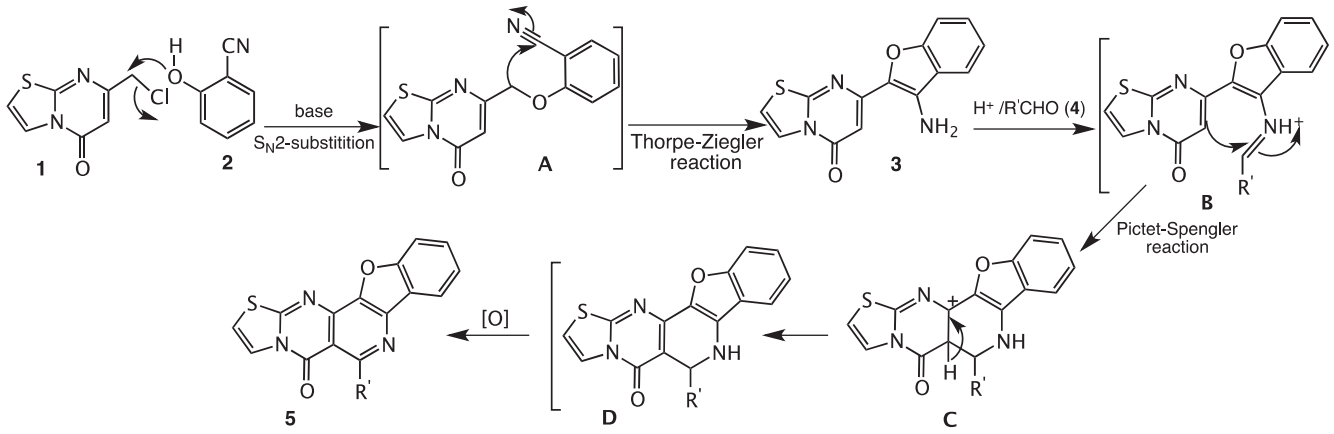
With these optimized reaction conditions in hand, we then planned to examine the versatility of the methodology for the preparation of benzofuro-fused thiazolo[3,2-*a*]pyrimidines. The substrate scope of the SA catalyzed coupling of **1** with aromatic aldehydes **4** is shown in Table 2 and it was found that this protocol could be applied not only to the aromatic aldehydes with either electron-donating groups (e.g., methyl, methoxy) or electron-withdrawing groups (e.g., fluoro, chloro, and nitro groups), but also to heterocyclic aldehydes. Therefore, we concluded that the electronic nature of the substituents of aldehydes has no significant effect on this reaction.

Table 2. Synthesis of benzofuro[3',2':2,3]pyrido[4,5:*d*]thiazolo[3,2-*a*]pyrimidin-5-ones (**5**)

Entry	**4** / R		Time / h	Product	Yield / %
1	**4a**	C_6H_5	9	**5a**	82
2	**4b**	4-MeC_6H_4	10	**5b**	80
3	**4c**	2-$MeOC_6H_4$	10	**5c**	85
4	**4d**	3-$MeOC_6H_4$	11	**5d**	84
5	**4e**	4-$MeOC_6H_4$	12	**5e**	87
6	**4f**	3,4-$(MeO)_2C_6H_3$	6	**5f**	78

7	**4g**	2-FC_6H_4	13	**5g**	80
8	**4h**	4-FC_6H_4	10	**5h**	84
9	**4i**	4-ClC_6H_4	12	**5i**	82
10	**4j**	4-$NO_2C_6H_4$	14	**5j**	79
11	**4k**	2-thienyl	16	**5k**	72

On the basis of these results, a plausible mechanism for the construction of fused thiazolo[3,2-*a*]-pyrimidinones is proposed (Scheme 2). The formation of ether **A** occurs through *O*-alkylation of 7-(chloromethyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **1** and salicylonitrile (**2**). Then, the ether **A** occurred *via* Thorpe-Ziegler isomerization reaction to generate 7-(3-amino-2-benzofuran)-5*H*-thiazolo[3,2-*a*]-pyrimidin-5-one (**3**). Next, the intermediate amine **3** underwent a cationic π-cyclization with aldehyde under Pictet-Spengler cyclization to form **D,** which effects aromatisation to give pentacyclic product **5**.



Scheme 2. Proposed reaction mechanism for the formation of compound **5**

In summary, we have developed an efficient synthesis of benzofuro[3',2':2,3]pyrido[4,5:*d*]thiazolo-[3,2-*a*]pyrimidin-5-ones in two steps with good yields in the presence of sulfamic acid. This method has the advantages of readily available starting materials, mild reaction conditions, and operational simplicity. Further study is underway to the scope of this methodology for some new fused heterocyclic systems.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The NMR spectra were recorded with a Bruker Avance 400 spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C) using TMS an internal reference. IR spectra were measured on Shimadzu FTIR-8300 spectrophotometer. C, H, and N analyses were performed by a HP-MOD 1106 microanalyzer. The preparation of 7-(chloromethyl)-5*H*-thiazolo-

[3,2-*a*]pyrimidin-5-one (**1**) was according to the literature procedure.[14] All other chemicals used in this study were commercially available.

Preparation of 7-(3-amino-2-benzofuran)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**3**): To a solution of 7-(chloromethyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **1** (2.01 g, 10.0 mmol) in DMF (25 mL) was added salicylonitrile (**2**) (1.19 g, 10.0 mmol) and anhydrous potassium carbonate (2.76 g, 20.0 mmol). The mixture was heated at 100 °C for 5 h (monitored by TLC). After cooling to rt, then water (50 mL) was added and stirred for 20 min. The solid was filtered and recrystallized from HOAc to give **3** (2.26 g, 80%). Yellow crystals; mp > 300 °C; IR (KBr): ν 3450, 3362 (NH_2), 1682 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6): δ 6.16 (s, 1H, 6-H), 6.59 (s, 2H, NH_2), 7.26-7.28 (m, 1H, Arom-H), 7.43-7.47 (m, 2H, Arom-H), 7.51 (d, 1H, *J* = 8.4 Hz, Ben-H), 7.93 (d, 1H, *J* = 8.0 Hz, Ben-H), 8.01 (d, 1H, *J* = 4.8 Hz, Thiazo-H). Anal. Calcd for $C_{14}H_9N_3O_2S$: C 59.35, H 3.20, N 14.83. Found: C 59.46, H 3.28, N 14.90.

Typical Procedure for the Preparation of 6-Aryl-5*H*-benzofuro[3',2':2,3]pyrido[4,5:*d*]thiazolo-[3,2-*a*]pyrimidin-5-ones 5a-k. To a stirred solution of 7-(3-amino-2-benzofuran)-5*H*-thiazolo[3,2-*a*]-pyrimidin-5-one (**3**) (283 mg, 1.0 mmol), aromatic aldehyde (1.0 mmol), and NH_2SO_3H (10 mg, 0.1 mmol) in DMF (20 mL) was heated at 120 °C (monitored by TLC). At the end of the reaction, the reaction mixture was cooled to rt, and then water (20 mL) was added to the mixture and stirred for 30 min. The solid was filtered and recrystallized from DMF to give **5a-k**.

6-Phenyl-5*H*-benzofuro[3',2':2,3]pyrido[4,5:*d*]thiazolo[3,2-*a*]pyrimidin-5-one (**5a**): Yellow crystals; mp > 300 °C; IR (KBr): ν 1670 cm^{-1} (C=O); ^{1}H NMR (400 MHz, CF_3CO_2D): δ 7.45 (d, *J* = 4.8 Hz, 1H, Thiazo-H), 7.57-7.65 (m, 4H, Ben-H), 7.69-7.72 (m, 1H, Ben-H), 7.86-7.92 (m, 3H, Ben-H), 8.18 (d, *J* = 8.0 Hz, 1H, Ben-H), 8.21 (d, *J* = 4.8 Hz, 1H, Thiazo-H); ^{13}C NMR (100 MHz, CF_3CO_2D): δ 107.7, 113.0, 114.2, 115.5, 121.7, 123.2, 126.3, 127.9, 128.9, 130.2, 132.3, 134.3, 135.5, 141.7, 142.7, 154.7, 156.9, 158.9, 168.7. Anal. Calcd for $C_{21}H_{11}N_3O_2S$: C 68.28, H 3.00, N 11.38. Found: C 68.36, H 3.07, N 11.46.

6-(4-Methylphenyl)-5*H*-benzofuro[3',2':2,3]pyrido[4,5:*d*]thiazolo[3,2-*a*]pyrimidin-5-one (5b): Yellow crystals; mp > 300 °C; IR (KBr): ν 1682 cm^{-1} (C=O); ^{1}H NMR (400 MHz, CF_3CO_2D): δ 2.46 (s, 3H, CH_3), 7.43-7.47 (m, 5H, Arom-H), 7.62-7.63 (m, 1H, Ben-H), 7.87-7.90 (m, 2H, Ben-H), 8.18-8.22 (m, 2H, Arom-H); ^{13}C NMR (100 MHz, CF_3CO_2D): δ 19.6, 107.5, 113.1, 114.3, 115.5, 121.7, 123.2, 126.3, 127.2, 128.0, 129.5, 134.3, 135.5, 141.4, 142.7, 144.4, 154.9, 157.3, 158.9, 168.5. Anal. Calcd for $C_{22}H_{13}N_3O_2S$: C 68.91, H 3.42, N 10.96. Found: C 68.98, H 3.53, N 11.04.

6-(2-Methoxyphenyl)-5*H*-benzofuro[3',2':2,3]pyrido[4,5:*d*]thiazolo[3,2-*a*]pyrimidin-5-one (5c): Yellow crystals; mp > 300 °C; IR (KBr): ν 1680 cm^{-1} (C=O); ^{1}H NMR (400 MHz, CF_3CO_2D): δ 3.75 (s, 3H, OCH_3), 7.15-7.22 (m, 2H, Arom-H), 7.39-7.42 (m, 1H, Ben-H), 7.47-7.50 (m, 1H, Ben-H), 7.63-7.72 (m, 2H, Ben-H), 7.86-7.94 (m, 2H, Ben-H), 8.19-8.26 (m, 2H, Arom-H); ^{13}C NMR (100 MHz, CF_3CO_2D): δ 54.8, 108.9, 111.4, 113.1, 114.3, 119.3, 121.1, 121.7, 123.2, 126.3, 128.9, 129.0, 134.3, 134.4, 135.9,

141.4, 142.0, 154.2, 154.3, 156.9, 158.8, 168.4. Anal. Calcd for $C_{22}H_{13}N_3O_3S$: C 66.15, H 3.28, N 10.52. Found: C 66.24, H 3.34, N 10.61.

6-(3-Methoxyphenyl)-5*H*-benzofuro[3',2':2,3]pyrido[4,5:*d*]thiazolo[3,2-*a*]pyrimidin-5-one (5d): Yellow crystals; mp > 300 °C; IR (KBr): ν 1686 cm^{-1} (C=O); ^1H NMR (400 MHz, CF_3CO_2D): δ 4.02 (s, 3H, OCH_3), 7.27 (d, 1H, *J* = 7.6 Hz, Ben-H), 7.32 (s, 1H, Ben-H), 7.39 (d, 1H, *J* = 8.0 Hz, Ben-H), 7.49 (d, 1H, *J* = 4.4 Hz, Thiazo-H), 7.61-7.68 (m, 2H, Ben-H), 7.70-7.97 (m, 2H, Ben-H), 8.23-8.26 (m, 2H, Arom-H); ^{13}C NMR (100 MHz, CF_3CO_2D): δ 55.2, 107.8, 113.0, 114.1, 115.3, 116.9, 121.3, 121.6, 123.1, 126.3, 130.6, 131.7, 134.3, 135.4, 135.5, 141.8, 142.7, 154.7, 155.7, 158.7, 158.9, 168.8. Anal. Calcd for $C_{22}H_{13}N_3O_3S$: C 66.15, H 3.28, N 10.52. Found: C 66.26, H 3.34, N 10.63.

6-(4-Methoxyphenyl)-5*H*-benzofuro[3',2':2,3]pyrido[4,5:*d*]thiazolo[3,2-*a*]pyrimidin-5-one (5e): Yellow crystals; mp > 300 °C; IR (KBr): ν 1678 cm^{-1} (C=O); ^1H NMR (400 MHz, CF_3CO_2D): δ 4.02 (s, 3H, OCH_3), 7.22 (d, 2H, *J* = 8.0 Hz, Ben-H), 7.50-7.51 (m, 1H, Benz-H), 7.63-7.68 (m, 3H, Arom-H), 7.87-7.95 (m, 2H, Ben-H), 8.23-8.25 (m, 2H, Arom-H); ^{13}C NMR (100 MHz, CF_3CO_2D): δ 54.9, 107.2, 113.0, 114.3, 114.6, 115.4, 121.8, 123.0, 123.4, 126.3, 130.5, 134.4, 135.9, 140.7, 141.6, 141.7, 154.3, 156.5, 159.0, 167.8. Anal. Calcd for $C_{22}H_{13}N_3O_3S$: C 66.15, H 3.28, N 10.52. Found: C 66.24, H 3.35, N 10.59.

6-(3,4-Dimethoxyphenyl)-5*H*-benzofuro[3',2':2,3]pyrido[4,5:*d*]thiazolo[3,2-*a*]pyrimidin-5-one (5f): Yellow crystals; mp > 300 °C; IR (KBr): ν 3316 (OH), 1682 cm^{-1} (C=O); ^1H NMR (400 MHz, CF_3CO_2D): δ 3.94 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 7.11-7.28 (m, 3H, Ben-H), 7.50-7.66 (m, 2H, Arom-H), 7.82-7.90 (m, 2H, Ben-H), 8.14-8.25 (m, 2H, Arom-H); ^{13}C NMR (100 MHz, CF_3CO_2D): δ 55.0, 55.3, 107.5, 111.3, 112.3, 113.0, 114.3, 121.7, 122.8, 123.0, 123.3, 123.6, 126.3, 134.4, 135.7, 141.2, 142.1, 148.3, 151.9, 154.3, 155.9, 158.9, 168.2. Anal. Calcd for $C_{23}H_{15}N_3O_4S$: C 64.33, H 3.52, N 9.78. Found: C 64.42, H 3.63, N 9.84.

6-(2-Fluorophenyl)-5*H*-benzofuro[3',2':2,3]pyrido[4,5:*d*]thiazolo[3,2-*a*]pyrimidin-5-one (5g): Yellow crystals; mp > 300 °C; IR (KBr): ν 1681 cm^{-1} (C=O); ^1H NMR (400 MHz, CF_3CO_2D): δ 7.33-7.36 (m, 1H, Ben-H), 7.45-7.51 (m, 2H, Arom-H), 7.59-7.61 (m, 1H, Ben-H), 7.69-7.75 (m, 1H, Ben-H), 7.78-7.89 (m, 1H, Ben-H), 7.90-7.97 (m, 2H, Ben-H), 8.25-8.27 (m, 2H, Arom-H); ^{13}C NMR (100 MHz, CF_3CO_2D): δ 109.0, 113.2, 114.2, 115.6, 116.0, 116.2, 121.8, 123.2, 124.9, 125.0, 126.4, 129.2, 134.4, 134.8, 134.9, 136.0, 150.6, 154.3, 158.4, 158.9, 168.9. Anal. Calcd for $C_{21}H_{10}FN_3O_2S$: C 65.11, H 2.60, N 10.85. Found: C 65.19, H 2.68, N 10.93.

6-(4-Fluorophenyl)-5*H*-benzofuro[3',2':2,3]pyrido[4,5:*d*]thiazolo[3,2-*a*]pyrimidin-5-one (5h): Yellow crystals; mp > 300 °C; IR (KBr): ν 1682 cm^{-1} (C=O); ^1H NMR (400 MHz, CF_3CO_2D): δ 7.09-7.11 (m, 2H, Ben-H), 7.27-7.28 (m, 1H, Ben-H), 7.45-7.47 (m, 3H, Arom-H), 7.69-7.77 (m, 2H, Ben-H), 8.01-8.03 (m, 2H, Arom-H); ^{13}C NMR (100 MHz, CF_3CO_2D): δ 107.9, 113.1, 114.2, 115.5,

116.1, 116.3, 121.7, 123.2, 126.2, 128.2, 128.3, 130.6, 130.7, 134.3, 135.6, 154.5, 155.7, 158.9, 168.7. Anal. Calcd for $C_{21}H_{10}FN_3O_2S$: C 65.11, H 2.60, N 10.85. Found: C 65.18, H 2.69, N 10.93.

6-(4-Chlorophenyl)-5*H*-benzofuro[3',2':2,3]pyrido[4,5:*d*]thiazolo[3,2-*a*]pyrimidin-5-one (5i): Yellow crystals; mp > 300 °C; IR (KBr): ν 1686 cm^{-1} (C=O); ^1H NMR (400 MHz, CF_3CO_2D): δ 7.45-7.58 (m, 6H, Arom-H), 7.88-7.91 (m, 2H, Ben-H), 8.19-8.20 (m, 2H, Arom-H); ^{13}C NMR (100 MHz, CF_3CO_2D): δ 107.8, 113.0, 114.2, 121.6, 123.1, 126.3, 128.3, 129.1, 129.3, 134.3, 135.2, 135.5, 139.6, 141.7, 142.6, 154.5, 155.5, 158.3, 168.7. Anal. Calcd for $C_{21}H_{10}ClN_3O_2S$: C 62.46, H 2.50, N 8.78. Found: C 62.54, H 2.58, N 8.86.

6-(4-Nitrophenyl)-5*H*-benzofuro[3',2':2,3]pyrido[4,5:*d*]thiazolo[3,2-*a*]pyrimidin-5-one (5j): Yellow crystals; mp > 300 °C; IR (KBr): ν 1689 cm^{-1} (C=O); ^1H NMR (400 MHz, CF_3CO_2D): δ 7.46 (d, 1H, J = 4.0 Hz, Thiazo-H), 7.64-7.68 (m, 1H, Ben-H), 7.85-7.95 (m, 4H, Ben-H), 8.18-8.21 (m, 2H, Arom-H), 8.47 (d, 2H, J = 8.0 Hz, Ben-H); ^{13}C NMR (100 MHz, CF_3CO_2D): δ 108.4, 113.1, 114.3, 115.5, 121.7, 123.0, 123.8, 126.4, 129.8, 134.5, 135.8, 137.1, 142.4, 142.8, 149.4, 153.3, 154.3, 159.0, 169.2. Anal. Calcd for $C_{21}H_{10}N_4O_4S$: C 60.87, H 2.43, N 13.52. Found: C 60.93, H 2.52, N 13.59.

6-(2-Thienyl)-5*H*-benzofuro[3',2':2,3]pyrido[4,5:*d*]thiazolo[3,2-*a*]pyrimidin-5-one (5k): Yellow crystals; mp > 300 °C; IR (KBr): ν 1679 cm^{-1} (C=O); ^1H NMR (400 MHz, CF_3CO_2D) : δ 7.31-7.33 (m, 1H, Arom-H), 7.54 (d, 1H, J = 8.4 Hz, Ben-H), 7.69-7.71 (m, 2H, Arom-H), 7.88-7.91 (m, 2H, Ben-H), 7.96 (dd, 1H, J = 7.4, 8.4 Hz, Ben-H), 8.28-8.32 (m, 2H, Arom-H); ^{13}C NMR (100 MHz, CF_3CO_2D): δ 108.0, 113.1, 114.5, 115.3, 122.0, 123.6, 126.4, 127.8, 128.6, 132.8, 133.3, 134.7, 136.3, 140.9, 141.1, 150.1, 153.7, 159.1, 167.6. Anal. Calcd for $C_{19}H_9N_3O_2S_2$: C 60.79, H 2.42, N 11.19. Found: C 60.87, H 2.49, N 11.26.

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