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A simple and efficient synthesis of novel pyranothiadiazolopyrimidine derivatives by three component reactions in solvent-free conditions

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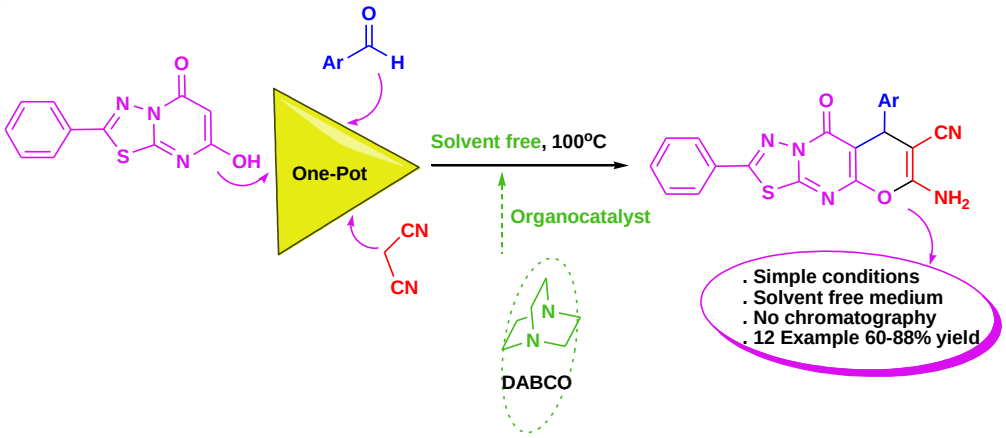
Abstract

A simple and efficient protocol for the synthesis of novel pyranothiadiazolopyrimidine derivatives via the reaction of aromatic aldehydes, malononitrile and 7-hydroxy-2-phenyl-5*H*-[1,3,4]thiadiazolo[3,2-a]pyrimidine-5-one in solvent-free conditions and in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as organ catalyst, is reported. The procedure involves initial Knoevenagel reaction, followed by Michael addition and subsequent internal heterocyclization. The short reaction time, environmentally friendly conditions and good to high yields are the main advantages of the protocol.



Keywords: Pyranothiadiazolopyrimidine, solvent-free, 1,4-diazabicyclo[2.2.2]octane, organocatalyst, three-component reactions

Introduction

Despite the fact that pyrimidine is pharmacologically inactive fused pyrimidines are a main constituent of living cells, since they serve as the essential building blocks of nucleic acids.[1] Nowadays, heterocyclic annulated pyrimidine derivatives have attracted a lot of attention due to the wide variety of biological activities they offer, including anticancer, antiviral, antitubercular, antitumor, antibacterial and cytotoxic activities.[2-5] In this context, thiadiazolo[3,2-*a*]pyrimidines are important heterocycles that are also present in a number of natural products. Such structure has been proven to act as an antifungal, antibacterial (Figure 1, **1-2**),[6,7] antitumor,[8] antimicrobial,[9] anti-allergy[10] and herbicidal agent.[11] Moreover, thiadiazolo[3,2-*a*]pyrimidin-7-ones are important heterocyclic cores, since they exhibit interesting biological activities. For instance, molecule **3** has been reported as a therapeutic target introduced as a candidate for the treatment of glaucoma, and molecules **4** and **5** were also reported to be effective for helminthic therapy and antibacterial activity, respectively (Figure 1, **3-5**).[12-14] Furthermore, it is well known that pyrans are important scaffolds and play a crucial role in organic synthesis and medicinal chemistry. Many of these compounds have gained prominence as they exhibit a wide range of biological properties such as antioxidant, anti-inflammatory, antibacterial, anticonvulsant, antimicrobial, spasmolytic and anticancer activities.[15-17] In addition, pyran derivatives have been effective agents against Alzheimer's disease and schizophrenia disorders.[18,19] Furthermore, they have been applied in laser dyes, cosmetics and pigments.[20,21]

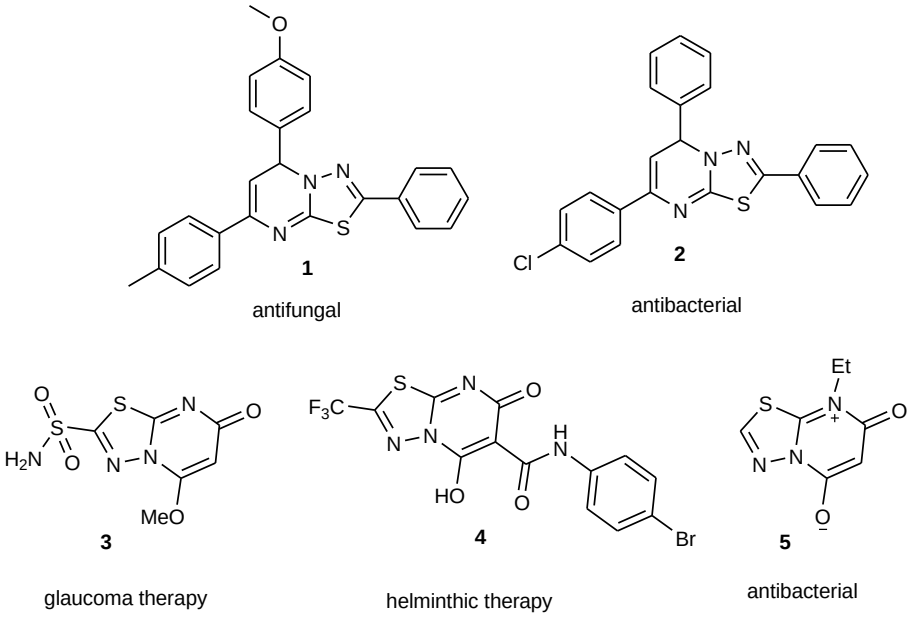
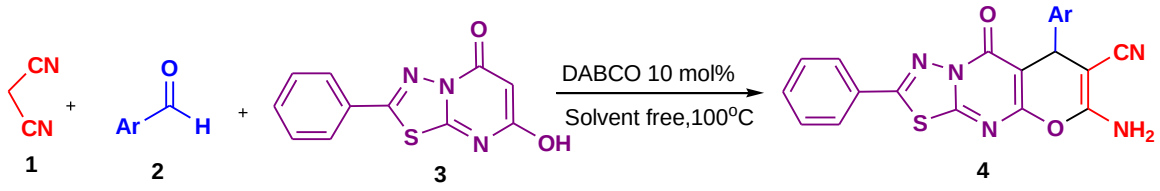


Figure 1. Examples of bioactive thiadiazolopyrimidines.

It is also well known that the development of environmentally benign and clean synthetic techniques is of particular interest Solvent-free procedures are usually recommended as a better substitute for classical protocols due to their pollution prevention and significant rate acceleration as well as less energy consumption.[22]

The use of organ catalysts which have unique characteristics, is associated with a low toxicity, easy availability, low cost and stability against air and water.[23] As a solid green organ catalyst, 1,4-diazabicyclo[2.2.2]octane (DABCO) has attracted considerable attention as an inexpensive, eco-friendly,

highly reactive, easy-to-handle and non-toxic base catalyst for various organic transformations and leads to excellent yields of products with a high selectivity.[24] Based on the above information this study aimed to combine thiadiazolopyrimidine and pyran moieties and lead to the synthesis of novel pyranothiadiazolopyrimidine frameworks as biologically-active agents via three-component reactions and specifically of 7-hydroxy-2-phenyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-5-one, aromatic aldehydes and malononitrile in the presence of DABCO in solvent-free conditions. Three-component reactions of aldehydes, malononitrile and heterocyclic 1,3-diones have already been investigated in other studies[25-47] however, According to our knowledge , there are not any literature reports on the use of 7-hydroxy-2-phenyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-5-one as a heterocyclic dione. Thus, a new, simple and eco-friendly one-pot synthetic strategy for the preparation of the desired new densely-functionalized pyranothiadiazolopyrimidine derivatives **4** (Scheme 1) is presented in this study.



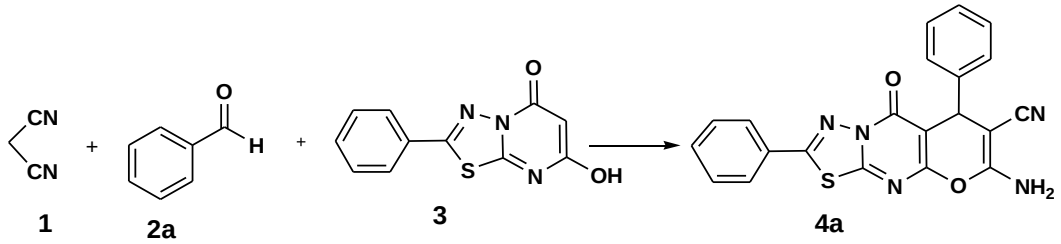
Scheme 1. The three-component synthesis of pyranothiadiazolopyrimidine derivatives.

Results and Discussion

Initially, the reaction of 7-hydroxy-2-phenyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-5-one (**3**) (1 mmol), benzaldehyde (1 mmol) and malononitrile (1 mmol) was taken as the model reaction, and the effect of various parameters, such as reaction catalyst, temperature, time and medium, was evaluated on the outcome of the desired product. The results about the optimization of conditions are summarized in Tables 1 and 2. The model reaction was investigated in the absence of catalysts in solvent-free conditions and the trace amount of the desired product was isolated after 12 h (Table 1, entry 1). The addition of *p*-TSA as a Brönsted acid catalyst did not enhance the product yield even after 12 h (Table 1, entry 2). In order to obtain higher yields, a variety of base catalysts, i.e. 1,8-diazabicyclo[5.4.0]undec-7-ene, diisopropylethylamine, piperidine, 4-dimethylaminopyridine, K_2CO_3 and 1,4-diazabicyclo[2.2.2]octane (DABCO), were investigated. Among these, DABCO led to the best results in terms of yield and reaction time (Table 1, entries 3-8).

The effect of various solvents, such as H_2O, EtOH, CH_3CN, Toluene, THF, PEG, DMF and glycerin, was investigated on the model reaction, leading to 32%, 55%, 71%, 25%, 30%, 70, 10% and trace amounts of the product respectively, in 12 h. According to the results presented in Table 2, a solvent-free medium can be used as a green and efficient condition for this reaction (Table 2, entries 1-9).

Table 1. Effect of different catalysts on the reaction of malononitrile (**1**), benzaldehyde (**2a**) and 7-hydroxy-2-phenyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-5-one (**3**) [a]



1 **2a** **3** **4a**

Entry	Catalyst (mol%)	Time (h)	Yield of **4a** (%)
1	no	12	trace
2	*p*-TSA[b] (10)	12	trace
3	DBU[c] (10)	12	10
4	DIEA[d] (10)	12	60
5	Piperidine (10)	12	50
6	DMAP[e] (10)	12	70
7	K_2CO_3 (10)	12	55
8	DABCO (10)	1	80

[a]Reaction condition: malononitrile (1 mmol), benzaldehyde (1 mmol) and 7-hydroxy-2-phenyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-5-one (1 mmol) at 100 ˚C in solvent free medium.
[b]*P*-toluenesulphonic acid, [c]1,8-Diazabicyclo[5.4.0]undec-7-ene, [d]Diisopropylethylamine.
[e]4-Dimethylaminopyridine.

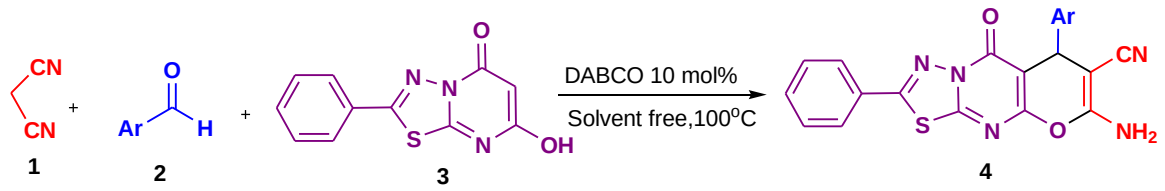
Table 2. Optimization of reaction conditions [a]

Entry	Solvent	Catalyst loading (mol%)	Temperature (°C)	Time (h)	Yield (%)
1	H_2O	DABCO (10)	reflux	12	32
2	EtOH	DABCO (10)	reflux	12	55
3	CH_3CN	DABCO (10)	reflux	12	71
4	Toluene	DABCO (10)	reflux	12	25
5	THF	DABCO (10)	Reflux	12	30
6	Glycerin	DABCO (10)	100	12	trace
7	PEG	DABCO (10)	80	12	70
8	DMF	DABCO (10)	110	12	10
9	no	DABCO (10)	100	1	80
10	no	DABCO (10)	80	5	75
11	no	DABCO (10)	60	5	56
12	no	DABCO (10)	110	1	80
13	no	DABCO (5)	100	4	60
14	no	DABCO (15)	100	1	80

[a] Reaction condition: malononitrile (1 mmol), benzaldehyde (1 mmol) and 7-hydroxy-2-phenyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-5-one (1 mmol) and solvent (5 ml).

When the model reaction was carried out at different temperatures, temperature was found to be an effective parameter in this synthetic protocol, and the most suitable temperature was found to be 100 °C in a solvent-free medium (Table 2, entries 9-12).

Table 3. One-pot synthesis of pyranothiadiazolopyrimidine derivatives [a]



Entry	Ar	Time (h)	Yield (%)[b]
4a	C_6H_5	1	80
4b	4-ClC_6H_4	1	84
4c	4-BrC_6H_4	1.5	86
4d	2-ClC_6H_4	1	85
4e	4-MeC_6H_4	2	80
4f	4-$MeOC_6H_4$	2.5	60
4g	4-$CF_3C_6H_4$	1	78
4h	4-$NO_2C_6H_4$	1	88
4i	3-MeC_6H_4	1.5	68
4j	3-$MeOC_6H_4$	2	63
4k	2,4-$(MeO)_2C_6H_3$	1.5	83
4l	4-Pyridyl	1	85

[a] Reagents and conditions: DABCO (10 mol%), malononitrile (1.5 mmol), aldehyde (1 mmol), 7-hydroxy-2-phenyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-5-one (1 mmol) at 100°C. [b] Isolated yield.

The amount of catalyst was then also optimized by performing the model reaction in the presence of different amounts of DABCO. Higher yields of the desired product in a short reaction time were obtained by applying 10 mol% of the catalyst. Using 5 mol% of the catalyst reduced the yield, and increasing the amount of catalyst was not significantly effective on the yield and the rate of reaction (Table 2, entries 13, 14). The best results were thus obtained in the presence of DABCO (10 mol%) in solvent-free conditions at 100 °C.

With the optimized conditions established, the versatility of the noted protocol was examined for the one-pot synthetic procedure, which proceeded smoothly under mild conditions with structurally-diverse aldehydes. The reactions were successfully performed with aromatic aldehydes and both electron-withdrawing and electron-donating groups on the aromatic ring, and good to excellent yields of the corresponding products, i.e. **4a**-**k,** were obtained in a short reaction time. The procedure was also adopted for 4-Pyridinecarboxaldehyde and **4l** was produced with an 85% yield.

The structures of all the synthesized products were confirmed with their IR, ^{1}HNMR and ^{13}CNMR spectra and by mass spectrometry (Ref. the supplementary data). The characteristic absorptions at 3444, 3336, 2191, 1700 and 1655 cm^{-1} in IR spectrum of **4a** imply the stretching vibration of NH_2, C≡N, C=O and C=N groups. The mass spectra of the compound **4a** displayed a molecular ion peak at *m/z* = 399. According to the ^{1}HNMR spectrum of **4a**, one singlet was exhibited at δ 4.59 for Ar-CH proton, one multiplet at δ 7.25-7.36 for aromatic

ring protons and NH_2 protons and another multiplet at δ 7.61-7.70 for the aromatic ring protons. Furthermore, two doublets appeared for the aromatic protons at δ 7.96 (*J*=1.8 Hz) and 7.98 (*J*=1.8 Hz), respectively. The ^{13}CNMR spectrum of the product **4a** indicated 17 distinct resonances –as closely consistent with the proposed structure. Additionally, the structure of product **4a** was further confirmed by single-crystal X-ray diffraction analysis and Figure 2 presents the ORTEP diagram for **4a** (See supplementary data).

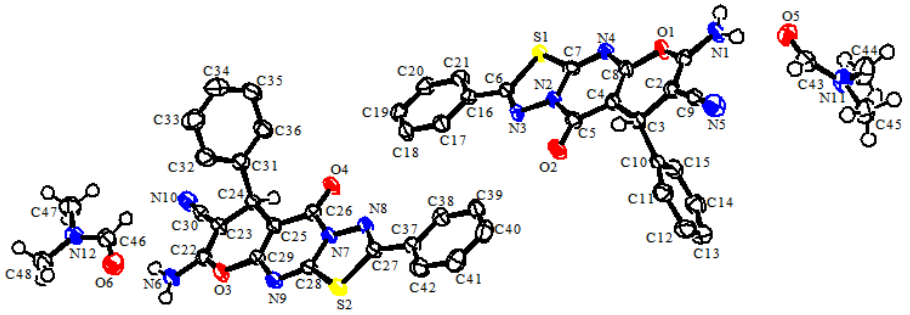
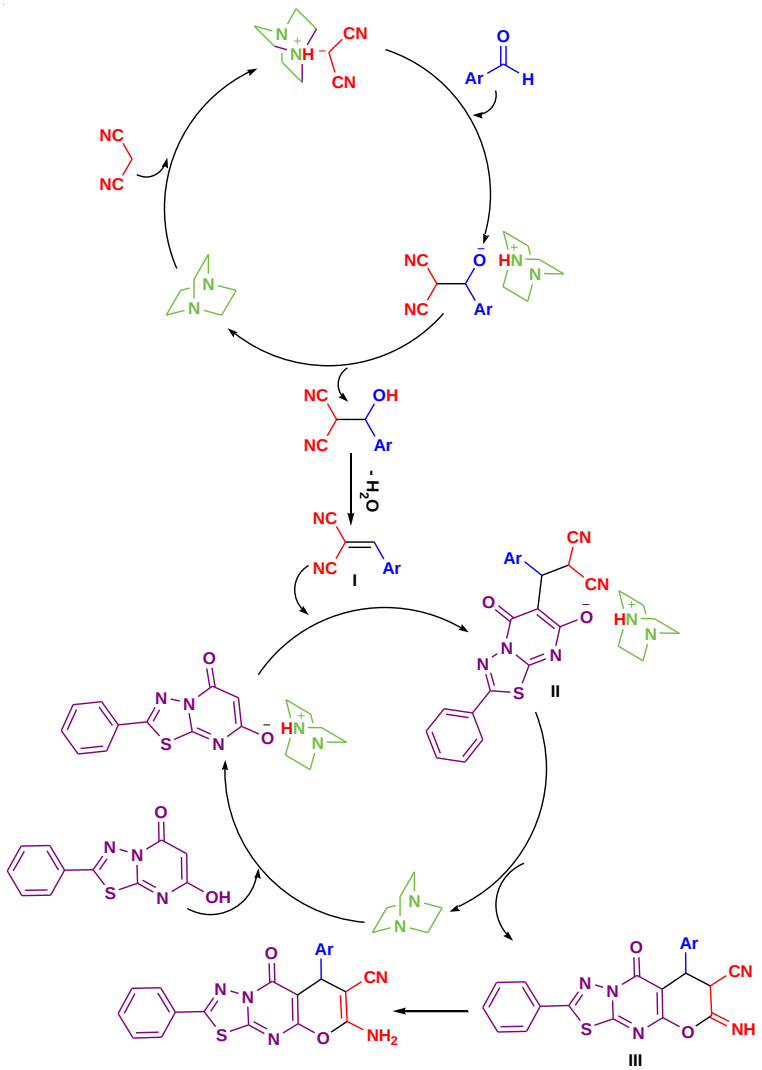


Figure 2. The ORTEP view of the compound **4a**.



Scheme 2. The mechanism proposed for the synthesis of **4a**-**l**.

Based on the reported catalytic activity of DABCO in the literature,[48] a relevant mechanism is proposed in Scheme 2. As a bicyclic amine base, DABCO facilitates Knoevenagel condensation of aldehyde and malononitrile. The synthetic pathway proceeds via the Michael-type addition of 7-hydroxy-2-phenyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-5-one to the Knoevenagel adduct (**I**) that accelerates with the catalytic activity of the solid base catalyst used. In the next step, the intramolecular cyclization of the intermediate (**II**) led to intermediate (**III**), which finally underwent tautomeric proton shift to generate the desired product, i.e. **4**.

Conclusions

A rapid and environmentally-benign one-pot protocol has been developed for preparing novel pyranothiadiazolopyrimidine derivatives as important hybrid frameworks containing both thiadiazolopyrimidine and pyran with biologically-valuable moieties. The advantages of this new synthetic protocol include the application of DABCO as an organocatalyst along with a solvent-free medium, a non-chromatographic purification process and good to high yields of products.

Experimental Section

General. Melting points were recorded on an Electrothermal type 9100 melting point apparatus. Fourier transform infrared (FT-IR) spectra were recorded with a Nicolet Avatar 370 FT-IR Therma spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. Mass spectra were scanned on a Varian Mat CH-7 at 70 eV. 7-hydroxy-2-phenyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-5-one was prepared according to the previously reported literature procedures.[49]

Typical one-pot procedure for the synthesis of 4a. A mixture of benzaldehyde (**2a**) (0.1 ml, 1 mmol), malononitrile (**1**) (0.100 g, 1.5 mmol), 7-hydroxy-2-phenyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-5-one (**3**) (0.250 g, 1 mmol) and DABCO (0.011 g, 10 mol%) was stirred at 100 °C. The reaction progress was monitored by thin-layer chromatography (hexane: ethylacetate 1:1). After completion of the reaction, the mixture was cooled to room temperature and ethanol (10 ml) was added. Then, the precipitated product was filtered. For further purification of product, the obtained crude mass was crystallized from EtOH:DMF (5:1). According to ORTEP diagram of **4a** as well as NMR spectrum, synthesized products were crystallized in the form of a 1:1 complex with DMF molecule. In order to remove the DMF molecule from product, consecutive evaporation under reduced pressure with H_2O (3x10 ml) and Toluene (3x10 ml) was applied. After removing DMF, the obtained powder was placed in oven at 110 °C overnight afforded to pure product.

6-Amino-9-oxo-2,8-diphenyl-8*H*,9*H*-pyrano[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-7-carbonitrile (4a). Yellow powder (320 mg, 80%). mp 276-278 °C. IR (solid, KBr, *v*max, cm^{-1}): 3444, 3336 (NH_2), 2191 (C≡N), 1700 (C=O), 1655 (C=N). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H 4.59 (1H, s, CH), 7.25-7.36 (7H, m, 5CH aromatic and NH_2), 7.61-7.70 (3H, m, CH aromatic), 7.96 (1H, d, $^{3}J_{HH}$ 1.8 Hz, CH aromatic), 7.98 (1H, d, $^{3}J_{HH}$ 1.8 Hz, CH aromatic). ^{13}C NMR (75.46 MHz, DMSO-d_6): δ_C 37.5 (CH), 57.7, 98.6, 120.0 (CN), 127.4, 127.9, 128.0, 128.5, 128.8, 130.2, 133.5, 144.3, 156.1, 158.2, 159.1, 159.5, 161.3. EI-MS: *m/z* (%) 399 (2, M^+), 329 (68), 319 (91),

261 (80), 202 (42), 176 (60), 153 (100), 126 (92), 103 (98), 66 (97), 39 (94). Anal. Calcd for $C_{21}H_{13}N_5O_2S$ (399.43): C, 63.15; H, 3.28; N, 17.53. Found: C, 63.38; H, 3.17; N, 17.75.

6-Amino-8-(4-chlorophenyl)-9-oxo-2-phenyl-8*H*,9*H*-pyrano[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-7-carbonitrile (4b). Yellow powder (360 mg, 84%). mp 265-267 °C. IR (solid, KBr, *v*max, cm^{-1}): 3318, 3284 (NH_2), 2197 (C≡N), 1711 (C=O), 1660 (C=N). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H 4.62 (1H, s, CH), 7.32 (4H, d, $^3J_{HH}$ 9.0 Hz, 2CH aromatic and NH_2), 7.40 (2H, d, $^3J_{HH}$ 9.0 Hz, CH aromatic), 7.61-7.73 (3H, m, CH aromatic), 7.95-7.98 (2H, m, CH aromatic). ^{13}C NMR (75.46 MHz, DMSO-d_6): δ_C 37.0 (CH), 57.2, 98.1, 119.8 (CN), 127.9, 128.4, 128.8, 130.0, 130.2, 132.0, 133.5, 143.2, 156.1, 158.1, 159.2, 159.5, 161.44. EI-MS: *m/z* (%) 434 (7, M^+), 365 (33), 319 (73), 295 (69), 202 (41), 187 (74), 152 (72), 103 (71), 66 (77), 44 (76). Anal. Calcd for $C_{21}H_{12}ClN_5O_2S$ (433.87): C, 58.13; H, 2.79; N, 16.14. Found: C, 58.33; H, 2.67; N, 16.25.

6-Amino-8-(4-bromophenyl)-9-oxo-2-phenyl-8*H*,9*H*-pyrano[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-7-carbonitrile (4c). Yellow powder (410 mg, 86%). mp 263-265 °C. IR (solid, KBr, *v*max, cm^{-1}): 3317, 3286 (NH_2), 2195 (C≡N), 1699 (C=O), 1658 (C=N). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H 4.60 (1H, s, CH), 7.25-7.28 (2H, m, CH aromatic), 7.33 (2H, broad s, NH_2), 7.52 (1H, d, $^3J_{HH}$ 2.1 Hz, CH aromatic), 7.54 (1H, d, $^3J_{HH}$ 1.8 Hz, CH aromatic), 7.61-7.72 (3H, m, CH aromatic), 7.95-7.98 (2H, m, CH aromatic). ^{13}C NMR (75.46 MHz, DMSO-d_6): δ_C 37.1 (CH), 57.1, 98.1, 119.8 (CN), 120.5, 127.9, 128.4, 130.2, 130.3, 131.7, 133.5, 143.6, 156.1, 158.1, 159.2, 159.5, 161.4. EI-MS: *m/z* (%) 478 (8, M^+), 411 (51), 329 (54), 319 (100), 202 (39), 152 (42), 120 (75), 103 (49), 77 (53), 66 (99), 29 (98). Anal. Calcd for $C_{21}H_{12}BrN_5O_2S$ (478.32): C, 52.73; H, 2.53; N, 14.64. Found: C, 52.88; H, 2.77; N, 14.35.

6-Amino-8-(2-chlorophenyl)-9-oxo-2-phenyl-8*H*,9*H*-pyrano[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-7-carbonitrile (4d). White powder (370 mg, 85%). mp 281-283 °C. IR (solid, KBr, *v*max, cm^{-1}): 3418, 3328 (NH_2), 2195 (C≡N), 1687 (C=O), 1666 (C=N). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H 5.07 (1H, s, CH), 7.26-7.30 (5H, m, NH_2 and 3CH aromatic), 7.40-7.43 (1H, m, CH aromatic), 7.59-7.71 (3H, m, CH aromatic), 7.92 (1H, d, $^3J_{HH}$ 1.5 Hz, CH aromatic), 7.95 (1H, d, $^3J_{HH}$ 1.2 Hz, CH aromatic). ^{13}C NMR (75.46 MHz, DMSO-d_6): δ_C 39.9 (CH), 61.1, 102.4, 124.3 (CN), 132.6, 132.7, 133.2, 133.8, 134.7, 134.9, 135.9, 137.6, 138.2, 145.9, 160.6, 163.3, 163.9, 164.3, 166.2. EI-MS: *m/z* (%) 434 (3, M^+), 397 (48), 329 (99), 319 (92), 228 (82), 152 (58), 135 (89), 121 (93), 77 (94), 66 (100), 29 (95). Anal. Calcd for $C_{21}H_{12}ClN_5O_2S$ (433.87): C, 58.13; H, 2.79; N, 16.14. Found: C, 58.22; H, 2.87; N, 16.35.

6-Amino-9-oxo-2-phenyl-8-(*p*-tolyl)-8*H*,9*H*-pyrano[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-7-carbonitrile (4e). White powder (330 mg, 80%). mp 265-267 °C. IR (solid, KBr, *v*max, cm^{-1}): 3321, 3291 (NH_2), 2196 (C≡N), 1712 (C=O), 1662 (C=N). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H 2.32 (3H, s, CH_3), 4.58 (1H, s, CH), 7.15-7.22 (4H, m, CH aromatic), 7.29 (2H, broad s, NH_2), 7.65-7.74 (3H, m, CH aromatic), 7.99 (1H, d, $^3J_{HH}$ 1.8 Hz, CH aromatic), 8.02 (1H, d, $^3J_{HH}$ 1.5 Hz, CH aromatic). ^{13}C NMR (75.46 MHz, DMSO-d_6): δ_C 21.1 (CH_3), 37.1 (CH), 57.9, 98.8, 120.0 (CN), 127.9, 128.5, 129.3, 130.2, 133.5, 136.5, 141.3, 156.0, 158.1, 159.1, 159.4, 159.5, 161.1. EI-MS: *m/z* (%) 413 (19, M^+), 343 (30), 329 (78), 319 (94), 275 (70), 202 (45), 167 (95), 140 (91), 115 (93) 77 (92), 66 (100), 39 (90). Anal. Calcd for $C_{22}H_{15}N_5O_2S$ (413.45): C, 63.91; H, 3.66; N, 16.94. Found: C, 64.11; H, 3.74; N, 17.14.

6-Amino-8-(4-methoxyphenyl)-9-oxo-2-phenyl-8*H*,9*H*-pyrano[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-7-carbonitrile (4f). White powder (260 mg, 60%). mp 247-249 °C. IR (solid, KBr, *v*max, cm^{-1}): 3323, 3290 (NH_2), 2197 (C≡N), 1712 (C=O), 1663 (C=N). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H 3.74 (3H, s, CH_3), 4.54 (1H, s, CH), 6.88 (1H, d, $^3J_{HH}$ 2.1 Hz, CH aromatic), 6.90 (1H, d, $^3J_{HH}$ 2.1 Hz, CH aromatic), 7.19-7.24 (4H, m, 2CH aromatic and NH_2), 7.61-7.72 (3H, m, CH aromatic), 7.95 (1H, d, $^3J_{HH}$ 1.8 Hz, CH aromatic), 7.97 (1H, d, $^3J_{HH}$ 2.1 Hz, CH aromatic). ^{13}C NMR (75.46 MHz, DMSO-d_6): δ_C 36.7 (CH), 55.6 (CH_3O), 57.9, 99.0, 114.2, 120.1 (CN), 127.8, 128.5, 129.1, 130.2, 133.5, 136.4, 156.0, 157.9, 158.7, 159.1, 159.4, 161.1. EI-MS: *m/z* (%) 429 (5, M^+), 358

(19), 319 (16), 290 (43), 202 (30), 183 (50), 120 (63), 77 (45), 66 (100), 29 (68). Anal. Calcd for $C_{21}H_{12}N_5O_2S$ (398.42): C, 63.31; H, 3.04; N, 17.58. Found: C, 63.38; H, 3.13; N, 17.36.

6-Amino-9-oxo-2-phenyl-8-(4-(trifluoromethyl)phenyl)-8*H*,9*H*-pyrano[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-7-carbonitrile (4g). White powder (370 mg, 78%). mp 279-281 ˚C. IR (solid, KBr, *v*max, cm^{-1}): 3317, 3286 (NH_2), 2197 (C≡N), 1711 (C=O), 1660 (C=N). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H 4.73 (1H, s, CH), 7.39 (2H, broad s, NH_2), 7.52 (1H, s, CH aromatic), 7.55 (1H, s, CH aromatic), 7.61-7.73 (5H, m, CH aromatic), 7.95 (1H, d, $^3J_{HH}$ 1.8 Hz, CH aromatic), 7.98 (1H, d, $^3J_{HH}$ 1.5 Hz, CH aromatic). ^{13}C NMR (75.46 MHz, DMSO-d_6): δ_C 37.5 (CH), 56.9, 97.8, 119.7 (CN), 125.7, 125.8, 126.6, 127.9, 128.4, 129.0, 130.2, 133.5, 148.8, 156.1, 158.2, 159.2, 159.6, 161.6. EI-MS: *m/z* (%) 467 (15, M^+), 319 (100), 220 (40), 120 (42), 102 (55), 66 (35), 29 (37). Anal. Calcd for $C_{22}H_{12}F_3N_5O_2S$ (467.42): C, 56.53; H, 2.59; N, 14.98. Found: C, 56.36; H, 2.63; N, 15.23.

6-Amino-8-(4-nitrophenyl)-9-oxo-2-phenyl-8*H*,9*H*-pyrano[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-7-carbonitrile (4h). White powder (390 mg, 88%). mp 276-278 °C. IR (solid, KBr, *v*max, cm^{-1}): 3326, 3292 (NH_2), 2193 (C≡N), 1705 (C=O), 1662 (C=N), 1527, 1351 (NO_2). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H 4.82 (1H, s, CH), 7.46 (2H, broad s, NH_2), 7.61-7.74 (5H, m, CH aromatic), 7.94 (1H, d, $^3J_{HH}$ 1.8 Hz, CH aromatic), 7.99 (1H, d, $^3J_{HH}$ 1.8 Hz, CH aromatic), 8.22-8.25 (2H, m, CH aromatic). ^{13}C NMR (75.46 MHz, DMSO-d_6): δ_C 37.5 (CH), 56.5, 97.4, 119.6 (CN), 124.1, 127.8, 128.4, 129.5, 130.2, 133.5, 145.0, 151.7, 156.1, 158.3, 159.3, 159.6, 161.8. EI-MS: *m/z* (%) 444 (5, M^+), 442 (17), 376 (48), 356 (47), 318 (78), 305 (35), 242 (27), 197 (81), 175 (85), 103 (79), 65 (100), 39 (80). Anal. Calcd for $C_{21}H_{12}N_6O_4S$ (444.42): C, 56.75; H, 2.72; N, 18.91. Found: C, 56.49; H, 2.91; N, 19.17.

6-Amino-9-oxo-2-phenyl-8-(*m*-tolyl)-8*H*,9*H*-pyrano[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-7-carbonitrile (4i). White powder (280 mg, 68%). mp 263-265 °C. IR (solid, KBr, *v*max, cm^{-1}): 3323, 3291 (NH_2), 2196 (C≡N), 1712 (C=O), 1662 (C=N); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H 2.32 (3H, s, CH_3), 4.58 (1H, s, CH), 7.15-7.22 (4H, m, CH aromatic), 7.29 (2H, broad s, NH_2), 7.65-7.77 (3H, m, CH aromatic), 7.99-8.02 (2H, m, CH aromatic). ^{13}C NMR (75.46 MHz, DMSO-d_6): δ_C 21.1 (CH_3), 37.1 (CH), 57.9, 98.8, 120.0 (CN), 127.9, 128.5, 129.3, 130.2, 133.5, 136.5, 141.3, 156.0, 158.1, 159.1, 159.5, 161.1. EI-MS: *m/z* (%) 413 (8, M^+), 409 (45), 341 (83), 317 (92), 273 (90), 241 (37), 201 (82), 166 (99), 120 (91), 76 (88), 65 (100), 39 (89). Anal. Calcd for $C_{22}H_{15}N_5O_2S$ (413.45): C, 63.91; H, 3.66; N, 16.94. Found: C, 63.78; H, 3.77; N, 17.21.

6-Amino-8-(3-methoxyphenyl)-9-oxo-2-phenyl-8*H*,9*H*-pyrano[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-7-carbonitrile (4j). Yellow powder (270 mg, 63%). mp 256-258 °C. IR (solid, KBr, *v*max, cm^{-1}): 3353, 3317 (NH_2), 2195 (C≡N), 1694 (C=O), 1656 (C=N). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H 3.79 (3H, s, CH_3), 4.61 (1H, s, CH), 6.85-6.89 (3H, m, CH aromatic), 7.26-7.32 (3H, m, NH_2 and CH aromatic), 7.65-7.74 (3H, m, CH aromatic), 7.99-8.02 (2H, m, CH aromatic). ^{13}C NMR (75.46 MHz, DMSO-d_6): δ_C 37.4 (CH), 55.5 (CH_3O), 57.6, 98.5, 112.3, 114.2, 120.0 (CN), 120.1, 127.9, 128.5, 130.0, 130.2, 133.5, 145.8, 156.1, 158.2, 159.1, 159.6, 159.7, 161.3. EI-MS: *m/z* (%) 429 (10, M^+), 360 (39), 329 (20), 319 (82), 291 (65), 243 (32), 202 (55), 183 (98), 120 (95), 103 (76), 77 (85), 66 (99), 51 (43), 39 (94), 29 (100). Anal. Calcd for $C_{21}H_{12}N_5O_2S$ (398.42): C, 63.31; H, 3.04; N, 17.58. Found: C, 63.45; H, 3.18; N, 17.39.

6-Amino-8-(2,4-dimethoxyphenyl)-9-oxo-2-phenyl-8*H*,9*H*-pyrano[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-7-carbonitrile (4k). White powder (380 mg, 83%). mp 259-261 °C. IR (solid, KBr, *v*max, cm^{-1}): 3398, 3305 (NH_2), 2202 (C≡N), 1690 (C=O), 1669 (C=N). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H 3.75 (6H, s, $2CH_3$), 4.73 (1H, s, CH), 6.44-6.48 (1H, m, CH aromatic), 6.56 (1H, d, $^3J_{HH}$ 2.4 Hz, CH aromatic), 7.00-7.06 (3H, m, CH aromatic and NH_2), 7.60-7.72 (3H, m, CH aromatic), 7.94-7.97 (2H, m, CH aromatic). ^{13}C NMR (75.46 MHz, DMSO-d_6): δ_C 32.6 (CH), 55.6 (CH_3O), 56.2 (CH_3O), 57.0, 98.2, 99.4, 105.2, 120.2 (CN), 124.2, 127.8, 128.5, 128.7, 130.2, 133.4, 155.9, 158.6, 158.7, 158.9, 159.9, 160.1, 160.6. EI-MS: *m/z* (%) 362 (15), 360 (68), 291 (32), 258 (69), 213 (98), 185

(70), 170 (67), 148 (86), 121 (92), 77 (88), 66 (100), 39 (91). Anal. Calcd for $C_{21}H_{11}N_5O_2S$ (397.41): C, 63.47; H, 2.79; N, 17.62. Found: C, 63.58; H, 2.62; N, 17.86.

6-Amino-9-oxo-2-phenyl-8-(pyridin-4-yl)-8*H*,9*H*-pyrano[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-7-carbonitrile (4l). Yellow powder (340 mg, 85%). mp 267-269 °C. IR (solid, KBr, *v*max, cm^{-1}): 3322, 3289 (NH_2), 2196 (C≡N), 1712 (C=O), 1663 (C=N). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H 4.64 (1H, s, CH), 7.32 (2H, d, $^3J_{HH}$ 6.0 Hz, CH aromatic), 7.41 (2H, s, CH aromatic), 7.61-7.72 (3H, m, CH aromatic), 7.97 (2H, d, $^3J_{HH}$ 6.0 Hz, CH aromatic), 8.54 (2H, broad s, NH_2). ^{13}C NMR (75.46 MHz, DMSO-d_6): δ_C 37.0 (CH), 56.2, 97.1, 119.7 (CN), 123.3, 127.9, 128.4, 130.2, 133.5, 150.1, 152.6, 156.1, 158.4, 159.3, 159.7, 161.8. EI-MS: *m/z* (%) 397 (1, $[M-3]^+$), 372 (2), 331 (20), 318 (66), 242 (25), 202 (46), 175 (53), 154 (86), 120 (80), 103 (100), 66 (97), 51 (70), 39 (50), 28 (89). Anal. Calcd for $C_{20}H_{12}N_6O_2S$ (400.41): C, 59.99; H, 3.02; N, 20.99. Found: C, 60.17; H, 3.15; N, 21.11.

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Supplementary Material

Supplementary material containing X-ray crystallographic data (for **4a** product), copies of IR, ^{1}H and ^{13}C NMR spectra associated with this paper can be found in the online version.

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