Tetrahedron Letters 50 (2009) 6223–6227

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of novel 2,3-substituted-2,4-dihydro-pyrazolo[4,3-*d*]-pyrimidine-5,7-diones

Thomas Brady, Khang Vu, Jack R. Barber, Shi Chung Ng, Yuefen Zhou *

CytRx Corporation, 3030 Bunker Hill Street, Suite 101, San Diego, CA 92109, USA

ARTICLE INFO

Article history:
Received 8 May 2009
Revised 27 August 2009
Accepted 27 August 2009
Available online 2 September 2009

Keywords:
2,3-Substituted-2,4-dihydro-pyrazolo-[4,3-*d*]pyrimidine-5,7-diones
2,4-Dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-dione derivatives
1,4-Dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-dione derivatives
Assignment of regio-isomer structures
Single crystal X-ray structure analysis

ABSTRACT

Novel 2,3-substituted-2,4-dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-diones were successfully synthesized with moderate to good yields using a new synthetic approach. The structures of the regio-isomers in this series were determined by single crystal X-ray analysis and NMR spectra.

Pyrazolo[4,3,*d*]pyrimidine-5,7-dione derivatives constitute an important class of pharmacologically active compounds with known activities as factor Xa inhibitors for treatment of thromboembolic disorders,[1] with desirable affinity at A1 adenosine receptors for the treatment of bronchoconstriction and cardiac insufficiency,[2] and as a potential purine antagonist for chemotherapy.[3] Therefore, synthesis of novel pyrazolo[4,3-*d*]pyrimidine-5,7-dione derivatives is of interest to scientists working in the drug discovery research field.

The majority of the pyrazolo[4,3-*d*]pyrimidine-5,7-dione derivatives that have been synthesized or studied so far are either those without substitution at C-3 (**1** and **2** where R^1 = H)[4–7] or those with substitution at N-1 but not at N-2 (**2**) (Fig. 1)[1] or no substitution at either N-1 or N-2.[8] There are only few examples reported in the literature for the analogs **1** which have substitutions at both N-2 and C-3 (e.g., 2-methyloxoformycin B) as shown in Figure 1.[9]

In the course of our research to develop novel small molecule chaperone amplifiers aiming to treat neurodegenerative diseases, we are highly interested in the design and synthesis of novel analogs of 2,3-substituted-2,4-dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-diones (**1**) for biological testing.

Previously reported literature methods for the synthesis of this class of pyrazolo[4,3-*d*]pyrimidine-5,7-dione compounds are shown in Schemes 1–3.[1,4–9] In the method shown in Scheme 1, the synthesis of the pyrazolo[4,3-*d*]pyrimidine-5,7-diones (**V** and **VII**) were accomplished by diazotization of 5-amino-6-methyl-1*H*-pyrimidine-2,4-dione (**Ia** and **Ib**) followed by the cyclization and subsequent methylation to give the N-1 alkylated compound as the major product (**V**).[4–6] The two isomers of **V** and **VII** were separated by flash chromatography purification on silica gel (**V**:**VII** = 71%:29%).

The method described in Scheme 2 applied 4-amino-5-carboxylate ester pyrazole (**VIII**) as starting material. The synthesis involved converting the ortho-aminoester pyrazole (**VIII**) to the corresponding *ortho*-amino-amide (**IX**) via a 4-step synthesis followed by the cyclization via the treatment of carbonyldiimidazole or other phosgene equivalent reagents.[1] This method generates

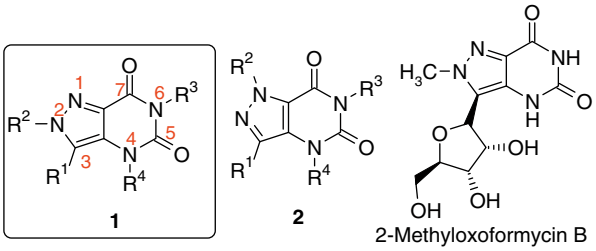
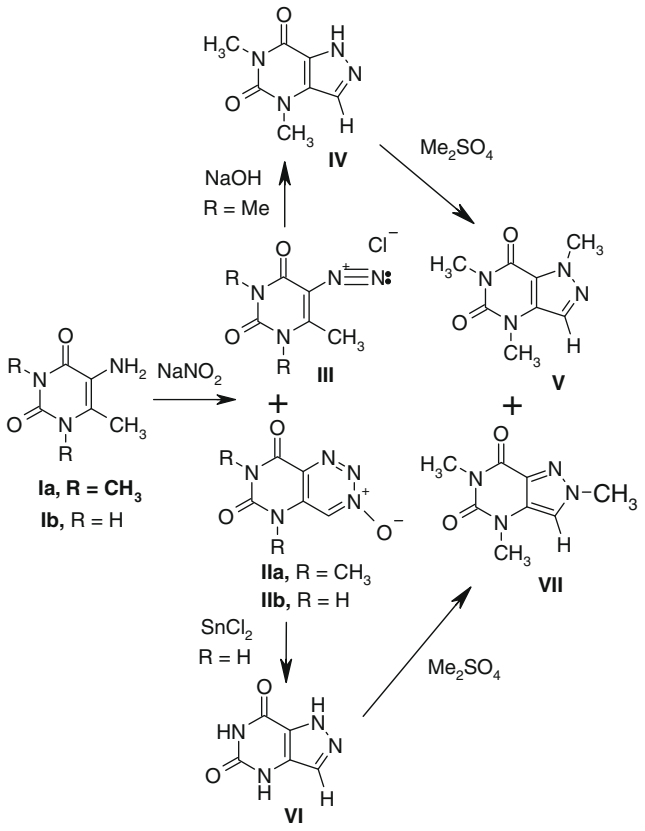


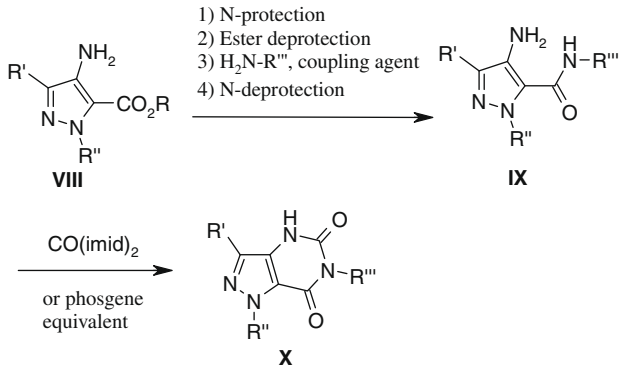
Figure 1. 2,4- and 1,4-Dihydro-pyrazolo[4,3-*d*]pyrimidine -5,7-dione derivatives.

* Corresponding author. Tel.: +1 858 273 2501x221; fax: +1 858 273 2697.
E-mail addresses: yuefen.zhou@gmail.com, yzhou@cytrx.com (Y. Zhou).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.08.098



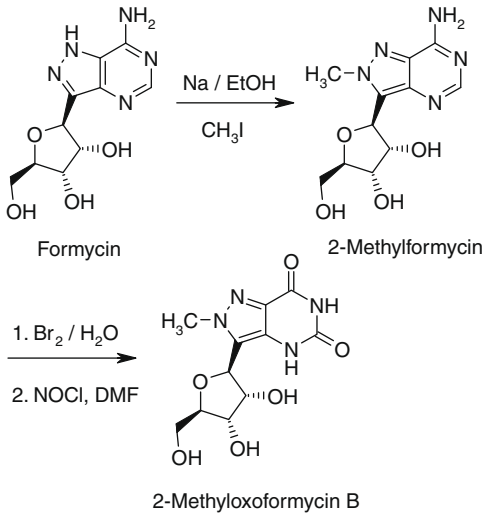
Scheme 1. Synthesis of 1,4,6-trimethyl-1,4-dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-dione (**V**) and 2,4,6-trimethyl-2,4-dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-dione (**VII**).



Scheme 2. Synthesis of N-1 and C-3 substituted-1,4-dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-dione derivatives.

exclusively the N-1 substituted-1,4-dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-dione derivatives, not the N-2 substituted analogs that we are particularly interested in.

The method shown in Scheme 3 describes the preparation of both the C-3 and N-2 substituted-2,4-dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-diones,[9] which was our desired substitution pattern for the analogs that we wished to make and submit for biological testing. In this method, 2-methyloxoformycin B was prepared from the methylation of formycin followed by oxidation and then deamination with nitrosyl chloride. However, this method does not provide a general application to meet our needs since we are not interested in adding the sugar moiety at C-3. Therefore



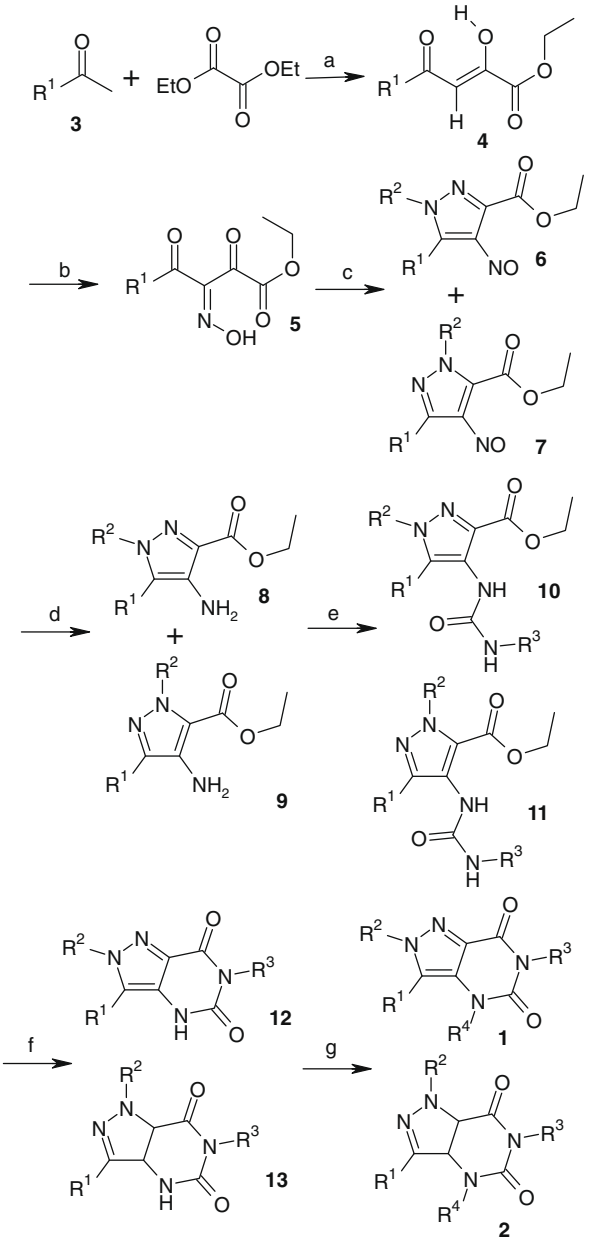
Scheme 3. Synthesis of 2-methyloxoformycin B.

we designed a new and general synthetic approach to make C-3 and N-2 substituted-2,4-dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-diones as shown in Scheme 4.

With this design, we started with ketones **3** which were easily transferred to the intermediates **4** by the treatment of diethyl oxalate in the presence of a base. The intermediates **4** were then reacted with N_2O_3 gas generated in situ to form oximine derivatives **5** according to literature procedures.[10,11] The oximine derivatives were then treated with substituted hydrazine at 0 °C to generate the key intermediates of *ortho*-nitroso-esters **6** and **7** as regio-isomers that were reduced by sodium dithionite to their corresponding *ortho*-amino-esters **8** and **9** according to the literature method.[12] The isomers of **8** and **9** were easily separated by flash column chromatography purification on silica gel. The key in this method was the ratio of the regio-isomers of **8** and **9**. Only when isomers **8** were the major products, the synthesis of the N-2 substituted-2,4-dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-diones would be practical. It turned out that intermediates **8** were always the major components (67–100%) based on their isolated yields.

According to the mechanism proposed by Corey and co-workers,[13] when a diketo oximine reacts with an un-substituted hydrazine, one of the hydrazine N-atoms first undergoes nucleophilic attack at one of the more reactive ketones. In the case of alkyl mono-substituted hydrazine like ours (R^2-$NHNH_2$), the N-atom directly connected to the R^2 alkyl group should be more nucleophilic. Meantime the carbonyl carbon directly connected to R^1 group in the diketo oximine **5** is likely more reactive (because it is more positively charged) than the other carbonyl carbon directly connected to the ester group according to the extended Hückel charge calculation using Chem3D Pro 11.0. Therefore when the diketo oximine **5** reacts with R^2-$NHNH_2$, the N-atom adjacent to R^2 alkyl group will likely first react with the ketone adjacent to R^1 to form **6** as a major product, which could explain why compound **8** was the major component.

The above pure 4-amino-5-carboxylated ester pyrazoles (**8**) were then reacted with isocyanate to form ureas (**10**), which were subsequently cyclized in the presence of KO^{t}Bu at room temperature to construct the pyrimidine rings to form compounds **12**. Finally, alkylation occurring at N-4 furnished the synthesis giving the desired products of N-2 and C-3 substituted-2,4-dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-diones (**1**) in good yields. Some of the minor products of N-1 and C-3 substituted-1,4-dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-diones (**13** and **2**) were also made follow-



Scheme 4. Reagents and conditions: (a) NaOEt, EtOH, 0 °C, 4 h; (b) N_2O_3 gas, EtOH, rt; (c) R^2-$NHNH_2$·oxalate salt, EtOH/H_2O (1:1), 0 °C, 40 min; (d) sodium dithionite, H_2O; (e) R^3NCO, DCM, rt, o.n.; (f) KO^{t}Bu (2.0 M in THF), THF, rt, 30 min; (g) R^4I, Cs_2CO_3, DMF, 80 °C, 1 h.

ing the same synthetic sequence for the comparison of NMR spectra to help assignment of the regio-isomers.

The assignment of the regio-isomers of **12 and 13:**

The structures of the N-1 and N-2 substituted isomers (**V** and **VII**, Scheme 1) were assigned by Dodson's group based on the comparison of their infrared spectra, ultraviolet spectra, and NMR spectra. They assigned the compounds with the N-CH_3 absorption at lower field in the NMR spectrum as the N-1 substituted analogs (e.g., **V**). In order to determine the structures of the isomers (**12** and **13**) we made, we specifically prepared the minor isomer **13a** to compare with the major isomer **12b** in their ^{1}H NMR spectra (Fig. 2).[14] Consistent with Dodson's result, the minor isomer **13a** had the chemical shift of 4.60 ppm (lower field) for the CH_2 adjacent to N-1 in its ^{1}H NMR spectrum; while the major isomer of **12b** had the chemical shift of 4.19 ppm (higher field) for the CH_2 adjacent to N-2.

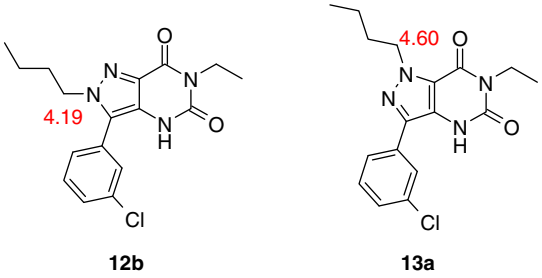


Figure 2. The chemical shift difference between the CH_2 adjacent to N-1 (**13a**) and adjacent to N-2 (**12b**).

In order to further confirm the absolute structure of the regio-isomers of **12** and **13**, compound **12a** (Fig. 3)[15] was re-crystallized in EtOAc/hexanes in a dilute solution to get single crystals. The single crystal thus formed was evaluated by X-ray analysis to determine the absolute structure of **12a**, the major isomer (Fig. 4).[17] As shown in Figure 4, the major product **12a** was clearly the desired N-2 (not as labeled in Fig. 4, but as labeled in Fig. 1) substituted-2,4-dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-dione. This single crystal X-ray structure analysis result confirmed the structure assignment based on the ^{1}H NMR spectra. Therefore, the structures for the rest of the novel analogs **12** we made (Table 1) were assigned based on their ^{1}H NMR spectra.

In conclusion, we have designed a new synthetic approach and used it successfully to synthesize a number of novel N-2 and C-3 substituted-2,4-dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-diones in fairly good yields. The structures of their *regio*-isomers were

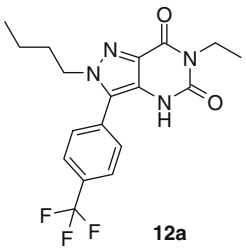


Figure 3. 2-Butyl-6-ethyl-3-(4-trifluoromethyl-phenyl)-2,4-dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-dione (**12a**).

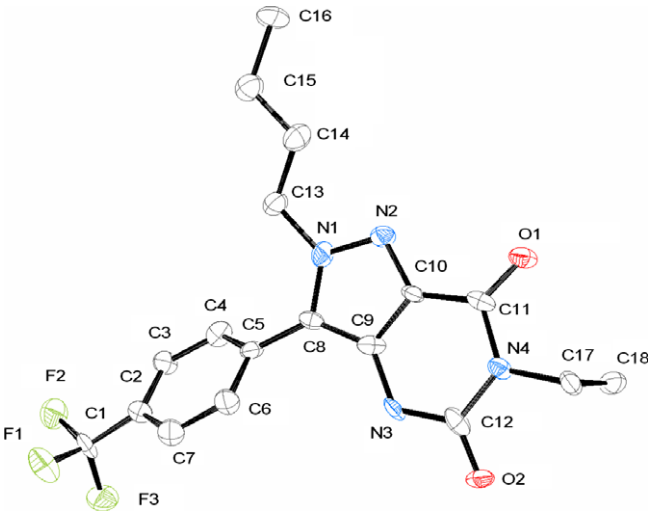
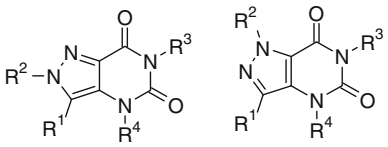


Figure 4. Single crystal structure of **12a** determined by X-ray analysis.

Table 1
Synthesis of the C-3 substituted-2,4- and 1,4-dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-dione derivatives (**1**, **12**, **2** and **13**)



12: R^4 = H
1: R^4 = not H

13: R^4 = H
2: R^4 = not H

Compd	R^1	R^2	R^3	R^4	Substitution position	Yield[a] (%)
12a	4-CF_3-Ph	*n*-Bu	Et	H	N-2	54
1a	4-CF_3-Ph	*n*-Bu	Et	Me	N-2	85
1b	4-CF_3-Ph	*n*-Bu	$(CH_3)_2CHCH_2$	H	N-2	71
12b	3-Cl-Ph	*n*-Bu	Et	H	N-2	54
1c	3-Cl-Ph	*n*-Bu	Et	Me	N-2	86
13a	3-Cl-Ph	*n*-Bu	Et	H	N-1	50
2a	3-Cl-Ph	*n*-Bu	Et	Me	N-1	86
12c	3,4-Di-Cl-Ph	Me	Et	H	N-2	24
1d	3,4-Di-Cl-Ph	Me	Et	Me	N-2	81
12d	Ph	*n*-Bu	Et	H	N-2	66
1e	Ph	*n*-Bu	Et	Me	N-2	88
12e	Me	*n*-Bu	Et	H	N-2	73
1f	Me	*n*-Bu	Et	Me	N-2	50
12f		*n*-Bu	Et	H	N-2	57

[a] The isolated yield for the last two steps (steps e and f) for **12** or **13**, and for the last step (step g) for **1** or **2**.

determined by single crystal X-ray structure analysis and ^{1}H NMR spectra. We believe our synthetic method has general application based on the readily available starting materials and reasonably good yields. More importantly, our method provides future access to this class of novel N-2 and C-3 substituted-2,4-dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-diones for potential pharmaceutical applications.

Acknowledgments

The authors would like to thank Professor Arnold L. Rheingold and Dr. Curtis Moore at University of California, San Diego for their single crystal X-ray structure analysis.

References and notes

1. Pinto, D. J. P.; Quan, M. L.; Woerner, F. J.; Li, R., International Patent WO 02000655 A1, 2002.
2. Hamilton, H. W. U.S. Patent 4,663,326, May 5, 1987.
3. Robins, R. K. *J. Am. Chem. Soc.* **1956**, *78*, 784.
4. Papesch, V.; Dodson, R. M. *J. Org. Chem.* **1965**, *30*, 199.
5. Robins, R. K.; Furcht, F. W.; Drauer, A. D.; Jones, J. W. *J. Am. Chem. Soc.* **1956**, *78*, 2418.
6. Papesch, V.; Dodson, R. M. *J. Org. Chem.* **1963**, *28*, 1329.
7. Gilbert, A. M.; Caltabiano, S.; Koehn, F. E.; Chen, Z.-J.; Francisco, G. D.; Ellingboe, J. W.; Kharode, Y.; Mangine, A.; Francis, R.; TrailSmith, M.; Gralnick, D. *J. Med. Chem.* **2002**, *45*, 2342.
8. (a) Robins, R. K.; Holum, L. B.; Furcht, F. W. *J. Org. Chem.* **1956**, *21*, 833; (b) Long, R. A.; Gerster, J. F.; Townsend, L. B. *J. Heterocycl. Chem.* **1970**, *7*, 863.
9. (a) Townsend, L. B. et al *J. Org. Chem.* **1974**, *39*, 2023; (b) Ugarker, B. G.; Revankar, G. R.; Robins, R. K. *J. Heterocycl. Chem.* **1984**, *21*, 1865.
10. Albrecht, W.; Greim, C.; Striegel, H.-G.; Tollmann, K.; Merckle, P.; Laufer, S. International Patent WO 2006/089798 A1, Aug. 31, 2006.
11. Takei, H.; Yasuda, N.; Takagaki, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 208.
12. Yuan, J.; Gulianello, M.; Lombaert, S. D.; Brodbeck, R.; Kieltyka, A.; Hodgetts, K. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2133. Note: This paper only briefly mentioned reagents for the synthesis of the intermediates **8** and **9**, and it did not give the ratio of intermediates **8** to **9** or their characterization.
13. Majid, T.; Hopkins, C. R.; Pedgrift, B.; Collar, N. *Tetrahedron Lett.* **2004**, *45*, 2137.
14. Comparison of the ^{1}H NMR data between **12b** (major) and **13a** (minor):
The major isomer: 2-butyl-3-(3-chloro-phenyl)-6-ethyl-2,4-dihydro-pyrazolo-[4,3-*d*]pyrimidine-5,7-dione (**12b**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.84 (t, 3H, J = 6 Hz), 1.16 (t, 3H, J = 5 .6 Hz), 1.25 (m, 2H, J = 5 Hz), 1.82 (m, 2H, J = 6 Hz), 3.99 (q, 2H, J = 5.6 Hz), 4.19 (t, 2H, J = 5.6 Hz), 7.28–7.26 (m, 1H), 7.38 (s, 1H), 7.51–7.49 (m, 2H), 9.54 (br s, 1H).
The minor isomer: 1-butyl-3-(3-chloro-phenyl)-6-ethyl-1,4-dihydro-pyrazolo-[4,3-*d*]pyrimidine-5,7-dione (**13a**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.96 (t, 3H, J = 6 Hz), 1.23 (t, 3H, J = 5.6 Hz), 1.38 (m, 2H, J = 6 Hz), 1.90 (m, 2H, J = 6 Hz), 4.09 (q, 2H, J = 5.6 Hz), 4.60 (t, 2H, J = 6 Hz), 7.42–7.36 (m, 2H), 7.63 (dd, 1H, J = 6, 1.2 Hz), 7.75 (m, 1H), 10.11 (br s, 1H).
15. *The typical procedure for the synthesis of compound* **12a** and **1a** (R^1 = *4-CF_3-Ph*, R^2 = *n-Bu*, R^3 = *Et*, R^4 = *H* (**12a**); R^4 = *Me* (**1a**)): Sodium ethoxide solution (21% by weight, 20 mL, 54 mmol) was added to a stirring solution of diethyl oxalate (9 g, 61 mmol) in ethanol (70 mL) cooled to 0 °C by an ice bath. The solution was stirred for 20 min at 0 °C and then 1-(4-trifluoromethyl-phenyl)-ethanone (**3a**) (5 g, 27 mmol) was added drop wise over 5 min. The reaction was stirred for 4 hours and then concentrated on a rotary evaporator. HCl (1.0 N, 110 mL) was added to the residue and the mixture was extracted into ethyl acetate (3 × 60 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. The crude oil was purified by silica gel chromatography to afford 2,4-dioxo-4-(4-trifluoromethyl-phenyl)-butyric acid ethyl ester (**4a**) (3 g, 38%) as an orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.41 (t, 3H, J = 5.6 Hz), 4.40 (q, 2H, J = 5.6 Hz), 7.07 (s, 1H, enolate C=CH), 7.75 (d, 2H, J = 6.8 Hz), 8.08 (d, 2H, J = 6.4 Hz), 15.2 (br s, 1H, enolate OH).
Into a solution of 2,4-dioxo-4-(4-trifluoromethyl-phenyl)-butyric acid ethyl ester (**4a**) (4 g, 15.6 mmol) in ethanol (150 mL), N_2O_3 gas[16] was bubbled in at ambient temperature until the starting material was completely consumed (by LC/MS). The solvent was removed and the residue was taken up in ethyl acetate (100 mL) and washed with water (2 × 50 mL). The organic phase was dried over sodium sulfate, filtered, concentrated on a rotary evaporator, and the residue was purified by silica gel chromatography (0–100% ethyl acetate in hexanes) to afford 3 g of a clear viscous oil (**5a**) which was directly taken up in ethanol (150 mL) and cooled to 0 °C. *n*-Butyl hydrazine oxalate (1.8 g, 10 mmol) dissolved in a mixture of ethanol/H_2O (1:1) (20 mL) was added drop-wise to the above cooled stirring solution. After 40 min the solution had turned an intense electric blue color to form the cyclized pyrazole nitroso moieties (**6a** and **7a**). Sodium dithionite (saturated in H_2O) was then added until the color faded, upon which time LC–MS analysis showed complete conversion to the corresponding amino-pyrazole product. The solids were filtered off and the filtrate was concentrated on a rotary evaporator and the residue was purified by silica gel chromatography (0–100% ethyl acetate in hexanes) to afford the key intermediate 4-amino-1-butyl-5-(4-trifluoromethyl-phenyl)-1*H*-pyrazole-3-carboxylic acid ethyl ester (**8a**) (1.4 g, 22%, three steps) as a light yellow oil and 0.7 g of the minor isomer 4-amino-2-butyl-5-(4-trifluoromethyl-phenyl)-2*H*-pyrazole-3-carboxylic acid ethyl ester (**9a**) for a total yield of 37.8% for three steps (**8a**:**9a** = 67%:33%). LC–MS (ESI^+) m/z = 356.1 $[M+H]^+$. The above 4-step synthesis was based on the literature procedures as described in the above Refs. 10–12.

Ethyl isocyanate (106 mg, 1,5 mmol) was added to a solution of 4-amino-1-butyl-5-(4-trifluoromethyl-phenyl)-1*H*-pyrazole-3-carboxylic acid ethyl ester (**8a**) (300 mg, 0.84 mmol) in DCM (5 mL). The reaction was stirred at ambient temperature for 18 h until complete conversion was confirmed by LC–MS analysis ((ESI$^+$) m/z = 427.0 [M+H]$^+$) to afford the pyrazole urea intermediate (**10a**). The solvent was removed under reduced pressure and the residue was taken up in THF (10 mL), potassium *tert*-butoxide (2.0 M in THF, 0.5 mL, 1 mmol) was added and the reaction was stirred for 30 min at ambient temperature. The solution was then diluted with aqueous 1.0 N HCl (100 mL) and extracted with ethyl acetate (3 × 75 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel chromatography (0–100% ethyl acetate in hexanes) to afford 2-butyl-6-ethyl-3-(4-trifluoromethyl-phenyl)-2,4-dihydro-pyrazolo*[4,3-*d*]pyrimidine-5,7-dione (**12a**) (175 mg, 54%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.83 (t, 3H, J = 6 Hz), 1.12 (t, 3H, J = 5.6 Hz), 1.23 (m, 2H, J = 6 Hz), 1.82 (m, 2H, J = 6 Hz), 3.90 (q, 2H, J = 5.6 Hz), 4.21 (t, 2H, J = 5.6 Hz), 7.56 (d, 2H, J = 6.8 Hz), 7.82 (d, 2H, J = 6.4 Hz), 10.45 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.29, 13.65, 19.87, 32.39, 36.22, 51.28, 122.83, 124.34, 124.99, 126.43, 126.63, 130.30, 130.73, 131.82 (1C, q, J = 32.9 Hz, CF_3), 153.03, 157.56; LC–MS (ESI$^+$) m/z = 381.1 [M+H]$^+$; Elemental Anal. Calcd for $C_{18}H_{19}F_3N_4O_2$: C, 56.84; H, 5.03; N, 14.73. Found: C, 56.89; H, 5.38; N, 15.07.

Methyl iodide (30 mg, 0.2 mmol) was added to a mixture of 2-butyl-6-ethyl-3-(4-trifluoromethyl-phenyl)-2,4-dihydro-pyrazolo[4,3-d]pyrimidine-5,7-dione (**12a**) (50 mg, 0.13 mmol) and cesium carbonate (43 mg, 0.13 mmol) in DMF (4 mL), and the reaction mixture was stirred at 80 °C for 1 h. The mixture was diluted with aqueous 1.0 N HCl (50 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, filtered, concentrated, and applied to silica gel chromatography purification (0–100% ethyl acetate in hexanes) to afford 2-butyl-6-ethyl-4-methyl-3-(4-trifluoromethyl-phenyl)-2,4-dihydro-pyrazolo[4,3-*d*]pyrimidine-5,7-dione (**1a**) (42 mg, 85%) as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.81 (t, 3H, J = 5.6 Hz), 1.19 (m, 2H, J = 6 Hz), 1.25 (t, 3H, J = 5.6 Hz), 1.75 (m, 2H, J = 6 Hz), 3.01 (s, 3H), 3.97 (q, 2H, J = 5.6 Hz), 4.14 (t, 2H, J = 5.6 Hz), 7.54 (d, 2H, J = 6.4 Hz), 7.82 (d, 2H, J = 6.8 Hz). LC–MS (ESI$^+$) m/z = 395.2 [M+H]$^+$. The other analogs in Table 1 were synthesized in similar way as that described above for the synthesis of **12a** and **1a**.

16. N_2O_3 gas was generated by slowly adding concentrated HCl to aqueous slurry of sodium nitrite in a 3-necked flask via an additional funnel. One of the necks was covered with a stopper and the other one was directed, via Tygon tubing, to a syringe immersed in the solvent in the reaction flask.
17. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications nos. The deposition number is CCDC 730905.